

INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY

ANALYTICAL CHEMISTRY DIVISION  
COMMISSION ON SOLUBILITY DATA

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**SOLUBILITY DATA SERIES**

Volume 16/17

**ANTIBIOTICS: I**  
 **$\beta$ -LACTAM ANTIBIOTICS**

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# SOLUBILITY DATA SERIES

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Volume 16/17

## ANTIBIOTICS: I $\beta$ -LACTAM ANTIBIOTICS

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## FOREWORD

*If the knowledge is  
undigested or simply wrong,  
more is not better*

How to communicate and disseminate numerical data effectively in chemical science and technology has been a problem of serious and growing concern to IUPAC, the International Union of Pure and Applied Chemistry, for the last two decades. The steadily expanding volume of numerical information, the formulation of new interdisciplinary areas in which chemistry is a partner, and the links between these and existing traditional subdisciplines in chemistry, along with an increasing number of users, have been considered as urgent aspects of the information problem in general, and of the numerical data problem in particular.

Among the several numerical data projects initiated and operated by various IUPAC commissions, the *Solubility Data Project* is probably one of the most ambitious ones. It is concerned with preparing a comprehensive critical compilation of data on solubilities in all physical systems, of gases, liquids and solids. Both the basic and applied branches of almost all scientific disciplines require a knowledge of solubilities as a function of solvent, temperature and pressure. Solubility data are basic to the fundamental understanding of processes relevant to agronomy, biology, chemistry, geology and oceanography, medicine and pharmacology, and metallurgy and materials science. Knowledge of solubility is very frequently of great importance to such diverse practical applications as drug dosage and drug solubility in biological fluids, anesthesiology, corrosion by dissolution of metals, properties of glasses, ceramics, concretes and coatings, phase relations in the formation of minerals and alloys, the deposits of minerals and radioactive fission products from ocean waters, the composition of ground waters, and the requirements of oxygen and other gases in life support systems.

The widespread relevance of solubility data to many branches and disciplines of science, medicine, technology and engineering, and the difficulty of recovering solubility data from the literature, lead to the proliferation of published data in an ever increasing number of scientific and technical primary sources. The sheer volume of data has overcome the capacity of the classical secondary and tertiary services to respond effectively.

While the proportion of secondary services of the review article type is generally increasing due to the rapid growth of all forms of primary literature, the review articles become more limited in scope, more specialized. The disturbing phenomenon is that in some disciplines, certainly in chemistry, authors are reluctant to treat even those limited-in-scope reviews exhaustively. There is a trend to preselect the literature, sometimes under the pretext of reducing it to manageable size. The crucial problem with such preselection - as far as numerical data are concerned - is that there is no indication as to whether the material was excluded by design or by a less than thorough literature search. We are equally concerned that most current secondary sources, critical in character as they may be, give scant attention to numerical data.

On the other hand, tertiary sources - handbooks, reference books and other tabulated and graphical compilations - as they exist today are comprehensive but, as a rule, uncritical. They usually attempt to cover whole disciplines, and thus obviously are superficial in treatment. Since they command a wide market, we believe that their service to the advancement of science is at least questionable. Additionally, the change which is taking place in the generation of new and diversified numerical data, and the rate at which this is done, is not reflected in an increased third-level service. The emergence of new tertiary literature sources does not parallel the shift that has occurred in the primary literature.

With the status of current secondary and tertiary services being as briefly stated above, the innovative approach of the *Solubility Data Project* is that its compilation and critical evaluation work involve consolidation and reprocessing services when both activities are based on intellectual and scholarly reworking of information from primary sources. It comprises compact compilation, rationalization and simplification, and the fitting of isolated numerical data into a critically evaluated general framework.

The *Solubility Data Project* has developed a mechanism which involves a number of innovations in exploiting the literature fully, and which contains new elements of a more imaginative approach for transfer of reliable information from primary to secondary/tertiary sources. *The fundamental trend of the Solubility Data Project is toward integration of secondary and tertiary services with the objective of producing in-depth critical analysis and evaluation which are characteristic to secondary services, in a scope as broad as conventional tertiary services.*

Fundamental to the philosophy of the project is the recognition that the basic element of strength is the active participation of career scientists in it. Consolidating primary data, producing a truly critically-evaluated set of numerical data, and synthesizing data in a meaningful relationship are demands considered worthy of the efforts of top scientists. Career scientists, who themselves contribute to science by their involvement in active scientific research, are the backbone of the project. The scholarly work is commissioned to recognized authorities, involving a process of careful selection in the best tradition of IUPAC. This selection in turn is the key to the quality of the output. These top experts are expected to view their specific topics dispassionately, paying equal attention to their own contributions and to those of their peers. They digest literature data into a coherent story by weeding out what is wrong from what is believed to be right. To fulfill this task, the evaluator must cover all relevant open literature. No reference is excluded by design and every effort is made to detect every bit of relevant primary source. Poor quality or wrong data are mentioned and explicitly disqualified as such. In fact, it is only when the reliable data are presented alongside the unreliable data that proper justice can be done. The user is bound to have incomparably more confidence in a succinct evaluative commentary and a comprehensive review with a complete bibliography to both good and poor data.

It is the standard practice that the treatment of any given solute-solvent system consists of two essential parts: I. Critical Evaluation and Recommended Values, and II. Compiled Data Sheets.

The Critical Evaluation part gives the following information:

- (i) a verbal text of evaluation which discusses the numerical solubility information appearing in the primary sources located in the literature. The evaluation text concerns primarily the quality of data after consideration of the purity of the materials and their characterization, the experimental method employed and the uncertainties in control of physical parameters, the reproducibility of the data, the agreement of the worker's results on accepted test systems with standard values, and finally, the fitting of data, with suitable statistical tests, to mathematical functions;
- (ii) a set of recommended numerical data. Whenever possible, the set of recommended data includes weighted average and standard deviations, and a set of smoothing equations derived from the experimental data endorsed by the evaluator;
- (iii) a graphical plot of recommended data.

The Compilation part consists of data sheets of the best experimental data in the primary literature. Generally speaking, such independent data sheets are given only to the best and endorsed data covering the known range of experimental parameters. Data sheets based on primary sources where the data are of a lower precision are given only when no better data are available. Experimental data with a precision poorer than considered acceptable are reproduced in the form of data sheets when they are the only known data for a particular system. Such data are considered to be still suitable for some applications, and their presence in the compilation should alert researchers to areas that need more work.

The typical data sheet carries the following information:

- (i) components - definition of the system - their names, formulas and Chemical Abstracts registry numbers;
- (ii) reference to the primary source where the numerical information is reported. In cases when the primary source is a less common periodical or a report document, published though of limited availability, abstract references are also given;
- (iii) experimental variables;
- (iv) identification of the compiler;
- (v) experimental values as they appear in the primary source. Whenever available, the data may be given both in tabular and graphical form. If auxiliary information is available, the experimental data are converted also to SI units by the compiler.

Under the general heading of Auxiliary Information, the essential experimental details are summarized:

- (vi) experimental method used for the generation of data;
- (vii) type of apparatus and procedure employed;
- (viii) source and purity of materials;
- (ix) estimated error;
- (x) references relevant to the generation of experimental data as cited in the primary source.

This new approach to numerical data presentation, formulated at the initiation of the project and perfected as experience has accumulated, has been strongly influenced by the diversity of background of those whom we are supposed to serve. We thus deemed it right to preface the evaluation/compilation sheets in each volume with a detailed discussion of the principles of the accurate determination of relevant solubility data and related thermodynamic information.

Finally, the role of education is more than corollary to the efforts we are seeking. The scientific standards advocated here are necessary to strengthen science and technology, and should be regarded as a major effort in the training and formation of the next generation of scientists and engineers. Specifically, we believe that there is going to be an impact of our project on scientific-communication practices. The quality of consolidation adopted by this program offers down-to-earth guidelines, concrete examples which are bound to make primary publication services more responsive than ever before to the needs of users. The self-regulatory message to scientists of the early 1970s to refrain from unnecessary publication has not achieved much. A good fraction of the literature is still cluttered with poor-quality articles. The Weinberg report (in 'Reader in Science Information', ed. J. Sherrod and A. Hodina, Microcard Editions Books, Indian Head, Inc., 1973, p. 292) states that 'admonition to authors to restrain themselves from premature, unnecessary publication can have little effect unless the climate of the entire technical and scholarly community encourages restraint...' We think that projects of this kind translate the climate into operational terms by exerting pressure on authors to avoid submitting low-grade material. The type of our output, we hope, will encourage attention to quality as authors will increasingly realize that their work will not be suited for permanent retrievability unless it meets the standards adopted in this project. It should help to dispel confusion in the minds of many authors of what represents a permanently useful bit of information of an archival value, and what does not.

If we succeed in that aim, even partially, we have then done our share in protecting the scientific community from unwanted and irrelevant, wrong numerical information.

A. S. Kertes

## PREFACE

Beta-lactam antibiotics constitute a large group of naturally occurring and semi-synthetic solutes possessing either a nucleus of 6-aminopenicillanic acid (i.e. the penicillins) or of 7-aminocephalosporanic acid (i.e. the cephalosporins). Both 6-aminopenicillanic acid and 7-aminocephalosporanic acid are ampholytes having a low activity against bacteria, however, their derivatives (substituted at the 2-carbon carboxylic group and at the 6-carbon amino group) are amongst the most effective chemotherapeutic drugs to have been developed.

Although the antibacterial activity of *Penicillium glaucum* was first demonstrated in 1896 by a French medical student, Ernest Duchesne, it was not until the further observations of Fleming in 1928, and the research and development of Florey, Chain and Abraham beginning in 1939, that penicillin was developed into a therapeutic agent - with the first clinical trial in the United States taking place in 1942 [see Chain, E.B. *Antibiot. Chemother.* 1954, 4, 215-41].

The basic structure of the penicillins (see Fig. below) consists of a thiazolidine ring connected to a beta-lactam ring, to which is attached a side chain.

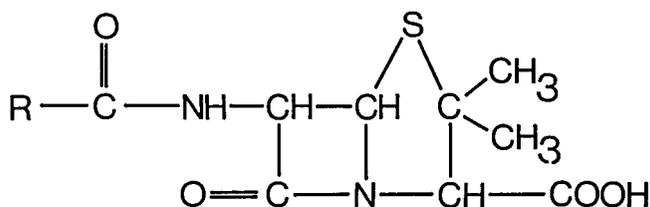


Figure 1. Structure of penicillins

### Unitage of Penicillin

The rapid acceptance of penicillin as a major chemotherapeutic agent led to the early introduction of a standard system for expressing its potency. Hence the International Conference on the Standardization of Penicillin established in 1944 the *international unit of penicillin* and the *international penicillin master standard*, with the latter being a sample of the crystalline sodium salt of penicillin G (benzylpenicillin). The unit is by definition given as the specific penicillin activity contained in 0.6 microgram of the master standard, with one milligram of pure penicillin G sodium being equal to 1 667 units. (Due to differences in molecular weight, 1.0 mg of pure penicillin G potassium is equal to 1 595 units, and so forth). In this present Volume, solubilities have been compiled and given as originally reported. In addition, in the evaluation of the solubilities of beta-lactam antibiotics, all reported values have been converted into S.I. units where possible.

The first source of the cephalosporins (*cephalosporium acremonium*) was isolated in 1948 from the sea near a sewer outlet off the Sardinian coast. Cultivation of this fungus gave rise to three antibiotics, (i) cephalosporin P, (active against gram-positive microorganisms, (ii) cephalosporin N, (active against both gram-positive and gram-negative microorganisms, and (iii) cephalosporin C, (similar to cephalosporin N in action, though less potent). From cephalosporin C it became possible to isolate the active nucleus of the cephalosporins, i.e. 7-aminocephalosporanic acid, and thence to synthetically develop this to produce antibacterial compounds having potencies far greater than that of 7-aminocephalosporanic acid itself. The basic structure of the cephalosporins is shown below.

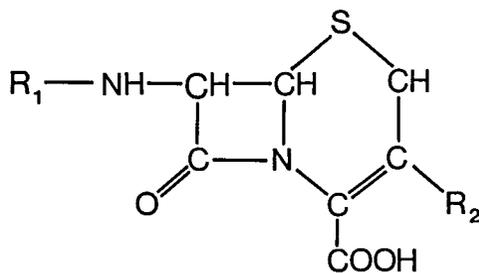


Figure 2. Basic structure of the cephalosporins.

This Volume also gives the solubility of cycloserine (D-4-amino-3-isoxazolidone), whose structural formula is given in Fig. 3.

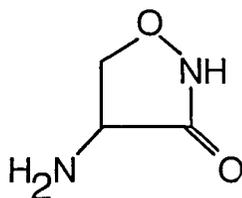


Figure 3. Structural formula of cycloserine.

In this Volume we have attempted to survey the literature up until 1983. A great concern of ours has been the difficulty in designating values of solubilities as "recommended" or even "tentative". This is because for the former case a significant number of values need to be available, and for the latter case, such a label is given to a value which, in our opinion, has been determined with good precision but has not (yet) been confirmed independently.

Since values of the solubilities of beta-lactam antibiotics are of significance *inter alia* during their manufacture (and isolation), and for consideration of their biopharmaceutic, pharmacokinetic and pharmacodynamic properties, it is hoped that the information given in this present Volume will be of use in those areas, and that those deficiencies in the literature revealed, will encourage more detailed work on the solubilities of these antibiotics.

Eric Tomlinson\*  
Amsterdam, December 1983

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# INTRODUCTION TO THE SOLUBILITY OF SOLIDS IN LIQUIDS

## Nature of the Project

The Solubility Data Project (SDP) has as its aim a comprehensive search of the literature for solubilities of gases, liquids, and solids in liquids or solids. Data of suitable precision are compiled on data sheets in a uniform format. The data for each system are evaluated, and where data from different sources agree sufficiently, recommended values are proposed. The evaluation sheets, recommended values, and compiled data sheets are published on consecutive pages.

This series of volumes includes solubilities of solids of all types in liquids of all types.

## Definitions

A *mixture* (1,2) describes a gaseous, liquid, or solid phase containing more than one substance, when the substances are all treated in the same way.

A *solution* (1,2) describes a liquid or solid phase containing more than one substance, when for convenience one of the substances, which is called the *solvent* and may itself be a mixture, is treated differently than the other substances, which are called *solutes*. If the sum of the mole fractions of the solutes is small compared to unity, the solution is called a *dilute solution*.

The *solubility* of a substance B is the relative proportion of B (or a substance related chemically to B) in a mixture which is saturated with respect to solid B at a specified temperature and pressure. *Saturated* implies the existence of equilibrium with respect to the processes of dissolution and precipitation; the equilibrium may be stable or metastable. The solubility of a metastable substance is usually greater than that of the corresponding stable substance. (Strictly speaking, it is the activity of the metastable substance that is greater.) Care must be taken to distinguish true metastability from supersaturation, where equilibrium does not exist.

Either point of view, mixture or solution, may be taken in describing solubility. The two points of view find their expression in the quantities used as measures of solubility and in the reference states used for definition of activities and activity coefficients.

The qualifying phrase "substance related chemically to B" requires comment. The composition of the saturated mixture (or solution) can be described in terms of any suitable set of thermodynamic components. Thus, the solubility of a salt hydrate in water is usually given as the relative proportion of anhydrous salt in solution, rather than the relative proportions of hydrated salt and water.

## Quantities Used as Measures of Solubility

1. Mole fraction of substance B,  $x_B$ :

$$x_B = n_B / \sum_{i=1}^c n_i \quad (1)$$

where  $n_i$  is the amount of substance of substance  $i$ , and  $c$  is the number of distinct substances present (often the number of thermodynamic components in the system). Mole per cent of B is  $100 x_B$ .

2. Mass fraction of substance B,  $w_B$ :

$$w_B = m'_B / \sum_{i=1}^c m'_i \quad (2)$$

where  $m'_i$  is the mass of substance  $i$ . Mass per cent of B is  $100 w_B$ . The equivalent terms weight fraction and weight per cent are not used.

3. Solute mole (mass) fraction of solute B (3,4):

$$x_{S,B} = n_B / \sum_{i=1}^{c'} n_i = x_B / \sum_{i=1}^{c'} x_i \quad (3)$$

where the summation is over the solutes only. For the solvent A,  $x_{S,A} = x_A$ . These quantities are called *Jänecke mole (mass) fractions* in many papers.

4. Molality of solute B (1,2) in a solvent A:

$$m_B = n_B/n_A M_A \quad \text{SI base units: mol kg}^{-1} \quad (4)$$

where  $M_A$  is the molar mass of the solvent.

5. Concentration of solute B (1,2) in a solution of volume V:

$$c_B = [B] = n_B/V \quad \text{SI base units: mol m}^{-3} \quad (5)$$

The terms molarity and molar are not used.

Mole and mass fractions are appropriate to either the mixture or the solution points of view. The other quantities are appropriate to the solution point of view only. In addition of these quantities, the following are useful in conversions between concentrations and other quantities.

6. Density:  $\rho = m/V$  SI base units: kg m<sup>-3</sup> (6)

7. Relative density:  $d$ ; the ratio of the density of a mixture to the density of a reference substance under conditions which must be specified for both (1). The symbol  $d_t^t$ , will be used for the density of a mixture at  $t^\circ\text{C}$ , 1 atm divided by the density of water at  $t^\circ\text{C}$ , 1 atm.

Other quantities will be defined in the prefaces to individual volumes or on specific data sheets.

### Thermodynamics of Solubility

The principal aims of the Solubility Data Project are the tabulation and evaluation of: (a) solubilities as defined above; (b) the nature of the saturating solid phase. Thermodynamic analysis of solubility phenomena has two aims: (a) to provide a rational basis for the construction of functions to represent solubility data; (b) to enable thermodynamic quantities to be extracted from solubility data. Both these aims are difficult to achieve in many cases because of a lack of experimental or theoretical information concerning activity coefficients. Where thermodynamic quantities can be found, they are not evaluated critically, since this task would involve critical evaluation of a large body of data that is not directly relevant to solubility. The following discussion is an outline of the principal thermodynamic relations encountered in discussions of solubility. For more extensive discussions and references, see books on thermodynamics, e.g., (5-10).

### Activity Coefficients (1)

(a) Mixtures. The activity coefficient  $f_B$  of a substance B is given by

$$RT \ln(f_B x_B) = \mu_B - \mu_B^* \quad (7)$$

where  $\mu_B$  is the chemical potential, and  $\mu_B^*$  is the chemical potential of pure B at the same temperature and pressure. For any substance B in the mixture,

$$\lim_{x_B \rightarrow 1} f_B = 1 \quad (8)$$

(b) Solutions.

(i) Solute substance, B. The molal activity coefficient  $\gamma_B$  is given by

$$RT \ln(\gamma_B m_B) = \mu_B - (\mu_B - RT \ln m_B)^\infty \quad (9)$$

where the superscript  $^\infty$  indicates an infinitely dilute solution. For any solute B,

$$\gamma_B^\infty = 1 \quad (10)$$

Activity coefficients  $\gamma_B$  connected with concentration  $c_B$ , and  $f_{x,B}$  (called the rational activity coefficient) connected with mole fraction  $x_B$  are defined in analogous ways. The relations among them are (1,9):

$$\gamma_B = x_A f_{x,B} = V_A^* (1 - \sum_S c_S) \gamma_B \quad (11)$$

or

$$f_{x,B} = (1 + M_A \sum_S m_S) \gamma_B = V_A^* y_B / V_m \quad (12)$$

or

$$y_B = (V_A + M_A \sum_S m_S V_S) \gamma_B / V_A^* = V_m f_{x,B} / V_A^* \quad (13)$$

where the summations are over all solutes,  $V_A^*$  is the molar volume of the pure solvent,  $V_i$  is the partial molar volume of substance  $i$ , and  $V_m$  is the molar volume of the solution.

For an electrolyte solute  $B \equiv C_{v+}A_{v-}$ , the molal activity is replaced by (9)

$$\gamma_B^{m_B} = \gamma_{\pm}^{v_+ v_-} Q^v \quad (14)$$

where  $v = v_+ + v_-$ ,  $Q = (v_+^{v_+} v_-^{v_-})^{1/v}$ , and  $\gamma_{\pm}$  is the mean ionic molal activity coefficient. A similar relation holds for the concentration activity  $y_{BCB}$ . For the mol fractional activity,

$$f_{x,B} x_B = v_+^{v_+} v_-^{v_-} f_{\pm}^{v_+ v_-} x_{\pm}^v \quad (15)$$

The quantities  $x_+$  and  $x_-$  are the ionic mole fractions (9), which for a single solute are

$$x_+ = v_+ x_B / [1 + (v-1) x_B]; \quad x_- = v_- x_B / [1 + (v-1) x_B] \quad (16)$$

(ii) Solvent, A:

The osmotic coefficient,  $\phi$ , of a solvent substance A is defined as (1):

$$\phi = (\mu_A^* - \mu_A) / RT M_A \sum_S m_S \quad (17)$$

where  $\mu_A^*$  is the chemical potential of the pure solvent.

The rational osmotic coefficient,  $\phi_x$ , is defined as (1):

$$\phi_x = (\mu_A - \mu_A^*) / RT \ln x_A = \phi M_A \sum_S m_S / \ln(1 + M_A \sum_S m_S) \quad (18)$$

The activity,  $a_A$ , or the activity coefficient  $f_A$  is often used for the solvent rather than the osmotic coefficient. The activity coefficient is defined relative to pure A, just as for a mixture.

### The Liquid Phase

A general thermodynamic differential equation which gives solubility as a function of temperature, pressure and composition can be derived. The approach is that of Kirkwood and Oppenheim (7). Consider a solid mixture containing  $c'$  thermodynamic components  $i$ . The Gibbs-Duhem equation for this mixture is:

$$\sum_{i=1}^{c'} x_i' (S_i' dT - V_i' dp + d\mu_i) = 0 \quad (19)$$

A liquid mixture in equilibrium with this solid phase contains  $c$  thermodynamic components  $i$ , where, usually,  $c \geq c'$ . The Gibbs-Duhem equation for the liquid mixture is:

$$\sum_{i=1}^c x_i (S_i dT - V_i dp + d\mu_i) + \sum_{i=c'+1}^c x_i (S_i dT - V_i dp + d\mu_i) = 0 \quad (20)$$

Eliminate  $d\mu_i$  by multiplying (19) by  $x_i'$  and (20)  $x_i'$ . After some algebra, and use of:

$$d\mu_i = \sum_{j=2}^c G_{ij} dx_j - S_i dT + V_i dp \quad (21)$$

where (7)

$$G_{ij} = (\partial \mu_i / \partial x_j)_{T,P,x_1 \neq x_j} \quad (22)$$

it is found that

$$\begin{aligned} & \sum_{i=2}^{c'} \sum_{j=2}^c (x_i' - x_i x_i' / x_1) G_{ij} dx_j - (x_1' / x_1) \sum_{i=c'+1}^c \sum_{j=2}^c x_i G_{ij} dx_j \\ & = \sum_{i=1}^{c'} x_i' (H_i - H_i') dT / T - \sum_{i=1}^{c'} x_i' (V_i - V_i') dp \end{aligned} \quad (23)$$

where

$$H_i - H_i' = T(S_i - S_i') \quad (24)$$

is the enthalpy of transfer of component  $i$  from the solid to the liquid phase, at a given temperature, pressure and composition, and  $H_i$ ,  $S_i$ ,  $V_i$  are the partial molar enthalpy, entropy, and volume of component  $i$ . Several special cases (all with pressure held constant) will be considered. Other cases will appear in individual evaluations.

(a) *Solubility as a function of temperature.*

Consider a binary solid compound  $A_nB$  in a single solvent  $A$ . There is no fundamental thermodynamic distinction between a binary compound of  $A$  and  $B$  which dissociates completely or partially on melting and a solid mixture of  $A$  and  $B$ ; the binary compound can be regarded as a solid mixture of constant composition. Thus, with  $c = 2$ ,  $c' = 1$ ,  $x_A' = n/(n+1)$ ,  $x_B' = 1/(n+1)$ , eqn (23) becomes

$$(1/x_B - n/x_A) \left\{ 1 + \left( \frac{\partial \ln f_B}{\partial \ln x_B} \right)_{T,P} \right\} dx_B = (nH_A + H_B - H_{AB}^*) dT/RT^2 \quad (25)$$

where the mole fractional activity coefficient has been introduced. If the mixture is a non-electrolyte, and the activity coefficients are given by the expression for a simple mixture (6):

$$RT \ln f_B = wx_A^2 \quad (26)$$

then it can be shown that, if  $w$  is independent of temperature, eqn (25) can be integrated (cf. (5), Chap. XXIII, sect. 5). The enthalpy term becomes

$$\begin{aligned} nH_A + H_B - H_{AB}^* &= \Delta H_{AB} + n(H_A - H_A^*) + (H_B - H_B^*) \\ &= \Delta H_{AB} + w(nx_B^2 + x_A^2) \end{aligned} \quad (27)$$

where  $\Delta H_{AB}$  is the enthalpy of melting and dissociation of one mole of pure solid  $A_nB$ , and  $H_A^*$ ,  $H_B^*$  are the molar enthalpies of pure liquid  $A$  and  $B$ . The differential equation becomes

$$R d \ln \{x_B(1-x_B)^n\} = -\Delta H_{AB} d\left(\frac{1}{T}\right) - w d\left(\frac{x_A^2 + nx_B^2}{T}\right) \quad (28)$$

Integration from  $x_B, T$  to  $x_B = 1/(1+n)$ ,  $T = T^*$ , the melting point of the pure binary compound, gives:

$$\begin{aligned} \ln \{x_B(1-x_B)^n\} &\approx \ln \left\{ \frac{n^n}{(1+n)^{n+1}} \right\} - \left\{ \frac{\Delta H_{AB}^* - T^* \Delta C_p^*}{R} \right\} \left( \frac{1}{T} - \frac{1}{T^*} \right) \\ &+ \frac{\Delta C_p^*}{R} \ln \left( \frac{T}{T^*} \right) - \frac{w}{R} \left\{ \frac{x_A^2 + nx_B^2}{T} - \frac{n}{(n+1)T^*} \right\} \end{aligned} \quad (29)$$

where  $\Delta C_p^*$  is the change in molar heat capacity accompanying fusion plus decomposition of the compound at temperature  $T^*$ , (assumed here to be independent of temperature and composition), and  $\Delta H_{AB}^*$  is the corresponding change in enthalpy at  $T = T^*$ . Equation (29) has the general form

$$\ln \{x_B(1-x_B)^n\} = A_1 + A_2/T + A_3 \ln T + A_4 (x_A^2 + nx_B^2)/T \quad (30)$$

If the solid contains only component  $B$ ,  $n = 0$  in eqn (29) and (30).

If the infinite dilution standard state is used in eqn (25), eqn (26) becomes

$$RT \ln f_{x,B} = w(x_A^2 - 1) \quad (31)$$

and (27) becomes

$$nH_A + H_B - H_{AB} = (nH_A^{\infty} + H_B^{\infty} - H_{AB}^{\infty}) + n(H_A - H_A^*) + (H_B - H_B^{\infty}) = \Delta H_{AB}^{\infty} + w(nx_B^2 + x_A^2 - 1) \quad (32)$$

where the first term,  $\Delta H_{AB}^{\infty}$ , is the enthalpy of melting and dissociation of solid compound  $A_nB$  to the infinitely dilute state of solute  $B$  in solvent  $A$ ;  $H_B^{\infty}$  is the partial molar enthalpy of the solute at infinite dilution. Clearly, the integral of eqn (25) will have the same form as eqn (29), with  $\Delta H_{AB}(T^*)$ ,  $\Delta C_p^{\infty}(T^*)$  replacing  $\Delta H_{AB}^*$  and  $\Delta C_p^*$  and  $x_A^2 - 1$  replacing  $x_A^2$  in the last term.

If the liquid phase is an aqueous electrolyte solution, and the solid is a salt hydrate, the above treatment needs slight modification. Using rational mean activity coefficients, eqn (25) becomes

$$Rv(1/x_B - n/x_A) \{1 + (\partial \ln f_{\pm} / \partial \ln x_{\pm})_{T,P}\} dx_B / \{1 + (v-1)x_B\} \\ = \{\Delta H_{AB}^{\infty} + n(H_A - H_A^*) + (H_B - H_B^*)\} d(1/T) \quad (33)$$

If the terms involving activity coefficients and partial molar enthalpies are negligible, then integration gives (cf. (11)):

$$\ln \left\{ \frac{x_B^v (1-x_B)^n}{1+(v-1)x_B} \right\}^{n+v} = \ln \left\{ \frac{n^n}{(n+v)^{n+v}} \right\} - \left\{ \frac{\Delta H_{AB}^{\infty}(T^*) - T^* \Delta C_P^*}{R} \right\} \left( \frac{1}{T} - \frac{1}{T^*} \right) + \frac{\Delta C_P^*}{R} \ln(T/T^*) \quad (34)$$

A similar equation (with  $v=2$  and without the heat capacity terms) has been used to fit solubility data for some  $MOH=H_2O$  systems, where  $M$  is an alkali metal; the enthalpy values obtained agreed well with known values (11). In many cases, data on activity coefficients (9) and partial molal enthalpies (8,10) in concentrated solution indicate that the terms involving these quantities are not negligible, although they may remain roughly constant along the solubility temperature curve.

The above analysis shows clearly that a rational thermodynamic basis exists for functional representation of solubility-temperature curves in two-component systems, but may be difficult to apply because of lack of experimental or theoretical knowledge of activity coefficients and partial molar enthalpies. Other phenomena which are related ultimately to the stoichiometric activity coefficients and which complicate interpretation include ion pairing, formation of complex ions, and hydrolysis. Similar considerations hold for the variation of solubility with pressure, except that the effects are relatively smaller at the pressures used in many investigations of solubility (5).

(b) *Solubility as a function of composition.*

At constant temperature and pressure, the chemical potential of a saturating solid phase is constant:

$$\mu_{A_n B}^* = \mu_{A_n B}(\text{sln}) = n\mu_A + \mu_B \quad (35)$$

$$= (n\mu_A^* + v_+ \mu_+^{\infty} + v_- \mu_-^{\infty}) + nRT \ln f_A x_A \\ + vRT \ln \gamma_{\pm} m_{\pm} Q_{\pm} \quad (36)$$

for a salt hydrate  $A_n B$  which dissociates to water, (A), and a salt, B, one mole of which ionizes to give  $v_+$  cations and  $v_-$  anions in a solution in which other substances (ionized or not) may be present. If the saturated solution is sufficiently dilute,  $f_A = x_A = 1$ , and the quantity  $K_{S_0}^0$  in

$$\Delta G^{\infty} \equiv (v_+ \mu_+^{\infty} + v_- \mu_-^{\infty} + n\mu_A^* - \mu_{AB}^*) \\ = -RT \ln K_{S_0}^0 \\ = -RT \ln Q^v \gamma_{\pm}^v m_+^{v_+} m_-^{v_-} \quad (37)$$

is called the *solubility product* of the salt. (It should be noted that it is not customary to extend this definition to hydrated salts, but there is no reason why they should be excluded.) Values of the solubility product are often given on mole fraction or concentration scales. In dilute solutions, the theoretical behaviour of the activity coefficients as a function of ionic strength is often sufficiently well known that reliable extrapolations to infinite dilution can be made, and values of  $K_{S_0}^0$  can be determined. In more concentrated solutions, the same problems with activity coefficients that were outlined in the section on variation of solubility with temperature still occur. If these complications do not arise, the solubility of a hydrate salt  $C_v A_{v_+} \cdot nH_2O$  in the presence of other solutes is given by eqn (36) as

$$v \ln \{m_B/m_B(0)\} = -v \ln \{\gamma_{\pm}/\gamma_{\pm}(0)\} - n \ln (a_{H_2O}/a_{H_2O}(0)) \quad (38)$$

where  $a_{H_2O}$  is the activity of water in the saturated solution,  $m_B$  is the molality of the salt in the saturated solution, and (0) indicates absence of other solutes. Similar considerations hold for non-electrolytes.

### The Solid Phase

The definition of solubility permits the occurrence of a single solid phase which may be a pure anhydrous compound, a salt hydrate, a non-stoichiometric compound, or a solid mixture (or solid solution, or "mixed crystals"), and may be stable or metastable. As well, any number of solid phases consistent with the requirements of the phase rule may be present. Metastable solid phases are of widespread occurrence, and may appear as polymorphic (or allotropic) forms or crystal solvates whose rate of transition to more stable forms is very slow. Surface heterogeneity may also give rise to metastability, either when one solid precipitates on the surface of another, or if the size of the solid particles is sufficiently small that surface effects become important. In either case, the solid is not in stable equilibrium with the solution. The stability of a solid may also be affected by the atmosphere in which the system is equilibrated.

Many of these phenomena require very careful, and often prolonged, equilibration for their investigation and elimination. A very general analytical method, the "wet residues" method of Schreinemakers (12) (see a text on physical chemistry) is usually used to investigate the composition of solid phases in equilibrium with salt solutions. In principle, the same method can be used with systems of other types. Many other techniques for examination of solids, in particular X-ray, optical, and thermal analysis methods, are used in conjunction with chemical analyses (including the wet residues method).

### COMPILATIONS AND EVALUATIONS

The formats for the compilations and critical evaluations have been standardized for all volumes. A brief description of the data sheets has been given in the FOREWORD; additional explanation is given below.

#### Guide to the Compilations

The format used for the compilations is, for the most part, self-explanatory. The details presented below are those which are not found in the FOREWORD or which are not self-evident.

*Components.* Each component is listed according to IUPAC name, formula, and Chemical Abstracts (CA) Registry Number. The formula is given either in terms of the IUPAC or Hill (13) system and the choice of formula is governed by what is usual for most current users: i.e. IUPAC for inorganic compounds, and Hill system for organic compounds. Components are ordered according to:

- (a) saturating components;
- (b) non-saturating components in alphanumerical order;
- (c) solvents in alphanumerical order.

The saturating components are arranged in order according to a 18-column, 2-row periodic table:

Columns 1,2: H, groups IA, IIA;  
 3,12: transition elements (groups IIIB to VIIB, group VIII, groups IB, IIB);  
 13-18: groups IIIA-VIIA, noble gases.

Row 1: Ce to Lu;

Row 2: Th to the end of the known elements, in order of atomic number.

Salt hydrates are generally not considered to be saturating components since most solubilities are expressed in terms of the anhydrous salt. The existence of hydrates or solvates is carefully noted in the texts, and CA Registry Numbers are given where available, usually in the critical evaluation. Mineralogical names are also quoted, along with their CA Registry Numbers, again usually in the critical evaluation.

*Original Measurements.* References are abbreviated in the forms given by *Chemical Abstracts Service Source Index (CASSI)*. Names originally in other than Roman alphabets are given as transliterated by *Chemical Abstracts*.

*Experimental Values.* Data are reported in the units used in the original publication, with the exception that modern names for units and quantities are used; e.g., mass per cent for weight per cent; mol dm<sup>-3</sup> for molar; etc. Both mass and molar values are given. Usually, only one type of value (e.g., mass per cent) is found in the original paper, and the compiler has added the other type of value (e.g., mole per cent) from computer calculations based on 1976 atomic weights (14). Errors in calculations and fitting equations in original papers have been noted and corrected, by computer calculations where necessary.

*Method. Source and Purity of Materials.* Abbreviations used in *Chemical Abstracts* are often used here to save space.

*Estimated Error.* If these data were omitted by the original authors, and if relevant information is available, the compilers have attempted to

estimate errors from the internal consistency of data and type of apparatus used. Methods used by the compilers for estimating and reporting errors are based on the papers by Ku and Eisenhart (15).

*Comments and/or Additional Data.* Many compilations include this section which provides short comments relevant to the general nature of the work or additional experimental and thermodynamic data which are judged by the compiler to be of value to the reader.

*References.* See the above description for Original Measurements.

#### *Guide to the Evaluations*

The evaluator's task is to check whether the compiled data are correct, to assess the reliability and quality of the data, to estimate errors where necessary, and to recommend "best" values. The evaluation takes the form of a summary in which all the data supplied by the compiler have been critically reviewed. A brief description of the evaluation sheets is given below.

*Components.* See the description for the Compilations.

*Evaluator.* Name and date up to which the literature was checked.

#### *Critical Evaluation*

(a) *Critical text.* The evaluator produces text evaluating *all* the published data for each given system. Thus, in this section the evaluator review the merits or shortcomings of the various data. Only published data are considered; even published data can be considered only if the experimental data permit an assessment of reliability.

(b) *Fitting equations.* If the use of a smoothing equation is justifiable, the evaluator may provide an equation representing the solubility as a function of the variables reported on all the compilation sheets.

(c) *Graphical summary.* In addition to (b) above, graphical summaries are often given.

(d) *Recommended values.* Data are *recommended* if the results of at least two independent groups are available and they are in good agreement, and if the evaluator has no doubt as to the adequacy and reliability of the applied experimental and computational procedures. Data are reported as *tentative* if only one set of measurements is available, or if the evaluator considers some aspect of the computational or experimental method as mildly undesirable but estimates that it should cause only minor errors. Data are considered as *doubtful* if the evaluator considers some aspect of the computational or experimental method as undesirable but still considers the data to have some value in those instances where the order of magnitude of the solubility is needed. Data determined by an inadequate method or under ill-defined conditions are *rejected*. However references to these data are included in the evaluation together with a comment by the evaluator as to the reason for their rejection.

(e) *References.* All pertinent references are given here. References to those data which, by virtue of their poor precision, have been rejected and not compiled are also listed in this section.

(f) *Units.* While the original data may be reported in the units used by the investigators, the final recommended values are reported in S.I. units (1,16) when the data can be accurately converted.

#### *References*

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## EDITORIAL NOTE

This volume on the solubilities of  $\beta$ -lactam antibiotics is the first in the *Subseries on Pharmaceuticals* to be published as part of the *IUPAC Solubility Data Series*. Over the next five years 10 volumes will be published in this subseries, and the titles of these volumes are given below.

Although many of the compounds included in this subseries cannot be classified as "pharmaceuticals," they represent compounds of major interest in the area of pharmaceutical chemistry and are therefore included in the *Subseries on Pharmaceuticals*.

All existing volumes dealing with solid-liquid systems, including the present volume, contain the general introductory chapter entitled INTRODUCTION TO THE SOLUBILITY OF SOLIDS IN LIQUIDS. Future volumes in the *Subseries on Pharmaceuticals* will contain a new introductory chapter dealing with the general physical and chemical properties of saturated solutions of compounds of pharmaceutical interest. Volumes presently being prepared for the *Subseries on Pharmaceuticals* are:

1. *Peptide Antibiotics*, E. Tomlinson and A. Regosz, editors.
2. *Macrocyclic Lactone Antibiotics*, E. Tomlinson and A. Regosz, editors.
3. *Carbohydrate Antibiotics*, E. Tomlinson and H. Foks, editors.
4. *Aromatic Antibiotics*, E. Tomlinson and A. Regosz, editors.
5. *4-Aminobenzenesulfonamides (Part I)*, A.N. Paruta and R. Piekos, editors.
6. *4-Aminobenzenesulfonamides (Part II)*, A.N. Paruta and R. Piekos, editors.
7. *4-Aminobenzenesulfonamides (Part III)*, A.N. Paruta and R. Piekos, editors.
8. *Alkylidenediantipyrines*, T.D. Sokoloski and R. Kaliszan, editors.
9. *Pyrazoles*, T.D. Sokoloski and R. Kaliszan, editors.
10. *Antipyrines*, T.D. Sokoloski and R. Kaliszan, editors.

July, 1984

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## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-amino-3,3-dimethyl-7-oxo- (6-aminopenicillanic acid);  $C_8H_{12}N_2O_3S$ ; [551-16-6]  
 (2) All solvents

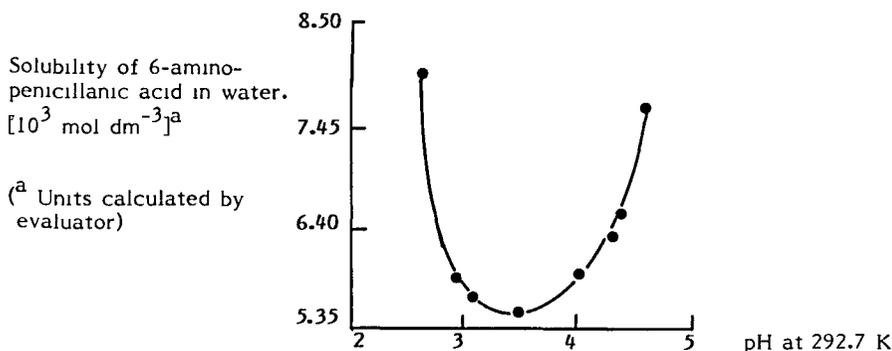
## EVALUATOR:

Eric Tomlinson,  
 Department of Pharmacy, University of Amsterdam, The Netherlands.  
 December 1983

## CRITICAL EVALUATION:

The solubility of 6-aminopenicillanic acid ( $C_8H_{12}N_2O_3S$ ) has been examined by two groups, (1,2). Both studies reported solubility values graphically. Solubility has been determined in aqueous solutions at various hydrogen ion concentrations and ionic strengths over the temperature range 273-303K and in the presence of various related solutes. The solubility in a 15 % (v/v) ethanol:water mixture at various temperatures has also been reported.

6-Aminopenicillanic acid is an ampholyte possessing a carboxyl group of  $pK = 2.29-2.30$ , and an amino group of  $pK = 4.90-4.92$  (3). At a pH equal to the isoelectric point ( $pI = 3.60$ ), the acid exists as the zwitterion. This form is both the most stable and the least soluble (in water). At lower or higher pH's, the solubility in water rises, since here 6-aminopenicillanic acid exists mainly in the ionized form, (Pages 3-5), i.e. (1),



From this figure a solubility in water at pH 3.3 to 3.7 (and at 292.7K) of  $5.5 \times 10^{-3} \text{ mol dm}^{-3}$  may be read. (All units given in this figure have been converted by the evaluator from the reported penicillin units  $\text{cm}^{-3}$ ). Consideration of the sample of 6-aminopenicillanic acid used, the microbiological assay procedure, and the fact that values are presented graphically, suggests a precision in this solubility value of approximately  $\pm 10\%$ . Nys et al (2) examined the solubility of 6-aminopenicillanic acid in water at 298 K at a constant ionic strength ( $\mu = 0.1$ ). They reported two values, an intrinsic solubility of  $1.07 \times 10^{-2} \text{ mol dm}^{-3}$ , (presumably of the zwitterion), and a solubility of  $8.70 \times 10^{-3} \text{ mol dm}^{-3}$ , (calculated according to the equation given on Page 7). Consideration of the method used to determine the solubility, the assay procedure (iodometric titration), and the reasonable agreement with the calculated value, suggests that the former value of  $1.07 \times 10^{-2} \text{ mol dm}^{-3}$  for the aqueous solubility of 6-aminopenicillanic acid at 298 K and an ionic strength of  $\mu = 0.1$ , may be regarded as tentative.

The effect of ionic strength on the solubility at  $pI = pH$  and at 298 K is reported (2) as being that an increase in aqueous solubility from about  $1.1 \times 10^{-2} \text{ mol dm}^{-3}$  to about  $1.2 \times 10^{-2} \text{ mol dm}^{-3}$  is caused by increasing the ionic strength from 0.1 to 1.0 mol  $\text{dm}^{-3}$ , (Page 8). Similarly (2), addition of potassium penicillin G in concentrations of  $1.0 \times 10^{-2} \text{ mol dm}^{-3}$  to  $3.6 \times 10^{-2} \text{ mol dm}^{-3}$  resulted in an increase in the aqueous solubility from about  $1 \times 10^{-2} \text{ mol dm}^{-3}$  to about  $4 \times 10^{-2} \text{ mol dm}^{-3}$ , (Page 9). Although these data were obtained using a more precise analytical method (i.e. iodometric titration), graphical presentation of the data mean that these latter results have a precision of  $\pm 10\%$ .

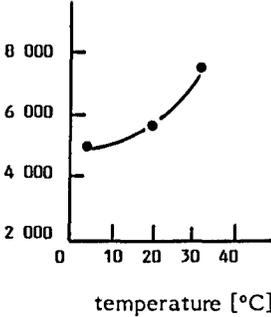
Further, from Page 2 (1) it may be read that the aqueous solubility of 6-aminopenicillanic acid rises from about  $5.3 \times 10^{-3} \text{ mol dm}^{-3}$  at 273K to about  $7.6 \times 10^{-3} \text{ mol dm}^{-3}$  at 303K, (units - Evaluator). All these values must be regarded as doubtful.

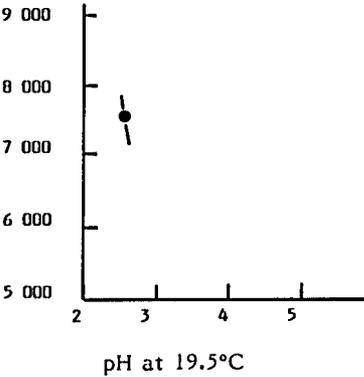
Bruns et al (2) determined the solubility of 6-aminopenicillanic acid in a 15 % (v/v) mixture of ethanol in water as a function of temperature 273-303 K. The solubility in the mixture was found to be approximately 50 times lower than in water, with values ranging from about  $1.0 \times 10^{-4} \text{ mol dm}^{-3}$  to about  $6.4 \times 10^{-4} \text{ mol dm}^{-3}$  over this temperature range, (units - Evaluator). These graphically presented values are doubtful.

(1) Bruns, B.P.; Savitskaya, H.M.; Shellenberg, N.N.; Libinson, G.S.; Kolygina, T.S.; Druzhnina, E.N. *Antibiotiki, Moscow* 1962, 7, 440.

(2) Nys, P.S.; Elizarovskaya, L.M.; Shellenberg, N.N.; Savitskaya, E.M. *Antibiotiki, Moscow* 1979, 24, 895.

(3) Rapson, H.D.C.; Bird, A.C. *J.Pharm.Pharmacol.* 1963, 15, 222.

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-amino-3,3-dimethyl-7-oxo-(6-aminopenicillanic acid); <math>C_8H_{12}N_2O_3S</math>; [551-16-6]</p> <p>(2) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Bruns, B.P.; Savitskaya, E.M.; Shellenberg, N.N.; Libinson, G.S.; Kolygina, T.S.; Druzhinina, E.N. <i>Antibiotiki, Moscow</i> 1962, 7, 440-2.</p>
<p>VARIABLES:</p> <p>Temperature</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <div style="display: flex; align-items: center; justify-content: center;"> <div style="margin-right: 20px;"> <p>solubility of 6-aminopenicillanic acid in water [Units/cm<sup>3</sup>]</p> </div>  </div>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of 6-aminopenicillanic acid and water were placed in a temperature controlled solubility apparatus, <math>N_2</math> was bubbled through the mixture. Aliquots of the saturated solution were withdrawn under vacuum at a given temp through a glass filter. The amount of the dissolved solute was determined microbiologically after conversion of 6-aminopenicillanic acid into phenoxymethylpenicillin using phenoxycetyl acid anhydride.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Crystalline 6-aminopenicillanic acid was obtained from the fermentation broth of <i>Penicillium chrysogenum</i> by carrying out the fermentation without adding the precursor. It had a melting point 204-6°C. The potency of the solubility product after conversion into phenoxymethylpenicillin was <math>2680 \pm 80</math> units.mg<sup>-1</sup>.</p> <p>Double distilled water was used.</p> <p>ESTIMATED ERROR:</p> <p>REFERENCES:</p>

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<p>VARIABLES:</p> <p>One temperature: 19.5°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <div style="display: flex; align-items: center; justify-content: center;"> <div style="margin-right: 20px;"> <p>solubility of 6-aminopenicillanic acid [Units/cm<sup>3</sup>]</p> </div>  </div>	
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<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-amino-3,3-dimethyl-7-oxo- (6-aminopenicillanic acid); <math>C_8H_{12}N_2O_3S</math>; [551-16-6]</p> <p>(2) Acetic acid; <math>C_2H_4O_2</math>; [64-19-7]</p> <p>(3) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Bruns, B.P.; Savitskaya, E.M.; Shellenberg, N.N.; Libinson, G.S.; Kolygina, T.S.; Druzhnina, E.N. <i>Antibiotiki, Moscow</i> <u>1962</u>, 7, 440-2.</p>
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<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of 6-aminopenicillanic acid and acetic acid solution were placed in a thermostatted solubility apparatus, <math>N_2</math> was bubbled through the mixture at 19.5°C. Aliquots of the saturated soln were withdrawn through a glass filter under vacuum and the pH of the clear filtrate, measured by use of glass electrode-calomel electrode system, was 2.92. The amount of the dissolved solute was determined microbiologically after conversion of the 6-aminopenicillanic acid into phenoxymethylpenicillin.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Crystalline 6-aminopenicillanic acid was obtained from the fermentation broth of <i>Penicillium chrysogenum</i> by carrying out the fermentation without adding the precursor. It had a melting point 204-6°C. The potency of the solubility product after conversion into phenoxymethylpenicillin was <math>2680 \pm 80</math> units.mg<sup>-1</sup>.</p> <p>The source and purity of acetic acid were not specified. Double-distilled water was used.</p> <p>ESTIMATED ERROR:</p> <p>REFERENCES:</p>

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<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of 6-aminopenicillanic acid and 0.2 M acetate buffer solution of the pH range from 3.05 to 4.75 were placed in a thermostatted solubility apparatus, <math>N_2</math> was bubbled through the mixture at 19.5°C. Aliquots of the saturated soln were withdrawn through a glass filter under vacuum and the pH of the clear filtrates accurately measured using a glass electrode-calomel electrode system. The amount of the dissolved solute was determined microbiologically after conversion of the 6-aminopenicillanic acid into phenoxymethylpenicillin.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Crystalline 6-aminopenicillanic acid was obtained from the fermentation broth of <i>Penicillium chrysogenum</i> by carrying out the fermentation without adding the precursor. It had a melting point 204-6°C. The potency of the solubility product after conversion into phenoxymethylpenicillin was <math>2680 \pm 80</math> units.mg<sup>-1</sup>.</p> <p>The source and purity of acetic acid and sodium acetate were not specified. Double-distilled water was used.</p> <p>ESTIMATED ERROR:</p> <p>REFERENCES:</p>																

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<p>VARIABLES:</p> <p>One temperature: 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>The authors report two values for the solubility of 6-aminopenicillanic acid in water at 25°C and constant ionic strength (<math>\mu = 0.1</math>)</p> <ol style="list-style-type: none"> <li>Intrinsic solubility <math>S_x^0 = 1.07 \times 10^{-2} \text{ mol dm}^{-3}</math> (based on experimental data)</li> <li>Solubility of the ampholyte zwitterion  <math>S_{AH\pm}^0 = 8.70 \times 10^{-3} \text{ mol dm}^{-3}</math> (based on calculated data)</li> </ol> <p>The following relationship between solubilities 1 and 2 was derived by the authors:</p> $S_{AH\pm}^0 = S_x^0 \frac{K_1 \cdot C_H^0}{(C_H^0)^2 + K_1 \cdot C_H^0 + K_1 \cdot K_2}$ <p>where <math>C_H^0</math> is the concentration of hydrogen ions, <math>K_1(\text{COOH}) = 2.14 \times 10^{-3} \text{ mol dm}^{-3}</math> and <math>K_2(\text{NH}_3^+) = 1.97 \times 10^{-5} \text{ mol dm}^{-3}</math> are dissociation constants.</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>A saturated mixture was prepared by stirring 6-aminopenicillanic acid and water at 25°C. The constant ionic strength was maintained to <math>\mu = 0.1</math> by adding adequate amounts of <math>NH_4Cl</math>. After separation of the precipitate by filtration the content of 6-aminopenicillanic acid was determined by iodometric titration.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>6-Aminopenicillanic acid was twice recrystallized from acid and alkaline solution. The obtained solubility product determined iodometrically, contained 97.5% by weight of 6-aminopenicillanic acid.</p> <p><math>NH_4Cl</math> was of analytical grade. Double-distilled water was used.</p> <p>ESTIMATED ERROR:</p> <p>REFERENCES:</p>

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<p>VARIABLES:</p> <p>Ionic strength at 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>																
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<p>METHOD APPARATUS/PROCEDURE:</p> <p>Accurately weighed samples of 6-aminopenicillanic acid were suspended in water at 25°C. The suspension was then adjusted to pH 7.5 using 2 N NaOH solution. To the above suspension equimolar amounts of benzeneacetic acid were added. After dilution, the suspension was cooled to 5°C and adjusted to pH = pI using 20% w/v HCl solution. The suspension was then shaken for about 3 hours at 5°C. After separation of the precipitate by filtrate, the amounts of 6-aminopenicillanic acid and benzeneacetic acid were determined iodometrically and by potentiometric titration. (The ionic strength was maintained by adding adequate amounts of <math>NH_4Cl</math> or <math>NaCl</math>).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>6-Aminopenicillanic acid was twice recrystallized from acid and alkaline solution. The obtained solubility product determined iodometrically, contained 97.5% by weight of 6-aminopenicillanic acid.</p> <p>Benzeneacetic acid was twice precipitated from aqueous and ethanol solution. Purity of the obtained product was 99%. All other reagents were of analytical grade. Double-distilled water was used.</p> <p>ESTIMATED ERROR:</p> <p>Nothing specified</p> <p>REFERENCES:</p> <p>(1) Bruns, B.P.; Savitskaya, H.N.; Shellenberg, N.N.; Libinson, G.S.; Kolygina, T.S.; Druzhinina, E.N. <i>Antibiotiki, Moscow</i> 1962, 7, 440</p>																

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<p>VARIABLES:</p> <p>Concentration of potassium penicillin G at 25°C.</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <div style="display: flex; align-items: center;"> <div style="flex: 1;"> <p>minimal solubility of 6-aminopenicillanic acid [<math>\text{mol dm}^{-3} \times 10^2</math>]</p> </div> <div style="flex: 2;"> </div> <div style="flex: 1;"> <p>concentration of potassium penicillin G [<math>\text{mol dm}^{-3} \times 10^3</math>] at 25°C and at pH=pI<sup>a</sup></p> </div> </div> <p><sup>a</sup>Isoelectric point (pH range 3.3. to 3.7). (Ref. 1)</p>	
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## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino] (phenoxymethyl penicillin);  
 $C_{16}H_{18}N_2O_5S$ ; [87-08-1]  
 (2) All solvents

## EVALUATOR:

Eric Tomlinson  
 Department of Pharmacy,  
 University of Amsterdam,  
 The Netherlands.

December 1983

## CRITICAL EVALUATION:

Values for the solubility of phenoxymethylpenicillin have been reported by four groups (1-4). The largest study is that due to Weiss et al. (1) who reported solubilities in 24 solvents at  $301 \pm 4$  K. Weiss et al used a pooled commercial sample of 95 to 100 % purity. The amount of penicillin dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than  $20 \text{ mg cm}^{-3}$ . All values reported were uncorrected for solvent blank, which was never greater than 0.05 mg total. All data according to Weiss et al have been recalculated to SI units (compiler), and are given in the following Table.

Solvent	Solubility <sub>3</sub> (at $301 \pm 4$ K) (mol dm <sup>-3</sup> )	
water	$2.57 \times 10^{-3}$	
methanol	a	
ethanol	a	
isopropanol	a	
isoamylalcohol	$4.84 \times 10^{-2}$	
cyclohexane	$2.28 \times 10^{-4}$	
benzene	$1.28 \times 10^{-3}$	
toluene	$7.42 \times 10^{-4}$	
ligroin	$6.99 \times 10^{-4}$	
isooctane	$1.06 \times 10^{-4}$	
carbon tetrachloride	$2.77 \times 10^{-4}$	
ethyl acetate	a	( <sup>a</sup> solubility greater than $5.70 \times 10^{-2} \text{ mol dm}^{-3}$ )
isoamylacetate	a	
acetone	a	
methyl ethyl ketone	a	
diethylether	$3.35 \times 10^{-2}$	
ethylene chloride	$3.61 \times 10^{-2}$	
1,4-dioxane	$3.60 \times 10^{-2}$	
chloroform	a	
carbon disulfide	$8.56 \times 10^{-4}$	
pyridine	a	
formamide	a	
ethylene glycol	a	
benzyl alcohol	a	

All these values have an estimated precision (evaluator) of  $\pm 5\%$ . However they are unconfirmed findings, and must be designated as **tentative**, except where the solubility is reported as being greater than  $5.70 \times 10^{-2} \text{ mol dm}^{-3}$ , for which cases values are considered **doubtful**.

Others have examined the aqueous solubility at  $310 \pm 1$  K (2-4). Jansholt et al (2) reported the solubility in a solution of  $0.05 \text{ mol dm}^{-3}$  phosphate buffer (pH 3) containing 0.1 % (w/v) Tween 80 as  $2.60 \times 10^{-3} \text{ mol dm}^{-3}$ , and in a 0.1 N HCl solution containing a similar amount of Tween 80 as  $9.13 \times 10^{-4} \text{ mol dm}^{-3}$ . These values have an estimated precision of  $\pm 5\%$ , (evaluator), and may be regarded as **tentative**. The data of Juncher and Raaschou (3) are rejected on the basis of inadequate information (Page 13).

A further study by Braun and Moll (4) reported the solubility of phenoxymethylpenicillin in synthetic gastric juice and in natural gastric juice (pH 4.6) to be  $9.8 \times 10^{-3} \text{ mol dm}^{-3}$ , and  $0.8 \times 10^{-2} \text{ mol dm}^{-3}$ , respectively. However, lack of information on the purity and source of the sample used means that these data must be rejected.

## REFERENCES

- (1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* 1957, 7, 374.  
 (2) Jansholt, A.L.; Solvang, S.; Sveen, K.; Finholt, P. *Med. Nor. Farm. Selsk.* 1971, 33, 1.  
 (3) Juncher, H.; Raaschou, F. *Antibiotic Med. Clin. Therap.* 1957, 4, 497.  
 (4) Braun, A.; Moll, F. *Acta Pharm. Technol.* 1980, 26, 258.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], phenoxyethylpenicillin, penicillin V; $C_{16}H_{18}N_2O_5S$ ; [87-08-1] (2) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of penicillin V in water at $28 \pm 4^\circ C$ was reported as: $0.90 \text{ mg cm}^{-3}$ . ( $2.57 \times 10^{-3} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a 15 $\text{cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ C$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 $\text{cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ C$ . The residue was further dried for 3 hr at $60^\circ C$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b> Penicillin V was a pooled commercial product of high purity (95 to 100%). Water was of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ C$ (authors).  <b>REFERENCES:</b>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], phenoxyethyl penicillin (penicillin V); $C_{16}H_{18}N_2O_5S$ ; [87-08-1] (2) Hydrochloric acid; HCl; [7647-01-0] (3) Phosphoric acid, trisodium salt; $Na_3O_4P$ ; [7601-54-9] (4) Sodium chloride; NaCl; [7647-14-5] (5) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Braun, A.; Moll, F. <i>Acta Pharm. Technol.</i> 1980, 26, 258-60.												
<b>VARIABLES:</b> One temperature: 37°C	<b>PREPARED BY:</b> A. Regosz												
<b>EXPERIMENTAL VALUES:</b>  <p>The authors determined maximal solubility of penicillin V in synthetic gastric juice<sup>a</sup> (without pepsin) and compared the results with those obtained for solubility in human natural gastric juice.</p> <p style="text-align: center;">Solubility</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="2" style="text-align: center;">Synthetic gastric juice<sup>a</sup> (without pepsin)</th> <th colspan="2" style="text-align: center;">Human natural gastric juice</th> </tr> <tr> <th style="text-align: center;"><math>10^2 \text{ mg cm}^{-3}</math></th> <th style="text-align: center;"><math>10^2 \text{ mol dm}^{-3b}</math></th> <th style="text-align: center;"><math>10^2 \text{ mg cm}^{-3}</math></th> <th style="text-align: center;"><math>10^2 \text{ mol dm}^{-3b}</math></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">343</td> <td style="text-align: center;">0.98</td> <td style="text-align: center;">292</td> <td style="text-align: center;">0.83</td> </tr> </tbody> </table> <p><sup>a</sup> According to USP XIX the composition of synthetic simulated gastric fluid, is: HCl(35%) - 7.0 <math>\text{cm}^3</math>; NaCl - 2.0 g, pepsin - 3.2 g, distilled water to 1000 <math>\text{cm}^3</math>.</p> <p><sup>b</sup> Calculated by compiler.</p>		Synthetic gastric juice <sup>a</sup> (without pepsin)		Human natural gastric juice		$10^2 \text{ mg cm}^{-3}$	$10^2 \text{ mol dm}^{-3b}$	$10^2 \text{ mg cm}^{-3}$	$10^2 \text{ mol dm}^{-3b}$	343	0.98	292	0.83
Synthetic gastric juice <sup>a</sup> (without pepsin)		Human natural gastric juice											
$10^2 \text{ mg cm}^{-3}$	$10^2 \text{ mol dm}^{-3b}$	$10^2 \text{ mg cm}^{-3}$	$10^2 \text{ mol dm}^{-3b}$										
343	0.98	292	0.83										
<b>AUXILIARY INFORMATION</b>													
<b>METHOD APPARATUS/PROCEDURE:</b> <p>An excess of penicillin V was added to a 250 <math>\text{cm}^3</math> flask, followed by addition of 100 <math>\text{cm}^3</math> of synthetic or natural gastric juice. The fluid was stirred at a speed of 55 rpm at 37°C for about 1 hour. The fluid was then buffered to pH 4.6 using <math>Na_3PO_4</math> solution and filtered through a Sartorius SM 11307 filter. The content of the penicillin V in the clear filtrate was determined spectrophotometrically at 322 nm (1).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Sources and purities of the penicillin V and the chemicals used were not specified.</p> <p><b>ESTIMATED ERROR:</b>            Solubility precision: none specified            Temperature precision: <math>\pm 1^\circ\text{C}</math> (compiler).</p> <p><b>REFERENCES:</b>            (1) Brandiss, M.W.; Denny, E.L.; Huber, M.A.; Steinmann, H.G. <i>Antimicrob. Agents and Chemother.</i> 1962, 626.</p>												



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], (phenoxymethyl penicillin, penicillin V); $C_{16}H_{18}N_2O_5S$ ; [87-08-1] (2) Sorbitan monooleate, polyoxyethylene derivatives (Tween 80); [9005-65-6] (3) Hydrochloric acid; HCl; [7647-01-0] (4) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Jansholt, A.L.; Solvang, S.; Sveen, K.; Finholt, P. <i>Med. Nor. Farm. Selsk.</i> 1971, 33, 1-11.
<b>VARIABLES:</b> One temperature 37°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>The solubility of phenoxymethylpenicillin in a saturated solution of 0.1 N HCl containing 0.1% Tween 80 at 37°C was reported as:</p> <p style="text-align: center;"><math>0.32 \text{ mg cm}^{-3}</math>. (<math>9.13 \times 10^{-4} \text{ mol dm}^{-3}</math> - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>500 mg of the antibiotic were added to about 250 cm<sup>3</sup> of 0.1 HCl solution containing 0.1% w/v Tween 80. The suspension was stirred at 37°C at 90 r.p.m. Ten cm<sup>3</sup> aliquots were withdrawn and filtered through a 0.45 micron membrane filter. The content of the antibiotic was determined iodometrically according to the Ph. Nord. method.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>The purity of penicillin V was 99.7%, its source was not given.</p> <p>All reagents used were of analytical grade.</p> <b>ESTIMATED ERROR:</b> Nothing specified
<b>REFERENCES:</b>	

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], phenoxyethyl penicillin (penicillin V); $C_{16}H_{18}N_2O_5S$ ; [87-08-1] (2) Sorbitan monooleate, polyoxyethylene derivatives (Tween 80); [9005-65-6] (3) Phosphoric acid; $H_3PO_4$ ; [7664-38-2] (4) Phosphoric acid, disodium salt; $Na_2HPO_4$ ; [7558-79-4] (5) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Jansholt, A.L.; Solvang, S.; Sveen, K.; Finholt, P. <i>Medd. Nor. Pharm. Selsk.</i> 1971, 33, 1-11.
<b>VARIABLES:</b> One temperature: 37°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  The concentration of penicillin V in a saturated solution of $0.05 \text{ mol dm}^{-3}$ phosphate buffer pH 3 containing $0.1\%^a$ Tween 80 was reported as: $91 \text{ mg per } 100 \text{ cm}^3$ . ( $2.60 \times 10^{-3} \text{ mol dm}^{-3}$ - compiler).  <sup>a</sup> probably v/v - compiler	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> 147.5 mg of the antibiotic ( $\pm 250000$ I.U.) were added to about $100 \text{ cm}^3$ of $0.05 \text{ mol dm}^{-3}$ phosphate buffer pH 3, containing $0.1\%$ Tween 80. Composition of the $0.05 \text{ mol dm}^{-3}$ phosphate buffer pH 3 was $5.95 \text{ cm}^3$ of one molar $H_3PO_4$ solution, $Na_2HPO_4 \cdot 2H_2O$ : 6.87 g, distilled water to $1000 \text{ cm}^3$ . The suspension was stirred at 37°C at a speed of 90 r.p.m., using an electric stirrer. Within 5 min of rotation, a homogeneous suspension was formed. One $\text{cm}^3$ samples were withdrawn and filtered through a glass wool filter. The samples were then mixed with a sufficient amount of $0.1 \text{ NaOH}$ and $0.01 \text{ mol dm}^{-3}$ acetate buffer to pH 6 and diluted to $25.0 \text{ cm}^3$ with distilled water. The amount of penicillin was determined iodometrically according to the Ph. Nord. method.	<b>SOURCE AND PURITY OF MATERIALS:</b> Purity of the penicillin V was 99.7%; its source was not specified. The particle size of the antibiotic was between 20 and 60 micron. All reagents used were of analytical grade.
<b>ESTIMATED ERROR:</b> Nothing specified	
<b>REFERENCES:</b>	



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], phenoxymethylpenicillin, penicillin V; $C_{16}H_{18}N_2O_5S$ ; [87-08-1] (2) Ethanol; $C_2H_6O$ ; [64-17-5]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of penicillin V in ethanol at $28 \pm 4^\circ\text{C}$ was greater than: $20 \text{ mg cm}^{-3}$ . (Greater than $5.70 \times 10^{-2} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ\text{C}$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b> Penicillin V was a pooled commercial product of high purity (95 to 100%). Ethanol was of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).  <b>REFERENCES:</b>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], phenoxymethylpenicillin, penicillin V; $C_{16}H_{18}N_2O_5S$ ; [87-08-1] (2) 2-Propanol (isopropanol); $C_3H_8O$ ; [67-63-0]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of penicillin V in isopropanol at <math>28 \pm 4^\circ\text{C}</math> was greater than:  <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.70 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ\text{C}</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Penicillin V was a pooled commercial product of high purity (95 to 100%).          Isopropanol was of A.C.S. or U.S.P. grade.</p> <hr/> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <hr/> <b>REFERENCES:</b>









<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], phenoxymethylpenicillin, penicillin V; $C_{16}H_{18}N_2O_5S$ ; [87-08-1] (2) Petroleum ether (ligroin)	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of penicillin V in ligroin at $28 \pm 4^\circ\text{C}$ was reported as: $0.25 \text{ mg cm}^{-3}$ . ( $6.99 \times 10^{-4} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ\text{C}$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ\text{C}$ . The residue was further dried for 3 hr at $60^\circ\text{C}$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b> Penicillin V was a pooled commercial product of high purity (95 to 100%). Ligroin was of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).  <b>REFERENCES:</b>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], phenoxymethylpenicillin, penicillin V; $C_{16}H_{18}N_2O_5S$ ; [87-08-1] (2) Methane, tetrachloro- (carbon tetrachloride); $CCl_4$ ; [56-23-5]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <b>7</b> , 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of penicillin V in carbon tetrachloride at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.10 \text{ mg cm}^{-3}</math>. (<math>2.77 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of the solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Penicillin V was a pooled commercial product of high purity (95 to 100%).          Carbon tetrachloride was of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], phenoxymethylpenicillin, penicillin V; $C_{16}H_{18}N_2O_5S$ ; [87-08-1] (2) 1-Butanol, 3-methyl acetate (isoamyl acetate); $C_7H_{14}O_2$ ; [123-92-2]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of penicillin V in isoamyl acetate at <math>28 \pm 4^\circ\text{C}</math> was greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.70 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a 15 $\text{cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ\text{C}$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b>  Penicillin V was a pooled commercial product of high purity (95 to 100%).  Isoamyl acetate was of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).  <b>REFERENCES:</b>







<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], phenoxyethylpenicillin, penicillin V; $C_{16}H_{18}N_2O_5S$ ; [87-08-1] (2) Ethane, dichloro- (ethylene chloride); $C_2H_4Cl_2$ ; [1300-21-6]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of penicillin V in ethylene chloride at $28 \pm 4^\circ\text{C}$ was reported as: $12.65 \text{ mg cm}^{-3}$ . ( $3.61 \times 10^{-2} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ\text{C}$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ\text{C}$ . The residue was further dried for 3 hr at $60^\circ\text{C}$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b> Penicillin V was a pooled commercial product of high purity (95 to 100%). Ethylene chloride was of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).  <b>REFERENCES:</b>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], phenoxyethylpenicillin, penicillin V; $C_{16}H_{18}N_2O_5S$ ; [87-08-1] (2) Methane, trichloro- (chloroform); $CHCl_3$ ; [67-66-3]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> 1957, 7, 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of penicillin V in chloroform at $28 \pm 4^\circ\text{C}$ was greater than: $20 \text{ mg cm}^{-3}$ . (Greater than $5.70 \times 10^{-2} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ\text{C}$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b> Penicillin V was a pooled commercial product of high purity (95 to 100%). Chloroform was of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).  <b>REFERENCES:</b>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], phenoxyethylpenicillin, penicillin V; $C_{16}H_{18}N_2O_5S$ ; [87-08-1] (2) Pyridine; $C_5H_5N$ ; [110-86-1]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of penicillin V in pyridine at <math>28 \pm 4^\circ\text{C}</math> was greater than:  <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.70 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ\text{C}</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Penicillin V was a pooled commercial product of high purity (95 to 100%).          Pyridine was of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], phenoxyethylpenicillin, penicillin V; $C_{16}H_{18}N_2O_5S$ ; [87-08-1] (2) Formamide; $CH_3NO$ ; [75-12-7]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of penicillin V in formamide at $28 \pm 4^\circ C$ was greater than: $20 \text{ mg cm}^{-3}$ . (Greater than $5.70 \times 10^{-2} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ C$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b> Penicillin V was a pooled commercial product of high purity (95 to 100%). Formamide was of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ C$ (authors).  <b>REFERENCES:</b>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], phenoxyethylpenicillin, penicillin V; $C_{16}H_{18}N_2O_5S$ ; [87-08-1] (2) 1,2-Ethanediol (ethylene glycol); $C_2H_6O_2$ ; [107-21-1]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of penicillin V in ethylene glycol at $28 \pm 4^\circ\text{C}$ was greater than: $20 \text{ mg cm}^{-3}$ . (Greater than $5.70 \times 10^{-2} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a 15 $\text{cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ\text{C}$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b> Penicillin V was a pooled commercial product of high purity (95 to 100%). Ethylene glycol was of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).  <b>REFERENCES:</b>



## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6[(phenoxyacetyl)amino], monopotassium salt (potassium penicillin V);  $C_{16}H_{17}N_2KO_5S$ ; [132-98-9]
- (2) All solvents

## EVALUATOR:

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University of Amsterdam,  
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December 1983.

## CRITICAL EVALUATION:

Values for the solubility of potassium penicillin V have been reported by three groups (1-3). The largest study is that due to Andrew and Weiss (1) who reported solubilities in 24 solvents at  $301 \pm 4$  K. Weiss et al used a pooled commercial sample of unknown purity (probably 95 to 100 % - ref. 4). The amount of penicillin dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than  $20 \text{ mg cm}^{-3}$ . All values reported were uncorrected for solvent blank, which was generally less than  $0.05 \text{ mg total}$ . All data according to Andrew and Weiss have been recalculated to SI units (compiler), and are given in the following Table.

Solvent	Solubility <sub>3</sub> (at $301 \pm 4$ K) (mol dm <sup>-3</sup> )	
water	a	
methanol	a	
ethanol	$3.47 \times 10^{-4}$	
isopropanol	$2.70 \times 10^{-4}$	
isoamylalcohol	$6.41 \times 10^{-4}$	
cyclohexane	$1.54 \times 10^{-5}$	
benzene	$5.15 \times 10^{-5}$	
toluene	$7.72 \times 10^{-5}$	
ligroin	0	
isooctane	0	
carbon tetrachloride	$1.03 \times 10^{-4}$	
ethyl acetate	$1.67 \times 10^{-3}$	( <sup>a</sup> solubility greater than $5.10 \times 10^{-2} \text{ mol dm}^{-3}$ )
isoamylacetate	$2.83 \times 10^{-4}$	
acetone	$5.71 \times 10^{-3}$	
methyl ethyl ketone	$1.54 \times 10^{-3}$	
diethylether	$2.16 \times 10^{-3}$	
ethylene chloride	$1.03 \times 10^{-3}$	
1,4-dioxane	$1.45 \times 10^{-3}$	
chloroform	$1.16 \times 10^{-3}$	
carbon disulfide	$1.93 \times 10^{-4}$	
pyridine	$3.35 \times 10^{-3}$	
formamide	$6.56 \times 10^{-3}$	
ethylene glycol	a	
benzyl alcohol	a	

All these values have an estimated precision (evaluator) of  $\pm 5\%$ . However they are unconfirmed findings, and must be designated as **tentative**, except for two cases, (i) where the solubility is reported as being greater than  $5.70 \times 10^{-2} \text{ mol dm}^{-3}$ , (for which cases values are considered **doubtful**), and (ii) where the solubility is reported as being less than  $5 \times 10^{-5} \text{ mol dm}^{-3}$ , (which are **rejected** due to their being reported uncorrected for the solvent blank).

Others have examined the aqueous solubility at  $310 \pm 1$  K (2,3). Jansholt et al (2) reported the solubility in a solution of  $0.05 \text{ mol dm}^{-3}$  phosphate buffer (pH 3) containing  $0.1\%$  (w/v) Tween 80 as  $3.45 \times 10^{-3} \text{ mol dm}^{-3}$ . This value has an estimated precision of  $\pm 5\%$ , (evaluator), and may be regarded as being **tentative**. The data of Juncher and Raaschou (3) are **rejected** on the basis of inadequate information concerning both the method used and the source and purity of the sample (Page 42).

## REFERENCES

- (1) Andrew, M.L.; Weiss, P.J.; *Antibiotics and Chemotherapy* 1959, 9, 277.
- (2) Jansholt, A.L.; Solvang, S.; Sveen, K.; Finholt, P. *Med. Nor. Farm. Selsk.* 1971, 33, 1.
- (3) Juncher, H.; Raaschou, F. *Antibiotic Med. Clin. Therap.* 1957, 4, 497.
- (4) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy*, 1957, 7, 374.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], monopotassium salt (potassium penicillin V); $C_{16}H_{17}N_2KO_5S$ ; [132-98-9] (2) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Andrew, M.L.; Weiss, P.J. <i>Antibiotics and Chemotherapy</i> <u>1959</u> , 9, 277-9.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of potassium penicillin V in water at <math>28 \pm 4^\circ C</math> was reported as greater than:  <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.1 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg. cm}^{-3}</math>.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Potassium penicillin V was a pooled commercial product. Its purity was not specified.</p> <p>Water was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i>, <u>1957</u>, 7, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], monopotassium salt (potassium penicillin V); <math>C_{16}H_{17}N_2KO_5S</math>; [132-98-9]</p> <p>(2) Sorbitan monooleate, polyoxyethylene derivatives (Tween 80); [9005-65-6]</p> <p>(3) Phosphoric acid; <math>H_3PO_4</math>; [7664-38-2]</p> <p>(4) Phosphoric acid, disodium salt; <math>Na_2HPO_4</math>; [7558-79-4]</p> <p>(5) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Jansholt, A.L.; Solvang, S.; Sveen, K.; Finholt, P. <i>Medd. Nor. Pharm. Selsk.</i> <u>1971</u>, <b>33</b>, 1-11.</p>
<p>VARIABLES:</p> <p>One temperature: 37°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>The concentration of potassium penicillin V in a saturated solution of <math>0.05 \text{ mol dm}^{-3}</math> phosphate buffer pH 3 containing 0.1% Tween 80 was reported as:</p> <p><math>1.34 \times 10^2 \text{ mg per } 100 \text{ cm}^3</math>. (<math>3.45 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>160 mg of the antibiotic (<math>\pm 250000</math> I.U.) were added to about <math>100 \text{ cm}^3</math> of <math>0.05 \text{ mol dm}^{-3}</math> phosphate buffer pH 3, containing 0.1% Tween 80. Composition of the <math>0.05 \text{ mol dm}^{-3}</math> phosphate buffer pH 3 was <math>5.95 \text{ cm}^3</math> of one molar <math>H_3PO_4</math> solution, <math>Na_2HPO_4 \cdot 2H_2O</math>: 6.87 g, distilled water to <math>1000 \text{ cm}^3</math>. The suspension was stirred at 37°C at a speed of 90 r.p.m., using an electric stirrer. Within 5 min of rotation, a homogeneous suspension was formed. One <math>\text{cm}^3</math> samples were withdrawn and filtered through a glass wool filter. The samples were then mixed with a sufficient amount of 0.1 NaOH and <math>0.01 \text{ mol dm}^{-3}</math> acetate buffer to pH 6 and diluted to <math>25.0 \text{ cm}^3</math> with distilled water. The amount of penicillin was determined iodometrically according to the Ph. Nord. method.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Purity of the potassium penicillin V was 94.2%; its source was not specified.</p> <p>All reagents used were of analytical grade.</p> <p>ESTIMATED ERROR:</p> <p>Nothing specified.</p> <p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], monopotassium salt (potassium penicillin V); <math>C_{16}H_{17}N_2KO_5</math>; [132-98-9]</p> <p>(2) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Juncher, H.; Raaschou, F. <i>Antibiotic Med. Clin. Therapy</i> 1957, 4, 497-507.</p>
<p>VARIABLES:</p> <p>One temperature: probably 37°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>The maximum solubility of potassium penicillin V in water was reported as greater than: 75 per cent<sup>a</sup> (Greater than 750 mg cm<sup>-3</sup>; 1.90 mol dm<sup>-3</sup> solution - compiler).</p> <p><sup>a</sup> probably w/v percents - compiler.</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Nothing specified. The dissolved active penicillin was titrated using an iodometric method.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>The source and purity of the antibiotic used were not described.</p> <p>Distilled water was probably used.</p> <p>ESTIMATED ERROR:</p> <p>Nothing specified</p> <p>REFERENCES:</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], monopotassium salt (potassium penicillin V); $C_{16}H_{17}N_2KO_5S$ ; [132-98-9] (2) Methanol; $CH_4O$ ; [67-56-1]	<b>ORIGINAL MEASUREMENTS:</b> Andrew, M.L.; Weiss, P.J. <i>Antibiotics and Chemotherapy</i> <u>1959</u> , 9, 277-9.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of potassium penicillin V in methanol at $28 \pm 4^\circ C$ was reported as greater than: $20 \text{ mg cm}^{-3}$ . (Greater than $5.10 \times 10^{-2} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a 15 $\text{cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ C$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg. cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b> Potassium penicillin V was a pooled commercial product. Its purity was not specified. Methanol was probably of A.C.S. or U.S.P. grade (1).  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ C$ (authors).  <b>REFERENCES:</b> (1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> , <u>1957</u> , 7, 374-7.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], monopotassium salt (potassium penicillin V); $C_{16}H_{17}N_2KO_5S$ ; [132-98-9] (2) Ethanol; $C_2H_6O$ ; [64-17-5]	<b>ORIGINAL MEASUREMENTS:</b> Andrew, M.L.; Weiss, P.J. <i>Antibiotics and Chemotherapy</i> <u>1959</u> , <b>9</b> , 277-9.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of potassium penicillin V in ethanol at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>1.35 \text{ mg cm}^{-3}</math>. (<math>3.47 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Potassium penicillin V was a pooled commercial product. Its purity was not specified.          Ethanol was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p>
	<b>REFERENCES:</b> <p>(1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i>, <u>1957</u>, <b>7</b>, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], monopotassium salt (potassium penicillin V); $C_{16}H_{17}N_2KO_5S$ ; [132-98-9] (2) 2-Propanol (isopropanol); $C_3H_8O$ ; [67-63-0]	<b>ORIGINAL MEASUREMENTS:</b> Andrew, M.L.; Weiss, P.J. <i>Antibiotics and Chemotherapy</i> 1959, 9, 277-9.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of potassium penicillin V in isopropanol at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.11 \text{ mg cm}^{-3}</math>. (<math>2.70 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Potassium penicillin V was a pooled commercial product. Its purity was not specified.           Isopropanol was probably of A.C.S. or U.S.P. grade (1).</p>
	<b>ESTIMATED ERROR:</b>  <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p>
	<b>REFERENCES:</b> (1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> , 1957, 7, 374-7.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], monopotassium salt (potassium penicillin V); $C_{16}H_{17}N_2KO_5S$ ; [132-98-9] (2) 1-Butanol, 3-methyl- (isoamyl alcohol); $C_5H_{12}O$ ; [123-51-3]	<b>ORIGINAL MEASUREMENTS:</b> Andrew, M.L.; Weiss, P.J. <i>Antibiotics and Chemotherapy</i> <u>1959</u> , <b>9</b> , 277-9.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of potassium penicillin V in isoamyl alcohol at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.25 \text{ mg cm}^{-3}</math>. (<math>6.45 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Potassium penicillin V was a pooled commercial product. Its purity was not specified.</p> <p>Isoamyl alcohol was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors). <b>REFERENCES:</b> (1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> , <u>1957</u> , <b>7</b> , 374-7.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], monopotassium salt (potassium penicillin V); $C_{16}H_{17}N_2KO_5S$ ; [132-98-9] (2) Cyclohexane; $C_6H_{12}$ ; [110-82-7]	<b>ORIGINAL MEASUREMENTS:</b> Andrew, M.L.; Weiss, P.J. <b>Antibiotics and Chemotherapy</b> <u>1959</u> , 9, 277-9.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of potassium penicillin V in cyclohexane at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.06 \text{ mg cm}^{-3}</math>. (<math>1.54 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Potassium penicillin V was a pooled commercial product. Its purity was not specified.</p> <p>Cyclohexane was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. <b>Antibiotics and Chemotherapy</b>, <u>1957</u>, 7, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], monopotassium salt (potassium penicillin V); $C_{16}H_{17}N_2KO_5S$ ; [132-98-9] (2) Benzene; $C_6H_6$ ; [71-43-2]	<b>ORIGINAL MEASUREMENTS:</b> Andrew, M.L.; Weiss, P.J. <i>Antibiotics and Chemotherapy</i> <u>1959</u> , <b>9</b> , 277-9.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of potassium penicillin V in benzene at $28 \pm 4^\circ C$ was reported as: $0.02 \text{ mg cm}^{-3}$ . ( $5.15 \times 10^{-5} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Potassium penicillin V was a pooled commercial product. Its purity was not specified.</p> <p>Benzene was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <b>REFERENCES:</b> (1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> , <u>1957</u> , <b>7</b> , 374-7.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], monopotassium salt (potassium penicillin V); $C_{16}H_{17}N_2KO_5S$ ; [132-98-9]  (2) Benzene, methyl- (toluene); $C_7H_8$ ; [108-88-3]	<b>ORIGINAL MEASUREMENTS:</b> Andrew, M.L.; Weiss, P.J. <i>Antibiotics and Chemotherapy</i> 1959, 9, 277-9.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of potassium penicillin V in toluene at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.03 \text{ mg cm}^{-3}</math>. (<math>7.72 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Potassium penicillin V was a pooled commercial product. Its purity was not specified.</p> <p>Toluene was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i>, 1957, 7, 374-7.</p>











<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], monopotassium salt (potassium penicillin V); $C_{16}H_{17}N_2KO_5S$ ; [132-98-9] (2) 2-Propanone (acetone); $C_3H_6O$ ; [67-64-1]	<b>ORIGINAL MEASUREMENTS:</b> Andrew, M.L.; Weiss, P.J. <i>Antibiotics and Chemotherapy</i> <u>1959</u> , <b>9</b> , 277-9.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of potassium penicillin V in acetone at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.22 \text{ mg cm}^{-3}</math>. (<math>5.71 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Potassium penicillin V was a pooled commercial product. Its purity was not specified.</p> <p>Acetone was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i>, <u>1957</u>, <b>7</b>, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], monopotassium salt (potassium penicillin V); $C_{16}H_{17}N_2KO_5S$ ; [132-98-9] (2) 2-Butanone (methyl ethyl ketone); $C_4H_8O$ ; [78-93-3]	<b>ORIGINAL MEASUREMENTS:</b> Andrew, M.L.; Weiss, P.J. <i>Antibiotics and Chemotherapy</i> <u>1959</u> , <b>9</b> , 277-9.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of potassium penicillin V in methyl ethyl ketone at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.60 \text{ mg cm}^{-3}</math>. (<math>1.54 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Potassium penicillin V was a pooled commercial product. Its purity was not specified.</p> <p>Methyl ethyl ketone was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> (1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> , <u>1957</u> , <b>7</b> , 374-7.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], monopotassium salt (potassium penicillin V); $C_{16}H_{17}N_2KO_5S$ ; [132-98-9] (2) Ethane, 1,1'-oxybis- (diethyl ether); $C_4H_{10}O$ ; [60-29-7]	<b>ORIGINAL MEASUREMENTS:</b> Andrew, M.L.; Weiss, P.J. <i>Antibiotics and Chemotherapy</i> 1959, 9, 277-9.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of potassium penicillin V in diethyl ether at $28 \pm 4^\circ C$ was reported as: $0.84 \text{ mg cm}^{-3}$ . ( $2.16 \times 10^{-3} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ C$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ C$ . The residue was further dried for 3 hr at $60^\circ C$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b> Potassium penicillin V was a pooled commercial product. Its purity was not specified. Diethyl ether was probably of A.C.S. or U.S.P. grade (1).  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ C$ (authors).  <b>REFERENCES:</b> (1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> , 1957, 7, 374-7.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], monopotassium salt (potassium penicillin V); $C_{16}H_{17}N_2KO_5S$ ; [132-98-9] (2) Ethane, dichloro- (ethylene chloride); $C_2H_4Cl_2$ ; [1300-21-6]	<b>ORIGINAL MEASUREMENTS:</b> Andrew, M.L.; Weiss, P.J. <i>Antibiotics and Chemotherapy</i> <u>1959</u> , 9, 277-9.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of potassium penicillin V in ethylene chloride at <math>28 \pm 4^\circ C</math> was reported as:  <math>0.40 \text{ mg cm}^{-3}</math>. (<math>1.03 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Potassium penicillin V was a pooled commercial product. Its purity was not specified.</p> <p>Ethylene chloride was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i>, <u>1957</u>, 7, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], monopotassium salt (potassium penicillin V); $C_{16}H_{17}N_2KO_5S$ ; [132-98-9] (2) 1,4-Dioxane; $C_4H_8O_2$ ; [123-91-1]	<b>ORIGINAL MEASUREMENTS:</b> Andrew, M.L.; Weiss, P.J. <i>Antibiotics and Chemotherapy</i> <u>1959</u> , <b>9</b> , 277-9.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of potassium penicillin V in 1,4-dioxane at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.57 \text{ mg cm}^{-3}</math>. (<math>1.45 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Potassium penicillin V was a pooled commercial product. Its purity was not specified.          1,4-Dioxane was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i>, <u>1957</u>, <b>7</b>, 374-7.</p>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], monopotassium salt (potassium penicillin V); $C_{16}H_{17}N_2KO_5S$ ; [132-98-9] (2) Carbon disulfide; $CS_2$ ; [75-15-0]	<b>ORIGINAL MEASUREMENTS:</b> Andrew, M.L.; Weiss, P.J. <i>Antibiotics and Chemotherapy</i> <u>1959</u> , 9, 277-9.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of potassium penicillin V in carbon disulfide at <math>28 \pm 4^\circ C</math> was reported as:  <math>0.08 \text{ mg cm}^{-3}</math>. (<math>1.93 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Potassium penicillin V was a pooled commercial product. Its purity was not specified.</p> <p>Carbon disulfide was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i>, <u>1957</u>, 7, 374-7.</p>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], monopotassium salt (potassium penicillin V); $C_{16}H_{17}N_2KO_5S$ ; [132-98-9] (2) Formamide; $CH_3NO$ ; [75-12-7]	<b>ORIGINAL MEASUREMENTS:</b> Andrew, M.L.; Weiss, P.J. <i>Antibiotics and Chemotherapy</i> <u>1959</u> , 9, 277-9.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of potassium penicillin V in formamide at $28 \pm 4^\circ C$ was reported as: $2.55 \text{ mg cm}^{-3}$ . ( $6.56 \times 10^{-3} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ C$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ C$ . The residue was further dried for 3 hr at $60^\circ C$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b> Potassium penicillin V was a pooled commercial product. Its purity was not specified. Formamide was probably of A.C.S. or U.S.P. grade (1).  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ C$ (authors).  <b>REFERENCES:</b> (1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> , <u>1957</u> , 7, 374-7.



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], monopotassium salt (potassium penicillin V); $C_{16}H_{17}N_2KO_5S$ ; [132-98-9] (2) Benzene methanol (benzyl alcohol); $C_7H_8O$ ; [100-51-6]	<b>ORIGINAL MEASUREMENTS:</b> Andrew, M.L.; Weiss, P.J. <i>Antibiotics and Chemotherapy</i> <u>1959</u> , <b>9</b> , 277-9.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of potassium penicillin V in benzyl alcohol at $28 \pm 4^\circ\text{C}$ was reported as: $2.65 \text{ mg cm}^{-3}$ . ( $6.82 \times 10^{-3} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ\text{C}$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ\text{C}$ . The residue was further dried for 3 hr at $60^\circ\text{C}$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b> Potassium penicillin V was a pooled commercial product. Its purity was not specified. Benzyl alcohol was probably of A.C.S. or U.S.P. grade (1).  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).  <b>REFERENCES:</b> (1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> , <u>1957</u> , <b>7</b> , 374-7.

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], calcium salt (2:1) (Calcium penicillin V); <math>C_{32}H_{34}N_4O_{10}S_2Ca</math>; [147-48-8]</p> <p>(2) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>EVALUATOR:</p> <p>Eric Tomlinson. Department of Pharmacy, University of Amsterdam, The Netherlands. December 1983.</p>
<p>CRITICAL EVALUATION:</p> <p>Juncher and Raaschou (1) have reported the solubility of calcium penicillin V in water as being <math>1.90 \times 10^{-2} \text{ mol dm}^{-3}</math>. Absence of information on the source and purity of the sample used, and with no details of the method used to determine the solubility leads to this value being rejected.</p> <p>REFERENCE</p> <p>(1) Juncher, H.; Raaschou, F. <i>Antibiotic Med. Clin. Therapy</i> <u>1957</u>, 4, 497.</p>	



## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, complexed with N-(phenylmethyl)benzene ethanamine (1:1) (benethamine penicillin V);  $C_{16}H_{18}N_2O_5S$ ,  $C_{15}H_{17}N$ ; [76082-02-5]  
 (2) Water;  $H_2O$ ; [7732-18-5]

## EVALUATOR:

Eric Tomlinson  
 Department of Pharmacy,  
 University of Amsterdam,  
 The Netherlands  
 December 1983

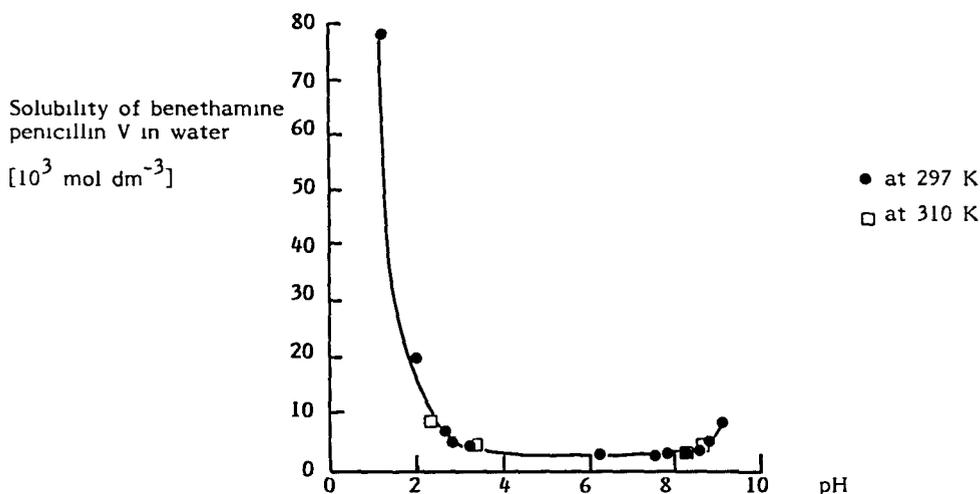
## CRITICAL EVALUATION:

The influence of pH (1.50 to 9.37) and temperature (297 K and 310 K) on the aqueous solubility of benethamine penicillin V have been studied by Brunner and Margreiter (1). The amount of penicillin dissolved in the solvent was determined by drying to constant weight. A precision  $\pm 2\%$  is estimated for all the solubility values reported, (evaluator). It is not possible to estimate the precision in the reported temperature or pH values, though for the latter it is probably  $\pm 0.02$  pH units.

The solubilities of benethamine penicillin V at 297 K and 310 K are reported as  $2.30 \times 10^{-3}$  mol dm $^{-3}$  and  $2.69 \times 10^{-3}$  mol dm $^{-3}$ , respectively. (Values converted to SI units by compiler). The Table gives the aqueous solubility of benethamine penicillin V at various pH's and at two temperatures. From this, and the figure, it is possible to see that the solubility increases sharply in strongly acid solutions, but only slightly in alkaline solutions. Temperature had little effect on the solubilities found. Brunner and Margreiter have made a detailed theoretical study concerning the calculation of this solute using appropriate acid and base dissociation constants (2). Their estimated values agree closely with those found in (1) except at pH less than 2. Values at these low pH's are rejected, other values are regarded as tentative.

Solubility ( $10^3$ mol dm $^{-3}$ ) <sup>a</sup>			
pH <sup>b</sup>	at 297 K	pH <sup>b</sup>	at 310 K
1.50	78.7	2.23	7.99
2.10	18.3	3.43	2.92
2.60	5.51	8.10	2.98
2.72	3.38	8.47	3.66
3.40	2.56		
6.20	2.31		
7.32	2.31		
7.53	2.42		
8.10	2.64		
8.64	3.19		
8.80	4.64		
9.37	9.97		

(<sup>a</sup> Calculated by compiler; <sup>b</sup> pH altered using either HCl or NaOH).



## REFERENCES

- (1) Brunner, R.; Margreiter, H. *Montash* 1955, 86, 958.  
 (2) Brunner, R.; Margreiter, H. *Montash* 1955, 86, 767.



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, compd with N-(phenylmethyl)benzene ethanamine(1:1) (benethamine penicillin V); $C_{16}H_{18}N_2O_5S$ . $C_{15}H_{17}N$ ; [76082-02-5] (2) Hydrochloric acid; HCl; [7647-01-0] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Brunner, R.; Margreiter, H. Montash <u>1955</u> , 86, 958-65.																																								
<b>VARIABLES:</b> pH at 24°C and 37°C	<b>PREPARED BY:</b> A. Regosz																																								
<b>EXPERIMENTAL VALUES:</b>  <div style="text-align: center;">Solubility</div> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th rowspan="2">pH</th> <th colspan="2">at 24°C</th> <th rowspan="2">pH</th> <th colspan="2">at 37°C</th> </tr> <tr> <th><math>g\ dm^{-3}</math></th> <th><math>10^3\ mol\ dm^{-3}^a</math></th> <th><math>g\ dm^{-3}</math></th> <th><math>10^3\ mol\ dm^{-3}^a</math></th> </tr> </thead> <tbody> <tr> <td>3.40</td> <td>1.44</td> <td>2.56</td> <td>3.43</td> <td>1.64</td> <td>2.92</td> </tr> <tr> <td>2.72</td> <td>1.90</td> <td>3.38</td> <td>2.23</td> <td>4.49</td> <td>7.99</td> </tr> <tr> <td>2.60</td> <td>3.09</td> <td>5.51</td> <td></td> <td></td> <td></td> </tr> <tr> <td>2.10</td> <td>10.25</td> <td>18.26</td> <td></td> <td></td> <td></td> </tr> <tr> <td>1.50</td> <td>44.21</td> <td>78.71</td> <td></td> <td></td> <td></td> </tr> </tbody> </table> <p><sup>a</sup> Calculated by compiler</p>		pH	at 24°C		pH	at 37°C		$g\ dm^{-3}$	$10^3\ mol\ dm^{-3}^a$	$g\ dm^{-3}$	$10^3\ mol\ dm^{-3}^a$	3.40	1.44	2.56	3.43	1.64	2.92	2.72	1.90	3.38	2.23	4.49	7.99	2.60	3.09	5.51				2.10	10.25	18.26				1.50	44.21	78.71			
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<b>AUXILIARY INFORMATION</b>																																									
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>To an accurately weighed sample of the antibiotic in a 50 cm<sup>3</sup> flask 20 cm<sup>3</sup> HCl solution of the required pH were added, and the suspension shaken for about 1 hour at 24°C or 37°C. The suspension was then filtered and the pH of the clear filtrates measured. The residues were quantitatively transferred into tared glass crucibles and dried in vacuum to constant weight. The solubilities were compared by the authors with calculated values obtained in (1).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Benethamine penicillin V contained 2.7% water (by weight). Its source was not specified. The water content was determined by Karl Fischer titration.</p> <p>The purity of water and hydrochloric acid were not specified.</p> <b>ESTIMATED ERROR:</b> <p>Nothing specified</p> <b>REFERENCES:</b> (1) Brunner, R.; Margreiter, H. Montash <u>1955</u> , 86, 767.																																								

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, compd with N-(phenylmethyl)benzene ethanamine(1:1) (benethamine penicillin V); $C_{16}H_{18}N_2O_5S$ . $C_{15}H_{17}N$ ; [76082-02-5] (2) Sodium hydroxide; NaOH; [1310-73-2] (3) Water; $H_2O$ ; [7732-18-5]			<b>ORIGINAL MEASUREMENTS:</b> Brunner, R.; Margreiter, H. Montash <u>1955</u> , 86, 958-65.		
<b>VARIABLES:</b> pH at 24°C and 37°C			<b>PREPARED BY:</b> A. Regosz		
<b>EXPERIMENTAL VALUES:</b>					
Solubility					
at 24°C			at 37°C		
pH	$g\ dm^{-3}$	$10^3\ mol\ dm^{-3}^a$	pH	$g\ dm^{-3}$	$10^3\ mol\ dm^{-3}^a$
6.20	1.30	2.31	8.10	1.68	2.98
7.32	1.30	2.31	8.47	2.06	3.66
7.53	1.36	2.42			
8.10	1.48	2.64			
8.64	1.79	3.19			
8.80	2.60	4.64			
9.37	5.60	9.97			
<sup>a</sup> Calculated by compiler					
AUXILIARY INFORMATION					
<b>METHOD/APPARATUS/PROCEDURE:</b> To an accurately weighed sample of the antibiotic in a 50 cm <sup>3</sup> flask 20 cm <sup>3</sup> NaOH solution of the required pH were added, and the suspension shaken for about 1 hour at 24°C or 37°C. The suspension was then filtered and the pH of the clear filtrates measured. The residues were quantitatively transferred into tared glass crucibles and dried in vacuum to constant weight. The solubilities were compared by the authors with calculated values obtained in (1).			<b>SOURCE AND PURITY OF MATERIALS:</b> Benethamine penicillin V contained 2.7% water (by weight). Its source was not specified. The water content was determined by Karl Fischer titration.  The purity of sodium hydroxide and water were not specified.		
			<b>ESTIMATED ERROR:</b> Nothing specified		
			<b>REFERENCES:</b> (1) Brunner, R.; Margreiter, H. Montash <u>1955</u> , 86, 767.		

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, complexed with N,N'-bis(phenylmethyl)-1,2-ethanediamine (2:1) (benzathine penicillin V); <math>C_{32}H_{36}N_4O_{10}S_2 \cdot C_{16}H_{20}N_2</math>; [5928-84-7]</p> <p>(2) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>EVALUATOR:</p> <p>Eric Tomlinson          Department of Pharmacy          University of Amsterdam          The Netherlands.</p> <p>December 1983</p>																																				
<p>CRITICAL EVALUATION:</p> <p>Three groups have reported on the aqueous solubility of benzathine penicillin V (1-3).</p> <p>The influence of pH (1.60 to 8.76) and temperature (297 K and 310 K) on the aqueous solubility have been studied by Brunner and Margreiter (1). The amount of penicillin dissolved in the solvent was determined by drying to constant weight. A precision of <math>\pm 2\%</math> is estimated for all the solubility values reported by these workers, (evaluator). It is not possible to estimate the precision in the reported temperature or pH values, though for the latter it is probably <math>\pm 0.02</math> pH units. The solubilities of benzathine penicillin V at 297 K and 310 K are reported as <math>3.61 \times 10^{-4} \text{ mol dm}^{-3}</math> and <math>8.61 \times 10^{-4} \text{ mol dm}^{-3}</math>, respectively. (Values converted to SI units by compiler). The Table gives the aqueous solubility of benzathine penicillin V in water at various pH's and at 297 K and at 310 K (1). From this it is possible to see that the solubility increases sharply in strongly acid solutions, but only slightly in alkaline solutions. Brunner and Margreiter have made a detailed theoretical study concerning the calculation of the solubility of this solute using appropriate acid and base dissociation constants (4). They found good agreement between results obtained experimentally and those obtained by calculation except at pH's below 2, (which could be indicative of degradation effects). Accordingly, all the values given in the Table are designated as being <b>tentative</b>, except for those determined below pH 2.00 - which are <b>rejected</b>.</p> <div style="text-align: center; margin: 10px 0;"> <hr/> <p>Solubility (<math>10^4 \text{ mol dm}^{-3}</math>)<sup>a</sup></p> <hr/> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;">pH<sup>b</sup></th> <th style="text-align: center;">at 297 K</th> <th style="text-align: left;">pH<sup>b</sup></th> <th style="text-align: center;">at 310 K</th> </tr> </thead> <tbody> <tr><td>1.54</td><td style="text-align: center;">343</td><td>1.62</td><td style="text-align: center;">407</td></tr> <tr><td>1.81</td><td style="text-align: center;">67.0</td><td>1.93</td><td style="text-align: center;">103</td></tr> <tr><td>2.31</td><td style="text-align: center;">9.93</td><td>2.36</td><td style="text-align: center;">30.8</td></tr> <tr><td>3.10</td><td style="text-align: center;">5.26</td><td>3.33</td><td style="text-align: center;">8.80</td></tr> <tr><td>6.90</td><td style="text-align: center;">5.84</td><td>5.95</td><td style="text-align: center;">11.9</td></tr> <tr><td>7.90</td><td style="text-align: center;">14.1</td><td>7.13</td><td style="text-align: center;">30.6</td></tr> <tr><td>8.29</td><td style="text-align: center;">23.4</td><td>7.60</td><td style="text-align: center;">39.8</td></tr> <tr><td>8.65</td><td style="text-align: center;">45.7</td><td>7.92</td><td style="text-align: center;">58.3</td></tr> </tbody> </table> <hr/> </div> <p>(<sup>a</sup> Calculated by compiler; <sup>b</sup> pH altered using either HCl or NaOH).</p> <p>Weiss et al reported the solubility in water of benzathine penicillin V at 301<sup>±</sup> K as <math>3.2 \times 10^{-4} \text{ mol dm}^{-3}</math> (units - compiler), which is similar to that reported by Brunner and Margreiter at 297 K (1). A precision of <math>\pm 5\%</math> may be estimated for this solubility value (evaluator). The value of Weiss et al is designated as <b>tentative</b>. However, the value of <math>3.2 \times 10^{-4} \text{ mol dm}^{-3}</math> at 310 K, reported by Juncher and Raaschou (3) is <b>rejected</b>, since no information is given on the source and purity of the sample and on the determination method used.</p> <p>REFERENCES</p> <p>(1) Brunner, R.; Margreiter, H. <i>Montash.</i> <u>1955</u>, <b>86</b>, 958.          (2) Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374.          (3) Juncher, H.; Raaschou, F. <i>Antibiotic Med. Clin. Therapy</i> <u>1957</u>, <b>4</b>, 497.          (4) Brunner, R.; Margreiter, H. <i>Montash.</i> <u>1955</u>, <b>86</b>, 767.</p>		pH <sup>b</sup>	at 297 K	pH <sup>b</sup>	at 310 K	1.54	343	1.62	407	1.81	67.0	1.93	103	2.31	9.93	2.36	30.8	3.10	5.26	3.33	8.80	6.90	5.84	5.95	11.9	7.90	14.1	7.13	30.6	8.29	23.4	7.60	39.8	8.65	45.7	7.92	58.3
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<b>VARIABLES:</b>  Temperature	<b>PREPARED BY:</b>  A. Regosz												
<b>EXPERIMENTAL VALUES:</b>  <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th colspan="3" style="text-align: center;">Solubility</th> </tr> <tr> <th style="text-align: center;"><math>t/^\circ C</math></th> <th style="text-align: center;"><math>g\ dm^{-3}</math></th> <th style="text-align: center;"><math>10^4\ mol\ dm^{-3}{}^a</math></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">24</td> <td style="text-align: center;">0.34</td> <td style="text-align: center;">3.61</td> </tr> <tr> <td style="text-align: center;">37</td> <td style="text-align: center;">0.81</td> <td style="text-align: center;">8.61</td> </tr> </tbody> </table> <p style="text-align: center;"><sup>a</sup>Calculated by compiler.</p>		Solubility			$t/^\circ C$	$g\ dm^{-3}$	$10^4\ mol\ dm^{-3}{}^a$	24	0.34	3.61	37	0.81	8.61
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<b>METHOD/APPARATUS/PROCEDURE:</b>  To an accurately weighed sample of the antibiotic in a 50 cm <sup>3</sup> flask 20 cm <sup>3</sup> of water were added and the suspension shaken for about 1 hour at 24°C or 37°C. The suspension was then filtered and the residue quantitatively transferred into a tared glass crucible and dried in vacuum to constant weight. The pH values of the clear filtrates measured were 5.12 and 4.80 at 24°C and 37°C, respectively.	<b>SOURCE AND PURITY OF MATERIALS:</b>  Benzathine penicillin V contained 6.5% of water by weight. The water content was determined by Karl Fischer titration.  The purity of the water was not described.  <b>ESTIMATED ERROR:</b> Nothing specified.  <b>REFERENCES:</b>												

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, compd with N,N'-bis(phenylmethyl)-1,2-ethanediamine(2:1) (benzathine penicillin V); $C_{32}H_{36}N_4O_{10}S_2C_{16}H_{20}N_2$ ; [5928-84-7] (2) Hydrochloric acid; HCl; [7647-01-0] (3) Water; $H_2O$ ; [7732-18-5]			<b>ORIGINAL MEASUREMENTS:</b> Brunner, R; Margreiter, H. <u>Montash</u> 1955, 86, 958-85.		
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<b>EXPERIMENTAL VALUES:</b>					
Solubility					
at 24°C			at 37°C		
pH	$g\ dm^{-3}$	$10^4\ mol\ dm^{-3}^a$	pH	$g\ dm^{-3}$	$10^4\ mol\ dm^{-3}^a$
3.10	0.50	5.26	3.33	0.83	8.80
2.31	0.94	9.93	2.36	2.90	30.8
1.81	6.31	67.05	1.93	9.63	102
1.54	32.3	343	1.62	38.3	407
<sup>a</sup> Calculated by compiler.					
AUXILIARY INFORMATION					
<b>METHOD/APPARATUS/PROCEDURE:</b> To an accurately weighed sample of the antibiotic in a 50 cm <sup>3</sup> flask 20 cm <sup>3</sup> HCl soln of the required pH were added and the suspension shaken for about 1 hour at 24°C or 37°C. The suspension was then filtered and the pH of the clear filtrates measured. The residues were quantitatively transferred into tared glass crucibles and dried in vacuum to constant weight. The solubilities were compared by the authors with calculated values obtained in (1).			<b>SOURCE AND PURITY OF MATERIALS:</b> Benzathine penicillin V contained 6.5% water by weight. The water content was determined by Karl Fischer titration. The purity of the water and hydrochloric acid were not specified.		
			<b>ESTIMATED ERROR:</b> Nothing specified		
			<b>REFERENCES:</b> (1) Brunner, R.; Margreiter, H. <u>Montash</u> . 1955, 86, 767.		

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], compd with N,N'-bis(phenylmethyl)-1,2-ethanediamine(2:1) (benzathine penicillin V); $C_{32}H_{36}N_4O_{10}S_2 \cdot C_{16}H_{20}N_2$ ; [5928-84-7] (2) Sodium hydroxide; NaOH; [1310-73-2] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Brunner, R.; Margreiter, H. <u>Montash</u> 1955, 86, 958-85.																																										
<b>VARIABLES</b> pH at 24°C and 37°C	<b>PREPARED BY:</b> A. Regosz																																										
<b>EXPERIMENTAL VALUES:</b>  <table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="6" style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Solubility</th> </tr> <tr> <th colspan="3" style="text-align: center; border-bottom: 1px solid black;">at 24°C</th> <th colspan="3" style="text-align: center; border-bottom: 1px solid black;">at 37°C</th> </tr> <tr> <th style="border-bottom: 1px solid black;">pH</th> <th style="border-bottom: 1px solid black;">g dm<sup>-3</sup></th> <th style="border-bottom: 1px solid black;">10<sup>4</sup> mol dm<sup>-3</sup><sup>a</sup></th> <th style="border-bottom: 1px solid black;">pH</th> <th style="border-bottom: 1px solid black;">g dm<sup>-3</sup></th> <th style="border-bottom: 1px solid black;">10<sup>4</sup> mol dm<sup>-3</sup><sup>a</sup></th> </tr> </thead> <tbody> <tr> <td>6.90</td> <td>0.55</td> <td>5.84</td> <td>5.95</td> <td>1.12</td> <td>11.9</td> </tr> <tr> <td>7.90</td> <td>1.34</td> <td>14.1</td> <td>7.13</td> <td>2.89</td> <td>30.6</td> </tr> <tr> <td>8.29</td> <td>2.21</td> <td>23.4</td> <td>7.60</td> <td>3.75</td> <td>39.8</td> </tr> <tr> <td>8.65</td> <td>4.31</td> <td>45.7</td> <td>7.92</td> <td>5.49</td> <td>58.3</td> </tr> </tbody> </table> <p><sup>a</sup>Calculated by compiler.</p>		Solubility						at 24°C			at 37°C			pH	g dm <sup>-3</sup>	10 <sup>4</sup> mol dm <sup>-3</sup> <sup>a</sup>	pH	g dm <sup>-3</sup>	10 <sup>4</sup> mol dm <sup>-3</sup> <sup>a</sup>	6.90	0.55	5.84	5.95	1.12	11.9	7.90	1.34	14.1	7.13	2.89	30.6	8.29	2.21	23.4	7.60	3.75	39.8	8.65	4.31	45.7	7.92	5.49	58.3
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<b>AUXILIARY INFORMATION</b>																																											
<b>METHOD/APPARATUS/PROCEDURE:</b>  To an accurately weighed sample of the antibiotic in a 50 cm <sup>3</sup> flask 20 cm <sup>3</sup> NaOH soln of the required pH were added and the suspension shaken for about 1 hour at 24°C or 37°C. The suspension was then filtered and the pH of the clear filtrates measured. The residues were quantitatively transferred into tared glass crucibles and dried in vacuum to constant weight. The solubilities were compared by the authors with calculated values obtained in (1).	<b>SOURCE AND PURITY OF MATERIALS:</b>  Benzathine penicillin V contained 6.5% water by weight. The water content was determined by Karl Fischer titration.  The purity of sodium hydroxide and water were not specified.  <b>ESTIMATED ERROR:</b> Nothing specified  <b>REFERENCES:</b> (1) Brunner, R.; Margreiter, H. <u>Montash</u> . 1955, 86, 767.																																										

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, compd with N,N'-bis(phenylmethyl)-1,2-ethanediamine (2:1) benzathine penicillin V; <math>C_{32}H_{36}N_4O_{10}S_2 \cdot C_{16}H_{20}N_2</math>; [5928-84-7]</p> <p>(2) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Juncher, H.; Raaschou, F. <i>Antibiotic Med. Clin. Therapy</i> 1957, 4, 497-507.</p>
<p>VARIABLES:</p> <p>One temperature: probably 37°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>The maximum solubility of benzathine penicillin V in water was reported as:</p> <p>0.03 per cent<sup>a</sup> (<math>0.3 \text{ mg cm}^{-3}</math>; <math>3.2 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p> <p><sup>a</sup> probably w/v percents - compiler.</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD / APPARATUS / PROCEDURE:</p> <p>Nothing specified. The dissolved active penicillin was titrated using an iodometric method.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>The source and purity of the antibiotic used were not described.</p> <p>Distilled water was probably used.</p> <p>ESTIMATED ERROR:</p> <p>Nothing specified</p> <p>REFERENCES:</p>

## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, complexed with N,N'-bis(phenylmethyl)-1,2-ethanediamine (2:1) (benzathine penicillin V);  $C_{32}H_{36}N_4O_{10}S_2 \cdot C_{16}H_{20}N_2$ ; [5928-84-7]
- (2) All non-aqueous solvents

## EVALUATOR:

Eric Tomlinson.  
Department of Pharmacy,  
University of Amsterdam,  
The Netherlands.  
December 1983

## CRITICAL EVALUATION:

Values for the solubility of benzathine penicillin V in 23 non-aqueous solvents at  $3 \pm 4$  K have been reported by Weiss et al (1). These workers used a pooled commercial sample of high purity (95-100%). The amount of penicillin dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than  $20 \text{ mg cm}^{-3}$ . All values reported were uncorrected for solvent blank, which was generally less than 0.05 mg total. All data according to Weiss et al have been recalculated to SI units (compiler), and are given in the following Table.

Solvent	Solubility <sub>23</sub> (at $301 \pm 4$ K) ( $\text{mol dm}^{-3}$ )	
methanol	a	
ethanol	$1.50 \times 10^{-2}$	
isopropanol	$7.60 \times 10^{-3}$	
isoamylalcohol	$1.70 \times 10^{-3}$	
cyclohexane	$4.99 \times 10^{-4}$	
benzene	$3.40 \times 10^{-4}$	
toluene	$7.12 \times 10^{-4}$	
ligroin	$5.37 \times 10^{-4}$	
isooctane	$2.12 \times 10^{-4}$	
carbon tetrachloride	$7.76 \times 10^{-3}$	
ethyl acetate	$9.60 \times 10^{-3}$	( <sup>a</sup> solubility greater than $2.10 \times 10^{-2} \text{ mol dm}^{-3}$ )
isoamylacetate	$5.84 \times 10^{-4}$	
acetone	a	
methyl ethyl ketone	a	
diethylether	$1.30 \times 10^{-3}$	
ethylene chloride	$2.00 \times 10^{-3}$	
1,4-dioxane	a	
chloroform	a	
carbon disulfide	$5.84 \times 10^{-4}$	
pyridine	a	
formamide	a	
ethylene glycol	a	
benzyl alcohol	a	

All these values have an estimated precision of  $\pm 5\%$  (evaluator). However they are unconfirmed findings, and must be designated as **tentative**, except for those cases where the solubility is reported as being greater than  $2.10 \times 10^{-2} \text{ mol dm}^{-3}$ , which are considered as **doubtful**.

## REFERENCE

- (1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* 1957, 7, 374.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, compd with N,N'-bis(phenylmethyl)-1,2-ethanediamine(2:1) (benzathine penicillin V); $C_{32}H_{36}N_4O_{10}S_2C_{16}H_{20}N_2$ ; [5928-84-7] (2) Methanol; $CH_4O$ ; [67-56-1]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <u>7</u> , 374-7.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of benzathine penicillin V in methanol at <math>28 \pm 4^\circ\text{C}</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>2.10 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ\text{C}</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg. cm}^{-3}</math>.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Benzathine penicillin V was a pooled commercial product of high purity (95 to 100%).          Methanol was of A.C.S. or U.S.P. grade.</p> <hr/> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <hr/> <b>REFERENCES:</b>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, compd with N,N'-bis(phenylmethyl)-1,2-ethanediamine(2:1) (benzathine penicillin V); $C_{32}H_{36}N_4O_{10}S_2 \cdot C_{16}H_{20}N_2$ ; [5928-84-7] (2) 2-Propanol (isopropanol); $C_3H_8O$ ; [67-63-0]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> 1957, 7, 374-7.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of benzathine penicillin V in isopropanol at $28 \pm 4^\circ\text{C}$ was reported as: $7.15 \text{ mg cm}^{-3}$ . ( $7.60 \times 10^{-3} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ\text{C}$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ\text{C}$ . The residue was further dried for 3 hr at $60^\circ\text{C}$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b> Benzathine penicillin V was a pooled commercial product of high purity (95 to 100%). Isopropanol was of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).  <b>REFERENCES:</b>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, compd with N,N'-bis(phenylmethyl)-1,2-ethanediamine(2:1) (benzathine penicillin V); $C_{32}H_{36}N_4O_{10}S_2 \cdot C_{16}H_{20}N_2$ ; [5928-84-7] (2) Cyclohexane; $C_6H_{12}$ ; [110-82-7]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> 1957, 7, 374-7.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of benzathine penicillin V in cyclohexane at $28 \pm 4^\circ\text{C}$ was reported as: $0.47 \text{ mg cm}^{-3}$ . ( $4.99 \times 10^{-4} \text{ mol dm}^{-3}$ solution - complex).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ\text{C}$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ\text{C}$ . The residue was further dried for 3 hr at $60^\circ\text{C}$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b> Benzathine penicillin V was a pooled commercial product of high purity (95 to 100%). Cyclohexane was of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).  <b>REFERENCES:</b>







<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, compd with N,N'-bis(phenylmethyl)-1,2-ethanediamine(2:1) (benzathine penicillin V); $C_{32}H_{36}N_4O_{10}S_2 \cdot C_{16}H_{20}N_2$ ; [5928-84-7] (2) Pentane, 2,2,4-trimethyl- (isooctane); $C_8H_{18}$ ; [540-84-1]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <b>7</b> , 374-7.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of benzathine penicillin V in isooctane at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.20 \text{ mg cm}^{-3}</math>. (<math>2.12 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD / APPARATUS / PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Benzathine penicillin V was a pooled commercial product of high purity (95 to 100%).          Isooctane was of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], compd with N,N'-bis(phenylmethyl)-1,2-ethanediamine(2:1) (benzathine penicillin V); $C_{32}H_{36}N_4O_{10}S_2 \cdot C_{16}H_{20}N_2$ ; [5928-84-7] (2) Acetic acid, ethyl ester (ethyl acetate); $C_4H_8O_2$ ; [141-78-6]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of benzathine penicillin V in ethyl acetate at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>9.00 \text{ mg cm}^{-3}</math>. (<math>9.60 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Benzathine penicillin V was a pooled commercial product of high purity (95 to 100%).          Ethyl acetate was of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, compd with N,N'-bis(phenylmethyl)-1,2-ethanediamine(2:1) (benzathine penicillin V); $C_{32}H_{36}N_4O_{10}S_2C_{16}H_{20}N_2$ ; [5928-84-7] (2) 1-Butanol, 3-methyl acetate (isoamyl acetate); $C_7H_{14}O_2$ ; [123-92-2]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <u>Antibiotics and Chemotherapy</u> 1957, 7, 374-7.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of benzathine penicillin V in isoamyl acetate at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.55 \text{ mg cm}^{-3}</math>. (<math>5.84 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Benzathine penicillin V was a pooled commercial product of high purity (95 to 100%).          Isoamyl acetate was of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p>
	<b>REFERENCES:</b>





<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, compd with N,N'-bis(phenylmethyl)-1,2-ethanediamine(2:1) (benzathine penicillin V); $C_{32}H_{36}N_4O_{10}S_2 \cdot C_{16}H_{20}N_2$ ; [5928-84-7] (2) Ethane, 1,1'-oxybis- (diethyl ether); $C_4H_{10}O$ ; [60-29-7]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of benzathine penicillin V in diethyl ether at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>1.20 \text{ mg cm}^{-3}</math>. (<math>1.30 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ\text{C}$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ\text{C}$ . The residue was further dried for 3 hr at $60^\circ\text{C}$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b>  Benzathine penicillin V was a pooled commercial product of high purity (95 to 100%).  Diethyl ether was of A.C.S. or U.S.P. grade.
	<b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).
	<b>REFERENCES:</b>







<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, compd with N,N'-bis(phenylmethyl)-1,2-ethanediamine(2:1) (benzathine penicillin V); $C_{32}H_{36}N_4O_{10}S_2C_{16}H_{20}N_2$ ; [5928-84-7] (2) Carbon disulfide; $CS_2$ ; [75-15-0]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <u>Antibiotics and Chemotherapy</u> 1957, 7, 374-7.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of benzathine penicillin V in carbon disulfide at <math>28 \pm 4^\circ C</math> was reported as:  <math>0.55 \text{ mg cm}^{-3}</math>. (<math>5.84 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Benzathine penicillin V was a pooled commercial product of high purity (95 to 100%).          Carbon disulfide was of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <b>REFERENCES:</b>





<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, compd with N,N'-bis(phenylmethyl)-1,2-ethanediamine(2:1) (benzathine penicillin V); $C_{32}H_{36}N_4O_{10}S_2C_{16}H_{20}N_2$ ; [5928-84-7] (2) 1,2-Ethanediol (ethylene glycol); $C_2H_6O_2$ ; [107-21-1]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> 1957, 7, 374-7.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of benzathine penicillin V in ethylene glycol at <math>28 \pm 4^\circ\text{C}</math> was reported as greater than:</p> <p style="text-align: center;"><math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>2.10 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ\text{C}$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg. cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b>  Benzathine penicillin V was a pooled commercial product of high purity (95 to 100%).  Ethylene glycol was of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).  <b>REFERENCES:</b>



<b>COMPONENTS:</b> (1) 4-Thia -1-azabicyclo[3,2,0]heptane-2-carboxylic acid,3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, complexed with N,N'-bis[(1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenyl)methyl]-1,2-ethanediamine (2:1) (hydrabamine penicillin V); $C_{16}H_{18}N_2O_5S \cdot 1/2C_{42}H_{64}N_2$ ; [6591-72-6] (2) All solvents	<b>EVALUATOR:</b> Eric Tomlinson, Department of Pharmacy, University of Amsterdam, The Netherlands. December 1983
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**CRITICAL EVALUATION:**

Values for the solubility of hydrabamine penicillin V in 24 solvents at  $301 \pm 4$  K have been reported by Weiss et al (1). These workers used a pooled commercial sample of high purity (95-100%). The amount of penicillin dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than  $20 \text{ mg cm}^{-3}$ . All values reported were uncorrected for solvent blank, which was generally less than 0.05 mg total. All data according to Weiss et al have been recalculated to SI units (compiler), and are given in the following Table.

Solvent	Solubility <sub>3</sub> (at $301 \pm 4$ K) ( $\text{mol dm}^{-3}$ )	
water	$7.70 \times 10^{-5}$	
methanol	$1.70 \times 10^{-2}$	
ethanol	$8.90 \times 10^{-3}$	
isopropanol	$2.70 \times 10^{-2}$	
isoamyl alcohol	$1.06 \times 10^{-4}$	
cyclohexane	$1.85 \times 10^{-3}$	
benzene	$2.20 \times 10^{-3}$	
toluene	$1.65 \times 10^{-3}$	
ligroin	$9.25 \times 10^{-4}$	
isooctane	$1.00 \times 10^{-3}$	
carbon tetrachloride	$5.09 \times 10^{-3}$	
ethyl acetate	$6.20 \times 10^{-3}$	( <sup>a</sup> solubility greater than $3.10 \times 10^{-2} \text{ mol dm}^{-3}$ )
isoamyl acetate	$7.50 \times 10^{-3}$	
acetone	$1.60 \times 10^{-2}$	
methyl ethyl ketone	$2.10 \times 10^{-2}$	
diethylether	$1.46 \times 10^{-4}$	
ethylene chloride	a	
1,4-dioxane	$1.20 \times 10^{-2}$	
chloroform	a	
carbon disulfide	$2.00 \times 10^{-3}$	
pyridine	a	
formamide	a	
ethylene glycol	a	
benzyl alcohol	a	

All these values have an estimated precision of  $\pm 5\%$  (evaluator). However they are unconfirmed findings, and must be designated as **tentative**, except for those cases where the solubility is reported as being greater than  $3.10 \times 10^{-2} \text{ mol dm}^{-3}$ , which are considered as **doubtful**.

**REFERENCE**

- (1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* 1957, 7, 374.









<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], compd with N,N'-bis[(1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenyl)methyl]-1,2-ethanediamine(2:1) (hydrabamine penicillin V); $C_{16}H_{18}N_2O_5S \cdot 1/2 C_{42}H_{64}N_2$ ; [6591-72-6] (2) 1-Butanol, 3-methyl- (isoamyl alcohol); $C_5H_{12}O$ ; [123-51-3]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of hydrabamine penicillin V in isoamyl alcohol at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>6.85 \text{ mg cm}^{-3}</math>. (<math>1.06 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Hydrabamine penicillin V was a pooled commercial product of high purity (95 to 100%).</p> <p>Isoamyl alcohol was of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, compd with N,N'-bis[(1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenyl)methyl]-1,2-ethanediamine(2:1) (hydrabamine penicillin V); $C_{16}H_{18}N_2O_5S \cdot 1/2C_{42}H_{64}N_2$ ; [6591-72-6] (2) Benzene; $C_6H_6$ ; [71-43-2]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <b>Antibiotics and Chemotherapy</b> <u>1957</u> , 7, 374-7.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of hydrabamine penicillin V in benzene at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>1.40 \text{ mg cm}^{-3}</math>. (<math>2.20 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Hydrabamine penicillin V was a pooled commercial product of high purity (95 to 100%).           Benzene was of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b>





<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, compd with N,N'-bis[(1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenyl)methyl]-1,2-ethanediamine(2:1) (hydrabamine penicillin V); $C_{16}H_{18}N_2O_5S \cdot 1/2C_{42}H_{64}N_2$ ; [6591-72-6] (2) Pentane, 2,2,4-trimethyl- (isooctane); $C_8H_{18}$ ; [540-84-1]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of hydrabamine penicillin V in isooctane at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.07 \text{ mg cm}^{-3}</math>. (<math>1.00 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ\text{C}$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ\text{C}$ . The residue was further dried for 3 hr at $60^\circ\text{C}$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b>  Hydrabamine penicillin V was a pooled commercial product of high purity (95 to 100%).  Isooctane was of A.C.S. or U.S.P. grade.
	<b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).
	<b>REFERENCES:</b>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, compd with N,N'-bis[(1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenyl)methyl]-1,2-ethanediamine(2:1) (hydrabamine penicillin V); $C_{16}H_{18}N_2O_5S \cdot 1/2C_{42}H_{64}N_2$ ; [6591-72-6] (2) Methane tetrachloro- (carbon tetrachloride); $CCl_4$ ; [56-23-5]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <b>Antibiotics and Chemotherapy</b> 1957, 7, 374-7.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of hydrabamine penicillin V in carbon tetrachloride at <math>28 \pm 4^\circ C</math> was reported as: <math>3.30 \text{ mg cm}^{-3}</math>. (<math>5.09 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Hydrabamine penicillin V was a pooled commercial product of high purity (95 to 100%).</p> <p>Carbon tetrachloride was of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <b>REFERENCES:</b>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, compd with N,N'-bis[(1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenyl)methyl]-1,2-ethanediamine (2:1) (hydrabamine penicillin V); $C_{16}H_{18}N_2O_5S \cdot 1/2 C_{42}H_{64}N_2$ ; [6591-72-6] (2) Acetic acid, ethyl ester (ethyl acetate); $C_4H_8O_2$ ; [141-78-6]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of hydrabamine penicillin V in ethyl acetate at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>4.00 \text{ mg cm}^{-3}</math>. (<math>6.20 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Hydrabamine penicillin V was a pooled commercial product of high purity (95 to 100%).          Ethyl acetate was of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b>







<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, compd with N,N'-bis[(1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenyl)methyl]-1,2-ethanediamine(2:1) (hydrabamine penicillin V); $C_{16}H_{18}N_2O_5S \cdot 1/2 C_{42}H_{64}N_2$ ; [6591-72-6] (2) Ethane, 1,1'-oxybis- (diethyl ether); $C_4H_{10}O$ ; [60-29-7]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> 1957, 7, 374-7.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of hydrabamine penicillin V in diethyl ether at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.10 \text{ mg cm}^{-3}</math>. (<math>1.46 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ\text{C}$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ\text{C}$ . The residue was further dried for 3 hr at $60^\circ\text{C}$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b>  Hydrabamine penicillin V was a pooled commercial product of high purity (95 to 100%).  Diethyl ether used was of A.C.S. or U.S.P. grade.
	<b>ESTIMATED ERROR:</b>  Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).
	<b>REFERENCES:</b>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, compd with N,N'-bis[(1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenyl)methyl]-1,2-ethanediamine(2:1) (hydrabamine penicillin V); $C_{16}H_{18}N_2O_5S \cdot 1/2 C_{42}H_{64}N_2$ ; [6591-72-6] (2) Ethane, dichloro- (ethylene chloride); $C_2H_4Cl_2$ ; [1300-21-6]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> 1957, 7, 374-7.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of hydrabamine penicillin V in ethylene chloride at <math>28 \pm 4^\circ\text{C}</math> was reported as greater than:</p> <p style="text-align: center;"><math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>3.10 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ\text{C}$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg. cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b>  Hydrabamine penicillin V was a pooled commercial product of high purity (95 to 100%).  Ethylene chloride was of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).  <b>REFERENCES:</b>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, compd with N,N'-bis[(1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenyl)methyl]-1,2-ethanediamine(2:1) (hydrabamine penicillin V); $C_{16}H_{18}N_2O_5 \cdot S \cdot 1/2 C_{42}H_{64}N_2$ ; [6591-72-6] (2) Methane, trichloro- (chloroform); $CHCl_3$ ; [67-66-3]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.
<b>VARIABLES:</b> One temperature 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of hydrabamine penicillin V in chloroform at <math>28 \pm 4^\circ C</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>3.10 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg. cm}^{-3}</math>.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Hydrabamine penicillin V was a pooled commercial product of high purity (95 to 100%).</p> <p>Chloroform was of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <b>REFERENCES:</b>











<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino], monopotassium salt (potassium penicillin G); C<sub>16</sub>H<sub>17</sub>N<sub>2</sub>KO<sub>4</sub>S; [113-98-4]</p> <p>(2) All solvents</p>	<p>EVALUATOR:</p> <p>Eric Tomlinson, Department of Pharmacy, University of Amsterdam, The Netherlands.</p> <p>December 1983</p>
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## CRITICAL EVALUATION:

There are four reports on the solubility of potassium penicillin G in aqueous and non-aqueous solvents (1-4).

Page and Waller (1) determined the solubility in acetone containing less than 0.05%, 1.0% and 2.0% (probably weight percents) of water over the temperature range 195 K to 313 K. The authors state that the precision in the reported solubility values is better than  $\pm 5\%$ . The precision in the temperature is probably  $\pm 1$  K (evaluator). Consideration of the stated purity of the sample and the solubility determination procedure used, gives that the values reported by these workers (Table 1) may be regarded as tentative.

Table 1. Solubilities of potassium penicillin G in acetone/water mixtures.

Solubility in acetone containing water ( $10^3 \text{ mol dm}^{-3}$ ) <sup>a</sup>			
K	<0.05% water <sup>b</sup>	1% water <sup>b</sup>	2% water <sup>b</sup>
313	0.27	0.40	2.28
298	0.11	0.54	2.42
273	0.11	0.54	2.28
253	0.11	0.54	2.01
233	0.11	0.40	1.88
195	0.40	0.81	1.48

(<sup>a</sup> units calculated by compiler; <sup>b</sup> probably weight percents).

A similar study using 1-butanol, though only at  $298 \pm 1$  K, has been reported by Inozemtseva et al (2). These workers determined the amount of penicillin dissolved both iodometrically and gravimetrically by drying to constant weight. No mention is made of a solvent blank. The values reported differ by between 3 and 40 %, with the gravimetric method giving the higher values. The values are given in Table 2. Those values where the concentration of water is 2% or greater, may be regarded as tentative, whereas other values in Table 2 are doubtful due to the large discrepancy in values.

Table 2. Solubility of potassium penicillin G in butanol and in butanol/water mixtures at  $298 \pm 1$  K (2).

Solubility in 1-butanol containing differing amounts of water ( $10^3 \text{ mol dm}^{-3}$ ) <sup>a</sup>		
Concentration of water (weight percent)	iodometric determination	gravimetric determination
0	0.81	0.97
0.5	1.21	1.32
1	1.34	1.83
2	4.11	4.46
2.5	6.93	7.03
3	10.4	10.7

(<sup>a</sup> units calculated by compiler).

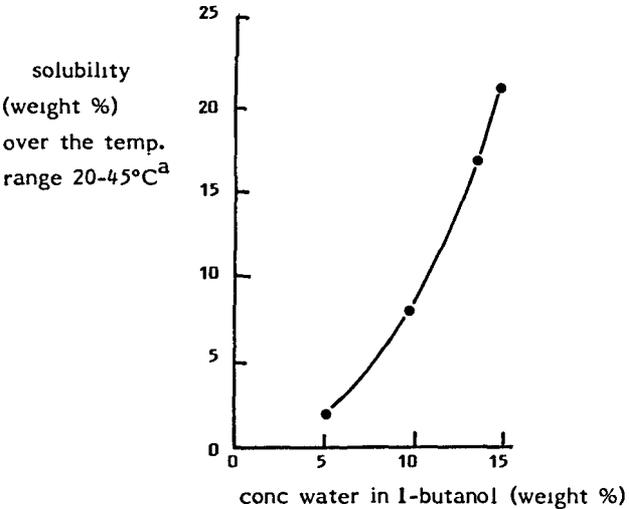
(Continued over)

<b>COMPONENTS:</b>  (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino], monopotassium salt (potassium penicillin G); C <sub>16</sub> H <sub>17</sub> N <sub>2</sub> KO <sub>4</sub> S; [113-98-4]  (2) All solvents	<b>EVALUATOR:</b>  Eric Tomlinson. Department of Pharmacy, University of Amsterdam, The Netherlands.  December 1983
<b>CRITICAL EVALUATION: continued</b>  Popova (3) has studied the solubility of potassium penicillin G in 1-butanol containing water at concentrations ranging from 2.5 to 15 % over the temperature range of 293 K to 318 K. Lack of information on the purity of the sample, and the method used to determine the solubility gives that the graphically reported solubility values be rejected.  The influence of both water and butyl acetate on the solubility of potassium penicillin G in 1-butanol has been studied by Torogova et al (4). Results were presented only graphically, no method of solubility determination is given, nor is there an indication of the temperature of the study. Accordingly values from this last study are rejected.  <b>REFERENCES</b>  (1) Page, J.E.; Waller, J.G. <i>Trans. Faraday Soc.</i> <u>1949</u> , <i>45</i> , 755. (2) Inozemtseva, I.I.; Trakhtenberg, D.M.; Zinatullina, E.S. <i>Antibiotiki (Moscow)</i> <u>1974</u> , <i>19</i> , 448. (3) Popova, M.V. <i>Khim.-Farm. Zh.</i> <u>1977</u> , <i>11</i> , 98. (4) Torogonova, T.V.; Zhukovskaya, S.A.; Markeleva, L.S.; Voronina, T.M.; Lukashina, V.F. <i>Antibiotiki (Moscow)</i> <u>1981</u> , <i>26</i> , 575.	

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino], monopotassium salt (potassium penicillin G); $C_{16}H_{17}N_2KO_4S$ ; [113-98-4] (2) 2-Propanone (acetone); $C_3H_6O$ ; [67-64-1] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Page, J.E.; Waller, J.G. Trans. Faraday Soc. <u>1949</u> , <u>45</u> , 755-7.																																																											
<b>VARIABLES:</b> Temperature and solvent composition	<b>PREPARED BY:</b> A. Regosz																																																											
<b>EXPERIMENTAL VALUES:</b> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th rowspan="2" style="text-align: left;">t/°C</th> <th colspan="3" style="text-align: center;">Solubility<sup>a</sup> in mg cm<sup>-3</sup> of acetone containing</th> </tr> <tr> <th style="text-align: center;">&lt;0.05%<sup>a</sup> water</th> <th style="text-align: center;">1 %<sup>a</sup> water</th> <th style="text-align: center;">2 %<sup>a</sup> water</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">40</td> <td style="text-align: center;">0.10</td> <td style="text-align: center;">0.15</td> <td style="text-align: center;">0.85</td> </tr> <tr> <td style="text-align: center;">25</td> <td style="text-align: center;">0.04</td> <td style="text-align: center;">0.20</td> <td style="text-align: center;">0.90</td> </tr> <tr> <td style="text-align: center;">0</td> <td style="text-align: center;">0.04</td> <td style="text-align: center;">0.20</td> <td style="text-align: center;">0.85</td> </tr> <tr> <td style="text-align: center;">-20</td> <td style="text-align: center;">0.04</td> <td style="text-align: center;">0.20</td> <td style="text-align: center;">0.75</td> </tr> <tr> <td style="text-align: center;">-40</td> <td style="text-align: center;">0.04</td> <td style="text-align: center;">0.15</td> <td style="text-align: center;">0.70</td> </tr> <tr> <td style="text-align: center;">-78</td> <td style="text-align: center;">0.15</td> <td style="text-align: center;">0.30</td> <td style="text-align: center;">0.55</td> </tr> <tr> <td></td> <th colspan="3" style="text-align: center;">Solubility in 10<sup>3</sup> mol dm<sup>-3</sup> - (compiler)</th> </tr> <tr> <td style="text-align: center;">40</td> <td style="text-align: center;">0.27</td> <td style="text-align: center;">0.40</td> <td style="text-align: center;">2.28</td> </tr> <tr> <td style="text-align: center;">25</td> <td style="text-align: center;">0.11</td> <td style="text-align: center;">0.54</td> <td style="text-align: center;">2.42</td> </tr> <tr> <td style="text-align: center;">0</td> <td style="text-align: center;">0.11</td> <td style="text-align: center;">0.54</td> <td style="text-align: center;">2.28</td> </tr> <tr> <td style="text-align: center;">-20</td> <td style="text-align: center;">0.11</td> <td style="text-align: center;">0.54</td> <td style="text-align: center;">2.01</td> </tr> <tr> <td style="text-align: center;">-40</td> <td style="text-align: center;">0.11</td> <td style="text-align: center;">0.40</td> <td style="text-align: center;">1.88</td> </tr> <tr> <td style="text-align: center;">-78</td> <td style="text-align: center;">0.40</td> <td style="text-align: center;">0.81</td> <td style="text-align: center;">1.48</td> </tr> </tbody> </table> <p><sup>a</sup>Percent units are not defined, though are probably weight percents, (compiler).</p>		t/°C	Solubility <sup>a</sup> in mg cm <sup>-3</sup> of acetone containing			<0.05% <sup>a</sup> water	1 % <sup>a</sup> water	2 % <sup>a</sup> water	40	0.10	0.15	0.85	25	0.04	0.20	0.90	0	0.04	0.20	0.85	-20	0.04	0.20	0.75	-40	0.04	0.15	0.70	-78	0.15	0.30	0.55		Solubility in 10 <sup>3</sup> mol dm <sup>-3</sup> - (compiler)			40	0.27	0.40	2.28	25	0.11	0.54	2.42	0	0.11	0.54	2.28	-20	0.11	0.54	2.01	-40	0.11	0.40	1.88	-78	0.40	0.81	1.48
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<b>METHOD/APPARATUS/PROCEDURE:</b> The soly apparatus consisted of two test tubes joined by a ground glass connector. The connector had a tube with a glass wool plug thus permitting soln to be transferred from one tube to the other. About 5 cm <sup>3</sup> of solvent were added to an excess of solid in the test tube, and N <sub>2</sub> presaturated with solvent was bubbled through the mixture. The bottom test tube with the connector was placed in a thermostat until thermal equilibrium was reached (1-2 hr). The apparatus was removed from the thermostat, fitted with the second test tube, inverted and returned to the thermostat. After complete filtration, the filtrate in the second test tube was allowed to attain room temp and a known volume of the supersaturated or cloudy soln was taken for analysis. The aliquot was diluted with $KH_2PO_4/K_2HPO_4$ buffer soln and analysed for penicillin G content by a microbiological method. Acetone soln warmed from -50°C to 0°C produced crystals which upon analysis (details not given) indicated that no solvate existed.	<b>SOURCE AND PURITY OF MATERIALS:</b> Potassium penicillin G was from Glaxo Laboratories, and was approx. 100% w/w. Acetone was A.R. quality, and was dried and redistilled from $K_2CO_3$ before use.  The purity and source of water used were not given.																																																											
	<b>ESTIMATED ERROR:</b> Solubility precision: better than 5% (authors). Temperature precision: not specified but probably ±1°C.																																																											
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<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino], monopotassium salt (potassium penicillin G); $C_{16}H_{17}N_2KO_4S$ ; [113-98-4] (2) 1-Butanol; $C_4H_{10}O$ ; [71-36-3]	<b>ORIGINAL MEASUREMENTS:</b> Inozemtseva, I.I.; Trakhtenberg, D.M.; Zinatullina, E.S. <i>Antibiotiki (Moscow)</i> 1974, 19, 448-51.												
<b>VARIABLES:</b>  One temperature: 25°C	<b>PREPARED BY:</b>  A. Regosz												
<b>EXPERIMENTAL VALUES:</b>   <p>Solubility of potassium penicillin G in 1-butanol at <math>25 \pm 1^\circ C</math> was given as:</p> <table border="1" data-bbox="175 721 1057 923"> <thead> <tr> <th colspan="2">determined iodometrically</th> <th colspan="2">determined gravimetrically</th> </tr> <tr> <th>mg cm<sup>-3</sup></th> <th>10<sup>4</sup> mol dm<sup>-3</sup><sup>a</sup></th> <th>mg cm<sup>-3</sup></th> <th>10<sup>4</sup> mol dm<sup>-3</sup><sup>a</sup></th> </tr> </thead> <tbody> <tr> <td>0.30</td> <td>8.05</td> <td>0.36</td> <td>9.66</td> </tr> </tbody> </table> <p><sup>a</sup> (Compiler)</p>		determined iodometrically		determined gravimetrically		mg cm <sup>-3</sup>	10 <sup>4</sup> mol dm <sup>-3</sup> <sup>a</sup>	mg cm <sup>-3</sup>	10 <sup>4</sup> mol dm <sup>-3</sup> <sup>a</sup>	0.30	8.05	0.36	9.66
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0.30	8.05	0.36	9.66										
<b>AUXILIARY INFORMATION</b>													
<b>METHOD/APPARATUS/PROCEDURE:</b>  A saturated mixture was prepared by stirring potassium penicillin G and 1-butanol in a thermostat at $25 \pm 1^\circ C$ . The state of saturation was determined by taking aliquots of the solution at different time intervals. The content of potassium penicillin G was determined both by iodometric titration and gravimetrically by drying to constant weight.	<b>SOURCE AND PURITY OF MATERIALS:</b>  Potassium penicillin G contained 98.5% benzylpenicillin ; its source was not specified. A fraction of 1-butanol boiling at $116-7^\circ C$ was used.												
	<b>ESTIMATED ERROR:</b>  Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).												
	<b>REFERENCES:</b>												



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino], monopotassium salt (potassium penicillin G); $C_{16}H_{17}N_2KO_4S$ ; [113-98-4] (2) 1-Butanol; $C_4H_{10}O$ ; [71-36-3] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Popova, M.V. <i>Khim.-Farm. Zh.</i> <u>1977</u> , <u>11</u> , 98-9.								
<b>VARIABLES:</b> Concentration of water over temperature range 20-45°C.	<b>PREPARED BY:</b> A. Regosz								
<b>EXPERIMENTAL VALUES:</b> <div style="text-align: center;">  <table border="1" style="margin: 10px auto;"> <caption>Data points from the solubility graph</caption> <thead> <tr> <th>conc water in 1-butanol (weight %)</th> <th>solubility (weight %)</th> </tr> </thead> <tbody> <tr> <td>5</td> <td>2</td> </tr> <tr> <td>10</td> <td>8</td> </tr> <tr> <td>15</td> <td>21</td> </tr> </tbody> </table> </div> <p><sup>a</sup> The author reported the solubility of potassium penicillin G in the 1-butanol-water solutions to be independent of temperature over the range indicated.</p>		conc water in 1-butanol (weight %)	solubility (weight %)	5	2	10	8	15	21
conc water in 1-butanol (weight %)	solubility (weight %)								
5	2								
10	8								
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<b>AUXILIARY INFORMATION</b>									
<b>METHOD/APPARATUS/PROCEDURE:</b> Nothing specified. The content of the dissolved solute was determined gravimetrically by drying to constant weight.	<b>SOURCE AND PURITY OF MATERIALS:</b> Potassium penicillin G was from the Medicinal Preparation Works, Kiev (USSR); its purity was not specified. Anhydrous and redistilled 1-butanol was used (source not given). The source and purity of water was not given.								
<b>ESTIMATED ERROR:</b> Nothing specified									
<b>REFERENCES:</b>									

<p><b>COMPONENTS:</b></p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino], monopotassium salt (potassium penicillin G); <math>C_{16}H_{17}N_2KO_4S</math>; [113-98-4]</p> <p>(2) Acetic acid, butyl ester (butyl acetate); <math>C_6H_{12}O_2</math>; [123-86-4]</p> <p>(3) 1-Butanol; <math>C_4H_{10}O</math>; [71-56-3]</p>	<p><b>ORIGINAL MEASUREMENTS:</b></p> <p>Torgonova, T.V.; Zhukovskaya, S.A.; Markeleva, L.S.; Voroninina, T.M.; Lukashina, V.F. <i>Antibiotiki (Moscow)</i> <u>1981</u>, 26, 575-7.</p>																		
<p><b>VARIABLES:</b></p> <p>Concentration of butyl acetate in 1-butanol and time of saturation at room temperature.</p>	<p><b>PREPARED BY:</b></p> <p>A. Regosz</p>																		
<p><b>EXPERIMENTAL VALUES:</b></p> <div style="text-align: center;"> <table border="1" style="margin: 10px auto;"> <caption>Estimated data from the solubility graph</caption> <thead> <tr> <th>Percent butyl acetate in 1-butanol</th> <th>10<sup>3</sup> mol dm<sup>-3</sup> (Compiler)<sup>a</sup></th> <th>Units/cm<sup>3</sup> (Authors)</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>~1.0</td> <td>~500</td> </tr> <tr> <td>20</td> <td>~0.8</td> <td>~400</td> </tr> <tr> <td>40</td> <td>~0.6</td> <td>~300</td> </tr> <tr> <td>60</td> <td>~0.4</td> <td>~200</td> </tr> <tr> <td>100</td> <td>0</td> <td>0</td> </tr> </tbody> </table> </div> <p>[Curves 1 and 2 are for 18 and 0.6 hours of saturation, respectively]</p> <p><sup>a</sup>According to the USP one milligram of potassium penicillin G is equal to 1 595 Units of penicillin (Compiler)</p> <p><sup>b</sup>It is most likely that weight percents were used (Compiler)</p>		Percent butyl acetate in 1-butanol	10 <sup>3</sup> mol dm <sup>-3</sup> (Compiler) <sup>a</sup>	Units/cm <sup>3</sup> (Authors)	0	~1.0	~500	20	~0.8	~400	40	~0.6	~300	60	~0.4	~200	100	0	0
Percent butyl acetate in 1-butanol	10 <sup>3</sup> mol dm <sup>-3</sup> (Compiler) <sup>a</sup>	Units/cm <sup>3</sup> (Authors)																	
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<p><b>AUXILIARY INFORMATION</b></p>																			
<p><b>METHOD/APPARATUS/PROCEDURE:</b></p> <p>Nothing specified, but concentrations of the antibiotic in the solutions tested were determined either iodometrically or by polarographic method.</p>	<p><b>SOURCE AND PURITY OF MATERIALS:</b></p> <p>Potassium penicillin G was of USSR Pharmacopoeial grade. 1-Butanol and butyl acetate conformed to the G.O.S.T. standard.</p> <p>The purity of water was not specified. The concentration of water in 1-butanol (upto 3%) was determined by Karl-Fischer titration. Higher concentrations were determined by G.L.C.</p> <p><b>ESTIMATED ERROR:</b></p> <p>Nothing specified.</p> <p><b>REFERENCES:</b></p>																		

<p><b>COMPONENTS:</b></p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino], monopotassium salt (potassium penicillin G); <math>C_{16}H_{17}N_2KO_4S</math>; [113-98-4]</p> <p>(2) Acetic acid, butyl ester (butyl acetate); <math>C_6H_{12}O_2</math>; [71-56-3]</p> <p>(3) 1-Butanol; <math>C_4H_{10}O</math>; [71-56-3]</p> <p>(4) Water; <math>H_2O</math>; [7732-18-5]</p>	<p><b>ORIGINAL MEASUREMENTS:</b></p> <p>Torgonova, T.V.; Zhukovskaya, S.A.; Markeleva, L.S.; Voronina, T.M.; Lukashina, V.F. <i>Antibiotiki (Moscow)</i> 1981, 26, 575-7.</p>
<p><b>VARIABLES:</b></p> <p>Concentration of water and butyl acetate in 1-butanol at room temperature.</p>	<p><b>PREPARED BY:</b></p> <p>A. Regosz</p>
<p><b>EXPERIMENTAL VALUES:</b></p> <div style="display: flex; align-items: flex-start;"> <div style="margin-right: 20px;"> <p><math>10^2 \text{ mol dm}^{-3}</math> (Compiler)<sup>a</sup></p> <p>solubility of potassium penicillin G</p> <p>2.0 1.5 1.0 0.5 0</p> </div> <div style="margin-right: 20px;"> <p>Units/cm<sup>3</sup> (Authors)</p> <p>15 000 10 000 5 000 0</p> </div> <div style="flex-grow: 1;"> <p style="text-align: center;">percent<sup>b</sup> water in 1-butanol</p> </div> </div> <p>[Curves 1 and 2 represent a concentration of butyl acetate in 1-butanol of 4% and 10%, respectively]</p> <p><sup>a</sup>According to the USP one milligram of potassium penicillin G is equal to 1 595 penicillin Units (Compiler)</p> <p><sup>b</sup>It is most likely that weight percents were used (Compiler)</p>	
<p><b>AUXILIARY INFORMATION</b></p>	
<p><b>METHOD/APPARATUS/PROCEDURE:</b></p> <p>Nothing specified, but concentrations of the antibiotic in the solutions tested were determined either iodometrically or by polarographic method.</p>	<p><b>SOURCE AND PURITY OF MATERIALS:</b></p> <p>Potassium penicillin G was of USSR Pharmacopoeial grade. 1-Butanol and butyl acetate conformed to the G.O.S.T. standard.</p> <p>The purity of water was not specified. The concentration of water in 1-butanol (upto 3%) was determined by Karl-Fischer titration. Higher concentrations were determined by G.L.C.</p> <p><b>ESTIMATED ERROR:</b></p> <p>Nothing specified.</p> <p><b>REFERENCES:</b></p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] monosodium salt (sodium penicillin G); <math>C_{16}H_{17}N_2NaO_4S</math>; [69-57-8]</p> <p>(2) All solvents</p>	<p>EVALUATOR:</p> <p>Eric Tomlinson Department of Pharmacy University of Amsterdam The Netherlands</p> <p>December 1983</p>
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## CRITICAL EVALUATION:

There are four reports on the solubility of sodium penicillin G in aqueous and non-aqueous solvents (1-4).

Page and Waller (1) determined the solubility in acetone containing less than 0.05%, 1.0% and 2.0% (probably weight percents - evaluator) of water over the temperature range 195 K to 313 K. The authors state that the precision in the reported solubility values is better than  $\pm 5\%$ . The precision in the temperature is probably  $\pm 1$  K (evaluator). Consideration of the stated purity of the sample and the solubility determination procedure used, gives that the values reported by these workers (Table 1) may be regarded as **tentative**.

Table 1. Solubilities of sodium penicillin G in acetone/water mixtures.

Solubility in acetone containing water ( $10^3 \text{ mol dm}^{-3}$ ) <sup>a</sup>			
K	<0.05% water	1% water	2% water
313	0.22	1.07	2.81
298	0.11	0.62	2.81
273	0.11	0.67	2.81
253	0.17	1.12	33.7
233	0.31	2.47	72.9
195	0.42	6.45	44.9

(<sup>a</sup> units calculated by compiler; <sup>b</sup> probably weight percents).

A similar study using 1-butanol, though only at  $298 \pm 1$  K, has been reported by Inozemtseva et al (2). These workers determined the amount of sodium penicillin G dissolved both iodometrically and gravimetrically by drying to constant weight. No mention is made of a solvent blank. The values reported differ by between 0.5 and 10 %, with the gravimetric method giving the higher values. The values are given in Table 2. Unlike that given for potassium penicillin G, all the values may be regarded as being **tentative**. (The precision of measurement for each method is considered to be  $\pm 5\%$  - evaluator).

Table 2. Solubility of sodium penicillin G in butanol and in butanol/water mixtures at  $298 \pm 1$  K (2).

Solubility in 1-butanol containing differing amounts of water ( $10^3 \text{ mol dm}^{-3}$ ) <sup>a</sup>		
Concentration of water (weight percent)	iodometric determination	gravimetric determination
0	1.91	1.96
0.5	2.24	2.41
1	2.97	3.37
2	10.8	11.0
2.5	18.9	19.2
3	25.8	25.9

(<sup>a</sup> units calculated by compiler).

Popova and Schurchkova (3) has studied the solubility of sodium penicillin G in 1-butanol containing water at concentrations ranging from 2.5 to 30 % over the temperature range 283 K to 313 K. Lack of information on the purity of the sample, and the method used gives that the graphically reported solubility values be **rejected**.

(continued over)

## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] monosodium salt (sodium penicillin G);  $C_{16}H_{17}N_2NaO_4S$ ; [69-57-8]  
 (2) All solvents

## EVALUATOR:

Eric Tomlinson  
 Department of Pharmacy  
 University of Amsterdam  
 The Netherlands  
 December 1983

## CRITICAL EVALUATION: continued

Values for the solubility of sodium penicillin G in 24 solvents at  $301 \pm 4$  K have been reported by Weiss et al (4). These workers used a pooled commercial sample of high purity (95-100%). The amount of penicillin dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than  $20 \text{ mg cm}^{-3}$ . All values reported were uncorrected for solvent blank, which was generally less than 0.05 mg total. All data according to Weiss et al have been recalculated to SI units (compiler), and are given in Table 3.

Solvent	Solubility (at $301 \pm 4$ K) ( $\text{mol dm}^{-3}$ )	
water	a	
methanol	a	
ethanol	$2.80 \times 10^{-2}$	
isopropanol	$2.10 \times 10^{-3}$	
isoamyl alcohol	$5.90 \times 10^{-3}$	
cyclohexane	$2.95 \times 10^{-4}$	
benzene	$1.32 \times 10^{-4}$	
toluene	$5.61 \times 10^{-5}$	
ligroin	0	
isooctane	$8.98 \times 10^{-5}$	
carbon tetrachloride	$1.18 \times 10^{-4}$	
ethyl acetate	$1.12 \times 10^{-3}$	( <sup>a</sup> solubility greater than $5.6 \times 10^{-2} \text{ mol dm}^{-3}$ )
isoamyl acetate	$6.17 \times 10^{-3}$	
acetone	$5.33 \times 10^{-4}$	
methyl ethyl ketone	$4.12 \times 10^{-4}$	
diethylether	$1.68 \times 10^{-4}$	
ethylene chloride	$8.42 \times 10^{-4}$	
1,4-dioxane	$5.30 \times 10^{-3}$	
chloroform	$1.40 \times 10^{-4}$	
carbon disulfide	$2.33 \times 10^{-4}$	
pyridine	$3.23 \times 10^{-3}$	
formamide	a	
ethylene glycol	a	
benzyl alcohol	$3.10 \times 10^{-2}$	

(All solvents are U.S.P. or A.C.S. grade)

All these values have an estimated precision of  $\pm 5\%$  (evaluator). However they are unconfirmed findings, and must be designated as **tentative**, except for (i) where the solubility is reported as being greater than  $5.6 \times 10^{-2} \text{ mol dm}^{-3}$ , (which are regarded as **doubtful**); (ii) the value for solubility in ligroin, (which is **rejected** since the assay procedure used is not sufficiently sensitive for this value to have any meaning); and (iii) the value for solubility in acetone may be compared with that obtained by Page and Waller (Table 1). U.S.P. grade acetone can contain up to 0.5% (by volume) of water, thus it appears that this is not the explanation for the discrepancy in the values. Both determination methods used appear to have a similar accuracy, however, Weiss et al did not consider whether a solvate existed in the acetone (unlike Page and Waller), and it is probable that this could be a reason for the much larger solubility reported by Weiss et al. Their value is regarded as **doubtful**.

## REFERENCES

- (1) Page, J.E.; Waller, J.E. *Trans. Faraday Soc.* **1949**, *45*, 755.  
 (2) Inozemtseva, I.I.; Trakhtenberg, D.M.; Zinatullina, E.S. *Antibiotiki (Moscow)* **1974**, *19*, 448.  
 (3) Popova, M.V.; Schurchkova, Yu. A.; Massavaya Krist. **1977**, *3*, 51.  
 (4) Weiss P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* **1957**, *7*, 374.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] monosodium salt (sodium penicillin G); $C_{16}H_{17}N_2NaO_4S$ ; [69-57-8] (2) 2-Propanone (acetone); $C_3H_6O$ ; [67-64-1] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Page, J.E.; Waller, J.G. <i>Trans. Faraday Soc.</i> 1949, 45, 755-7.																																																				
<b>VARIABLES:</b>  Temperature and solvent composition	<b>PREPARED BY:</b>  A. Regosz																																																				
<b>EXPERIMENTAL VALUES:</b>  <div style="text-align: center;">Solubility<sup>a</sup> in g 100 cm<sup>-3</sup> of acetone containing</div> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;">t/°C</th> <th style="text-align: center;">less than 0.05% water</th> <th style="text-align: center;">1.0% water</th> <th style="text-align: center;">2% water</th> </tr> </thead> <tbody> <tr><td>40</td><td style="text-align: center;">0.008</td><td style="text-align: center;">0.038</td><td style="text-align: center;">0.10</td></tr> <tr><td>25</td><td style="text-align: center;">0.004</td><td style="text-align: center;">0.022</td><td style="text-align: center;">0.10</td></tr> <tr><td>0</td><td style="text-align: center;">0.004</td><td style="text-align: center;">0.024</td><td style="text-align: center;">0.10</td></tr> <tr><td>-20</td><td style="text-align: center;">0.006</td><td style="text-align: center;">0.040</td><td style="text-align: center;">1.2</td></tr> <tr><td>-40</td><td style="text-align: center;">0.011</td><td style="text-align: center;">0.088</td><td style="text-align: center;">2.6</td></tr> <tr><td>-78</td><td style="text-align: center;">0.015</td><td style="text-align: center;">0.23</td><td style="text-align: center;">1.6</td></tr> </tbody> </table> <div style="text-align: center;">Solubility in 10<sup>3</sup> mol dm<sup>-3</sup> - (calculated by compiler)</div> <table border="1" style="width: 100%; border-collapse: collapse;"> <tbody> <tr><td>40</td><td style="text-align: center;">0.22</td><td style="text-align: center;">1.07</td><td style="text-align: center;">2.81</td></tr> <tr><td>25</td><td style="text-align: center;">0.11</td><td style="text-align: center;">0.62</td><td style="text-align: center;">2.81</td></tr> <tr><td>0</td><td style="text-align: center;">0.11</td><td style="text-align: center;">0.67</td><td style="text-align: center;">2.81</td></tr> <tr><td>-20</td><td style="text-align: center;">0.17</td><td style="text-align: center;">1.12</td><td style="text-align: center;">33.7</td></tr> <tr><td>-40</td><td style="text-align: center;">0.31</td><td style="text-align: center;">2.47</td><td style="text-align: center;">27.9</td></tr> <tr><td>-78</td><td style="text-align: center;">0.42</td><td style="text-align: center;">6.45</td><td style="text-align: center;">44.9</td></tr> </tbody> </table> <sup>a</sup> The authors report solubilities in acetone containing small percentages of water, but do not define what type of percent units employed. It is most likely that weight percents were used.		t/°C	less than 0.05% water	1.0% water	2% water	40	0.008	0.038	0.10	25	0.004	0.022	0.10	0	0.004	0.024	0.10	-20	0.006	0.040	1.2	-40	0.011	0.088	2.6	-78	0.015	0.23	1.6	40	0.22	1.07	2.81	25	0.11	0.62	2.81	0	0.11	0.67	2.81	-20	0.17	1.12	33.7	-40	0.31	2.47	27.9	-78	0.42	6.45	44.9
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<b>METHOD APPARATUS/PROCEDURE:</b>  The solubility apparatus consisted of two test tubes joined by a ground-glass connector. The connector had a tube with a glass wool plug thus permitting solution to be transferred from one tube to the other. About 5 cm <sup>3</sup> of solvent were added to an excess of solid in the test tube and N <sub>2</sub> , presaturated with solvent, was bubbled through the mixture. The bottom test tube with the connector was placed in a thermostat until thermal equilibrium was reached (1-2 hour). The apparatus was removed from the thermostat, fitted with the second test tube, inverted and returned to the thermostat. After complete filtration, the filtrate in the second test tube was allowed to attain room temperature, and a known volume of the supersaturated or cloudy solution was analysed. The aliquot was diluted with $KH_2PO_4/K_2HPO_4$ buffer solution and analysed for penicillin by the cup plate method (1). Acetone solution, warmed from -50°C to 0°C, produced crystals which upon analysis (details not given) indicated that no solvate existed.	<b>SOURCE AND PURITY OF MATERIALS:</b>  Sodium penicillin G was supplied by Glaxo Laboratories, and was approx. 100% benzylpenicillin. A.R. Acetone was dried and redistilled from anhydrous $K_2CO_3$ . Water content was determined by Karl-Fischer titration.  The quality of the water was not described.  <b>ESTIMATED ERROR:</b>  Solubility precision: better than 5% (authors). Temperature precision: none specified.  <b>REFERENCES:</b> (1) Clark; Johnson; Robinson. <i>The Chemistry of Penicillin</i> . Princeton University Press, Princeton, N.J., 1949, p. 1031.																																																				



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] monosodium salt (sodium penicillin G); $C_{16}H_{17}N_2NaO_4S$ ; [69-57-8] (2) 1-Butanol; $C_4H_{10}O$ ; [71-36-3] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Inozemtseva, I.I.; Trakhtenberg, D.M.; Zinatullina, E.S. <i>Antibiotiki</i> 1974, 19, 448-51.																																						
<b>VARIABLES:</b>  Concentration of water	<b>PREPARED BY:</b>  A. Regosz																																						
<b>EXPERIMENTAL VALUES:</b>  <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th rowspan="3" style="text-align: left; vertical-align: bottom;">Concentration of water weight per cent</th> <th colspan="4" style="text-align: center;">Solubility of sodium penicillin G at <math>25 \pm 1^\circ C</math></th> </tr> <tr> <th colspan="2" style="text-align: center;">detd iodometrically</th> <th colspan="2" style="text-align: center;">detd gravimetrically</th> </tr> <tr> <th style="text-align: center;"><math>mg\ cm^{-3}</math></th> <th style="text-align: center;"><math>10^3\ mol\ dm^{-3}{}^a</math></th> <th style="text-align: center;"><math>mg\ cm^{-3}</math></th> <th style="text-align: center;"><math>10^3\ mol\ dm^{-3}{}^a</math></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">0.5</td> <td style="text-align: center;">0.80</td> <td style="text-align: center;">2.24</td> <td style="text-align: center;">0.86</td> <td style="text-align: center;">2.41</td> </tr> <tr> <td style="text-align: center;">1.0</td> <td style="text-align: center;">1.06</td> <td style="text-align: center;">2.97</td> <td style="text-align: center;">1.20</td> <td style="text-align: center;">3.37</td> </tr> <tr> <td style="text-align: center;">2.0</td> <td style="text-align: center;">3.86</td> <td style="text-align: center;">10.83</td> <td style="text-align: center;">3.92</td> <td style="text-align: center;">11.00</td> </tr> <tr> <td style="text-align: center;">2.5</td> <td style="text-align: center;">6.74</td> <td style="text-align: center;">18.91</td> <td style="text-align: center;">6.86</td> <td style="text-align: center;">19.25</td> </tr> <tr> <td style="text-align: center;">3.0</td> <td style="text-align: center;">9.20</td> <td style="text-align: center;">25.85</td> <td style="text-align: center;">9.26</td> <td style="text-align: center;">25.98</td> </tr> </tbody> </table> <p><sup>a</sup> Calculated by the compiler</p>		Concentration of water weight per cent	Solubility of sodium penicillin G at $25 \pm 1^\circ C$				detd iodometrically		detd gravimetrically		$mg\ cm^{-3}$	$10^3\ mol\ dm^{-3}{}^a$	$mg\ cm^{-3}$	$10^3\ mol\ dm^{-3}{}^a$	0.5	0.80	2.24	0.86	2.41	1.0	1.06	2.97	1.20	3.37	2.0	3.86	10.83	3.92	11.00	2.5	6.74	18.91	6.86	19.25	3.0	9.20	25.85	9.26	25.98
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<b>METHOD, APPARATUS/PROCEDURE:</b>  Saturated mixture was prepared by stirring Na penicillin G and a 1-butanol-water solution in a thermostat at $25 \pm 1^\circ C$ . The state of saturation was determined by taking aliquots of the solution at different time intervals. The content of the antibiotic was determined by both iodometric titration and gravimetrically by drying to constant weight.	<b>SOURCE AND PURITY OF MATERIALS:</b>  Sodium penicillin G was 98% benzylpenicillin: its source was not specified. A fraction of 1-butanol boiling at $116-7^\circ C$ was used. The water content was determined by Karl-Fischer titration.  The purity of water was not given.  <b>ESTIMATED ERROR:</b>  Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b>																																						

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] monosodium salt (sodium penicillin G); $C_{16}H_{17}N_2NaO_4S$ ; [69-57-8] (2) 1-Butanol; $C_4H_{10}O$ ; [71-36-3] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Popova, M.V.; Schurchkova, Yu.A. <i>Massavaya Krist.</i> 1977, 3, 51-5.
<b>VARIABLES:</b> Temperature and solvent composition	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b> <div style="text-align: center;"> </div> <p style="text-align: center;">solubility (weight percent)</p> <p style="text-align: center;">1-butanol/water weight ratio            1 - 2.5            2 - 5            3 - 15            4 - 30</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> An excess of sodium penicillin G and a 1-butanol/water mixture were placed in a flask and stirred in an ultrathermostat for 3-5 hours. Aliquots of the saturated solution were withdrawn at a given temperature through a filter under vacuum. The content of the dissolved solute was determined gravimetrically by drying the filter to constant weight. In some experiments the results were confirmed by iodometric titration.	<b>SOURCE AND PURITY OF MATERIALS:</b> The sources and purities of sodium penicillin G and 1-butanol were not specified. Water was distilled. <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: none specified <b>REFERENCES:</b>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] monosodium salt (sodium penicillin G); <math>C_{16}H_{17}N_2NaO_4S</math>; [69-57-8]</p> <p>(2) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of sodium penicillin G in water at <math>28 \pm 4^\circ C</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.6 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS.</p> <p>Sodium penicillin G was a pooled commercial product of high purity (95 to 100%).</p> <p>Water was of U.S.P. or A.C.S. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] monosodium salt (sodium penicillin G); <math>C_{16}H_{17}N_2NaO_4S</math>; [69-57-8]</p> <p>(2) Methanol; <math>CH_4O</math>; [67-56-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of sodium penicillin G in methanol at <math>28 \pm 4^\circ C</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.6 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Sodium penicillin G was a pooled commercial product of high purity (95 to 100%).</p> <p>Methanol was of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <p>REFERENCES:</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] monosodium salt (sodium penicillin G); $C_{16}H_{17}N_2NaO_4S$ ; [69-57-8] (2) Ethanol; $C_2H_6O$ ; [64-17-5]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of sodium penicillin G in ethanol at $28 \pm 4^\circ\text{C}$ was reported as: $10.0 \text{ mg cm}^{-3}$ . ( $2.8 \times 10^{-2} \text{ mol dm}^{-3}$ solution - compiler)	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $28 \pm 4^\circ\text{C}$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ\text{C}$ . The residue was further dried for 3 hr at $60^\circ\text{C}$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b> Sodium penicillin G was a pooled commercial product of high purity (95 to 100%). Ethanol was of U.S.P. or A.C.S. grade.  <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 4^\circ\text{C}$ (authors).  <b>REFERENCES:</b>







<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] monosodium salt (sodium penicillin G); $C_{16}H_{17}N_2NaO_4S$ ; [69-57-8] (2) Benzene; $C_6H_6$ ; [71-43-2]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of sodium penicillin G in benzene at $28 \pm 4^\circ C$ was reported as: $0.047 \text{ mg cm}^{-3}$ . ( $1.32 \times 10^{-4} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $28 \pm 4^\circ C$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ C$ . The residue was further dried for 3 hr at $60^\circ C$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b> Sodium penicillin G was a pooled commercial product of high purity (95 to 100%). Benzene was of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 4^\circ C$ (authors).  <b>REFERENCES:</b>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] monosodium salt (sodium penicillin G); $C_{16}H_{17}N_2NaO_4S$ ; [69-57-8] (2) Petroleum ether (ligroin)	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> 1957, 7, 374-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of sodium penicillin G in ligroin at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.0 \text{ mg cm}^{-3}</math>. (<math>0.0 \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Sodium penicillin G was a pooled commercial product of high purity (95 to 100%).           Ligroin was of A.C.S. or U.S.P. grade.</p> <hr/> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <hr/> <b>REFERENCES.</b>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] monosodium salt (sodium penicillin G); $C_{16}H_{17}N_2NaO_4S$ ; [69-57-8] (2) Pentane, 2,2,4-trimethyl- (isooctane); $C_8H_{18}$ ; [540-84-1]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of sodium penicillin G in isooctane at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.032 \text{ mg cm}^{-3}</math>. (<math>8.98 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Sodium penicillin G was a pooled commercial product of high purity (95 to 100%).          Isooctane was of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b>



<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] monosodium salt (sodium penicillin G); <math>C_{16}H_{17}N_2NaO_4S</math>; [69-57-8]</p> <p>(2) Acetic acid, ethyl ester (ethyl acetate); <math>C_4H_8O_2</math>; [141-78-6]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of sodium penicillin G in ethyl acetate at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.40 \text{ mg cm}^{-3}</math>. (<math>1.12 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Sodium penicillin G was a pooled commercial product of high purity (95 to 100%).</p> <p>Ethyl acetate was of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p>





<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] monosodium salt (sodium penicillin G); <math>C_{16}H_{17}N_2NaO_4S</math>; [69-57-8]</p> <p>(2) 2-Butanone; <math>C_4H_8O</math>; [78-93-3]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of sodium penicillin G in 2-butanone at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.15 \text{ mg cm}^{-3}</math>. (<math>4.12 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Sodium penicillin G was a pooled commercial product of high purity (95 to 100%).</p> <p>2-Butanone was of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] monosodium salt (sodium penicillin G); <math>C_{16}H_{17}N_2NaO_4S</math>; [69-57-8]</p> <p>(2) Ethane, 1,1'-oxybis- (diethyl ether); <math>C_4H_{10}O</math>; [60-29-7]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of sodium penicillin G in diethyl ether at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.06 \text{ mg cm}^{-3}</math>. (<math>1.68 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Sodium penicillin G was a pooled commercial product of high purity (95 to 100%).</p> <p>Diethyl ether was of U.S.P. or A.C.S. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] monosodium salt (sodium penicillin G); $C_{16}H_{17}N_2NaO_4S$ ; [69-57-8] (2) Ethane, dichloro- (ethylene chloride); $C_2H_4Cl_2$ ; [1300-21-6]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of sodium penicillin G in ethylene chloride at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.30 \text{ mg cm}^{-3}</math>. (<math>8.42 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Sodium penicillin G was a pooled commercial product of high purity (95 to 100%).</p> <p>Ethylene chloride was of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] monosodium salt (sodium penicillin G); <math>C_{16}H_{17}N_2NaO_4S</math>; [69-57-8]</p> <p>(2) 1,4-Dioxane; <math>C_4H_8O_2</math>; [123-91-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of sodium penicillin G in 1,4-dioxane at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>1.9 \text{ mg cm}^{-3}</math>. (<math>5.3 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Sodium penicillin G was a pooled commercial product of high purity (95 to 100%).</p> <p>1,4-Dioxane was of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] monosodium salt (sodium penicillin G); $C_{16}H_{17}N_2NaO_4S$ ; [69-57-8] (2) Methane, trichloro- (chloroform); $CHCl_3$ ; [67-66-3]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <b>Antibiotics and Chemotherapy</b> <u>1957</u> , 7, 374-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of sodium penicillin G in chloroform at <math>28 \pm 4^\circ C</math> was reported as:  <math>0.05 \text{ mg cm}^{-3}</math>. (<math>1.40 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $28 \pm 4^\circ C$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ C$ . The residue was further dried for 3 hr at $60^\circ C$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b> Sodium penicillin G was a pooled commercial product of high purity (95 to 100%).  Chloroform was of U.S.P. or A.C.S. grade.
	<b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 4^\circ C$ (authors).
	<b>REFERENCES:</b>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] monosodium salt (sodium penicillin G); <math>C_{16}H_{17}N_2NaO_4S</math>; [69-57-8]</p> <p>(2) Carbon disulfide; <math>CS_2</math>; [75-15-0]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of sodium penicillin G in carbon disulfide at <math>28 \pm 4^\circ C</math> was reported as:  <math>0.083 \text{ mg cm}^{-3}</math>. (<math>2.33 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Sodium penicillin G was a pooled commercial product of high purity (95 to 100%).</p> <p>Carbon disulfide was of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <p>REFERENCES:</p>



<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] monosodium salt (sodium penicillin G); <math>C_{16}H_{17}N_2NaO_4S</math>; [69-57-8]</p> <p>(2) Formamide; <math>CH_3NO</math>; [75-12-7]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of sodium penicillin G in formamide at <math>28 \pm 4^\circ C</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.6 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Sodium penicillin G was a pooled commercial product of high purity (95 to 100%).</p> <p>Formamide was of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <p>REFERENCES:</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] monosodium salt (sodium penicillin G); $C_{16}H_{17}N_2NaO_4S$ ; [69-57-8] (2) 1,2-Ethanediol (ethylene glycol); $C_2H_6O_2$ ; [107-21-1]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of sodium penicillin G in ethylene glycol at <math>28 \pm 4^\circ\text{C}</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.6 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ\text{C}$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b>  Sodium penicillin G was a pooled commercial product of high purity (95 to 100%).  Ethylene glycol was of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b>  Solubility precision: none specified Temperature precision: $\pm 4^\circ\text{C}$ (authors).  <b>REFERENCES:</b>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] monosodium salt (sodium penicillin G); <math>C_{16}H_{17}N_2NaO_4S</math>; [69-57-8]</p> <p>(2) Benzenemethanol (benzyl alcohol); <math>C_7H_8O</math>; [100-51-6]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of sodium penicillin G in benzyl alcohol at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>11.2 \text{ mg cm}^{-3}</math>. (<math>3.1 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - complex)</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Sodium penicillin G was a pooled commercial product of high purity (95 to 100%).</p> <p>Benzyl alcohol was of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p>

## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino], monoammonium salt (ammonium penicillin G);  $C_{16}H_{20}N_3O_4S$ ; [75333-20-9]  
 (2) 2-propanone (acetone);  $C_3H_6O$ ; [67-64-1]  
 (3) Water:  $H_2O$ ; [7732-18-5]

## EVALUATOR:

Eric Tomlinson  
 Department of Pharmacy,  
 University of Amsterdam,  
 The Netherlands.  
 December 1983

## CRITICAL EVALUATION:

Page and Waller (1) determined the solubility in acetone containing less than 0.05%, 1.0% and 2.0% (probably weight percents - evaluator) of water over the temperature range 195 K to 313 K. The authors state that the precision in the reported solubility values is better than  $\pm 5\%$ . The precision in the temperature is probably  $\pm 1$  K (evaluator). Consideration of the stated purity of the sample and the solubility determination procedure used, gives that the values reported by these workers (Table 1) may be regarded as tentative.

Table 1. Solubilities of sodium penicillin G in acetone/water mixtures.

K	Solubility in acetone containing water ( $10^3 \text{ mol dm}^{-3}$ ) <sup>a</sup>		
	<0.05% water	1% water	2% water
313	51	14	26
298	34	8.6	10
273	10	4.3	5.7
253	7.7	2.3	4.3
233	9.4	1.9	4.3
195	13	4.3	7.1

(<sup>a</sup> units calculated by compiler; <sup>b</sup> probably weight percents).

Contrary to the results found by the same workers for potassium penicillin G and for sodium penicillin G, the solubility of ammonium penicillin G was reduced by the addition 1% of water to acetone, though it increased with the addition of 2% water. The workers found no evidence of solvate formation in the acetone, and it is possible that the observed effect is due to a precipitation of the penicillin upon the addition of small amounts of water.

## REFERENCE

- (1) Page, J.E.; Waller, J.E. *Trans. Faraday Soc.* 1949, *45*, 755.

COMPONENTS:		ORIGINAL MEASUREMENTS:	
(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino], monoammonium salt, (ammonium penicillin G); $C_{16}H_{20}N_3O_4S$ ; [75333-20-9] (2) 2-Propanone (acetone); $C_3H_6O$ ; [67-64-1] (3) Water; $H_2O$ ; [7732-18-5]		Page, J.E.; Waller, J.G. Trans. Faraday Soc. 1949, 45, 755-7.	
VARIABLES:		PREPARED BY:	
Temperature and solvent composition		A. Regosz	
EXPERIMENTAL VALUES:			
Solubility in $mg\ cm^{-3}$ of acetone containing			
t/°C	<0.05 % <sup>a</sup> water	1 % <sup>a</sup> water	2 % <sup>a</sup> water
40	18	5.0	9.0
25	12	3.0	3.5
0	3.5	1.5	2.0
-20	2.7	0.80	1.5
-40	3.3	0.65	1.5
-78	4.5	1.5	2.5
Solubility in $10^3\ mol\ dm^{-3}$ - (compiler)			
40	51	14	26
25	34	8.6	10
0	10	4.3	5.7
-20	7.7	2.3	4.3
-40	9.4	1.9	4.3
-78	13	4.3	7.1
<sup>a</sup> Percent units are not defined, though are probably weight percents -(compiler).			
AUXILIARY INFORMATION			
METHOD/APPARATUS/PROCEDURE:		SOURCE AND PURITY OF MATERIALS:	
<p>The soly apparatus consisted of two test tubes joined by a ground glass connector. The connector had a tube with a glass wool plug thus permitting soln to be transferred from one tube to the other. About 5 <math>cm^3</math> of solvent were added to an excess of solid in the test tube, and <math>N_2</math> presaturated with solvent was bubbled through the mixture. The bottom test tube with the connector was placed in a thermostat until thermal equilibrium was reached (1-2 hr). The apparatus was removed from the thermostat, fitted with the second test tube, inverted and returned to the thermostat. After complete filtration, the filtrate in the second test tube was allowed to attain room temp and a known volume of the supersaturated or cloudy soln was taken for analysis. The aliquot was diluted with <math>KH_2PO_4/K_2HPO_4</math> buffer soln and analysed for penicillin G content by a microbiological method. Acetone soln warmed from <math>-50^\circ C</math> to <math>0^\circ C</math> produced crystals which upon analysis (details not given) indicated that no solvate existed.</p>		<p>Ammonium penicillin G was from Glaxo Laboratories, and was approx. 100% w/w. Acetone was A.R. quality, and was dried and redistilled from <math>K_2CO_3</math> before use.</p> <p>The purity and source of water used were not given.</p>	
		ESTIMATED ERROR:	
		Solubility precision: better than 5% (authors). Temperature precision: not specified but probably $\pm 1^\circ C$ .	
		REFERENCES:	

## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, compd with N-(phenylmethyl) benzene ethanamine (1:1) (benethamine penicillin G);  $C_{16}H_{18}N_2O_4S \cdot C_{15}H_{17}N$ ; [751-84-8]  
 (2) Water;  $H_2O$ ; [7732-18-5]

## EVALUATOR:

Eric Tomlinson.  
 Department of Pharmacy  
 University of Amsterdam,  
 The Netherlands.  
 December 1983

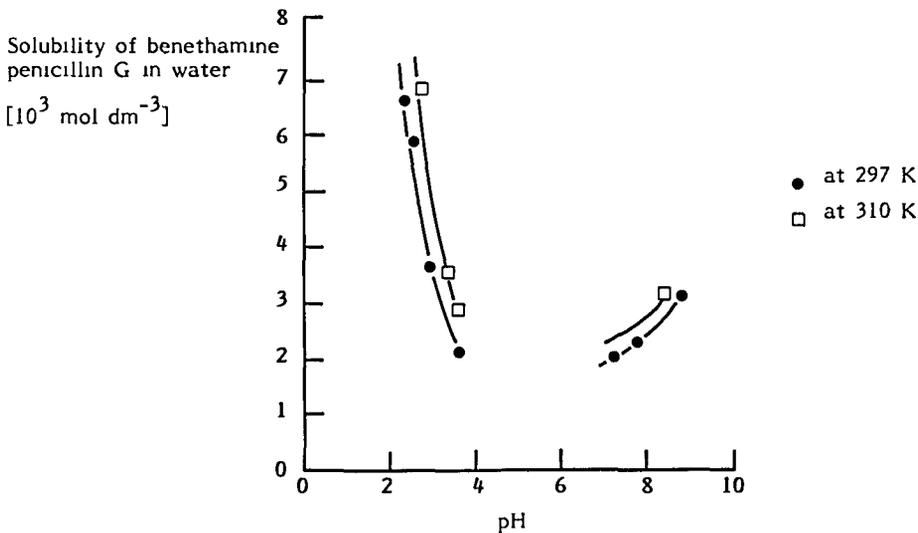
## CRITICAL EVALUATION:

The influence of pH (1.40 to 8.30) and temperature (297 K and 310 K) on the aqueous solubility of benethamine penicillin G have been studied by Brunner and Margreiter (1). The amount of penicillin dissolved in the solvent was determined by drying to constant weight. A precision  $\pm 2\%$  is estimated for all the solubility values reported, (evaluator). It is not possible to estimate the precision in the reported temperature or pH values, though for the latter it is probably  $\pm 0.02$  pH units.

The solubilities of benethamine penicillin G at 297 K and 310 K are reported as  $1.91 \times 10^{-3}$  mol dm<sup>-3</sup> and  $2.54 \times 10^{-3}$  mol dm<sup>-3</sup>, respectively. (Values converted to SI units by compiler). The Table gives the aqueous solubility of benethamine penicillin G at various pH's and at two temperatures. From this, and the figure, it is possible to see that the solubility increases sharply in strongly acid solutions, but only slightly in alkaline solutions. At pH 1.40 and below the authors suggest that the sharp increase in solubility is due to acid degradation of the penicillin molecule (see also benethamine penicillin V). Temperature had little effect on the solubilities found. Values at pH 1.4 and below are rejected, others are regarded as tentative.

Solubility ( $10^3$ mol dm <sup>-3</sup> ) <sup>a</sup>			
pH <sup>b</sup>	at 297 K	pH <sup>b</sup>	at 310 K
1.40	>27.5	1.35	>27.5
2.38	6.60	2.73	6.69
2.70	5.95	3.30	3.48
2.78	3.67	3.60	2.85
3.50	2.07	8.30	3.10
7.07	2.03		
7.80	2.20		
8.78	3.03		

(<sup>a</sup> Calculated by compiler; <sup>b</sup> pH altered using either HCl or NaOH).



## REFERENCE

- (1) Brunner, R.; Margreiter, H. *Montash.* 1955, 86, 958.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, compd with N-(phenylmethyl) benzene ethanamine (1:1) (benethamine penicillin G); $C_{16}H_{18}N_2O_4 \cdot C_{15}H_{17}N$ ; [751-84-8] (2) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Brunner, R.; Margreiter, H. <i>Monatsh.</i> <u>1955</u> , <b>86</b> , 958-85.									
<b>VARIABLES:</b> Temperature	<b>PREPARED BY:</b> A. Regosz									
<b>EXPERIMENTAL VALUES:</b>  <div style="text-align: center;">Solubility</div> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;">t/°C</th> <th style="text-align: center;">mg cm<sup>-3</sup></th> <th style="text-align: center;">10<sup>3</sup> mol dm<sup>-3</sup><sup>a</sup></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">24</td> <td style="text-align: center;">1.04</td> <td style="text-align: center;">1.91</td> </tr> <tr> <td style="text-align: center;">37</td> <td style="text-align: center;">1.39</td> <td style="text-align: center;">2.54</td> </tr> </tbody> </table> <p><sup>a</sup>Compiler</p>		t/°C	mg cm <sup>-3</sup>	10 <sup>3</sup> mol dm <sup>-3</sup> <sup>a</sup>	24	1.04	1.91	37	1.39	2.54
t/°C	mg cm <sup>-3</sup>	10 <sup>3</sup> mol dm <sup>-3</sup> <sup>a</sup>								
24	1.04	1.91								
37	1.39	2.54								
<b>AUXILIARY INFORMATION</b>										
<b>METHOD APPARATUS/PROCEDURE:</b> <p>To an accurately weighed sample of the antibiotic in a 50 cm<sup>3</sup> flask 20 cm<sup>3</sup> of water was added and the suspension shaken for about 1 hr at 24°C or 37°C. The suspension was then filtered and the residue quantitatively transferred into a tared glass crucible and dried in vacuum to const weight. The pH values of the clear filtrates measured were 5.40 and 5.50 at 24°C and 37°C, respectively.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>The anhydrous salt of benethamine penicillin G was used; its source and purity were not specified.</p> <p>The purity of the water was not specified.</p> <hr/> <b>ESTIMATED ERROR:</b> <p>Nothing specified.</p> <hr/> <b>REFERENCES:</b>									

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, compd with N-(phenylmethyl) benzene ethanamine (1:1) (benethamine penicillin G); $C_{16}H_{18}N_2O_4 \cdot S \cdot C_{15}H_{17}N$ ; [751-84-8] (2) Hydrochloric acid; HCl; [7647-01-0] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Brunner, R.; Margreiter, H. <i>Monatsh.</i> <u>1955</u> , <b>86</b> , 958-85.																																										
<b>VARIABLES:</b> pH at 24°C and 37°C	<b>PREPARED BY:</b> A. Regosz																																										
<b>EXPERIMENTAL VALUES:</b> <p style="text-align: center;">Solubility</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="3" style="text-align: center;">at 24°C</th> <th colspan="3" style="text-align: center;">at 37°C</th> </tr> <tr> <th style="text-align: center;">pH</th> <th style="text-align: center;"><math>mg\ cm^{-3}</math></th> <th style="text-align: center;"><math>10^3\ mol\ dm^{-3}^a</math></th> <th style="text-align: center;">pH</th> <th style="text-align: center;"><math>mg\ cm^{-3}</math></th> <th style="text-align: center;"><math>10^3\ mol\ dm^{-3}^a</math></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">3.50</td> <td style="text-align: center;">1.13</td> <td style="text-align: center;">2.07</td> <td style="text-align: center;">3.60</td> <td style="text-align: center;">1.56</td> <td style="text-align: center;">2.85</td> </tr> <tr> <td style="text-align: center;">2.78</td> <td style="text-align: center;">2.00</td> <td style="text-align: center;">3.67</td> <td style="text-align: center;">3.30</td> <td style="text-align: center;">1.90</td> <td style="text-align: center;">3.48</td> </tr> <tr> <td style="text-align: center;">2.70</td> <td style="text-align: center;">3.25</td> <td style="text-align: center;">5.95</td> <td style="text-align: center;">2.73</td> <td style="text-align: center;">3.65</td> <td style="text-align: center;">6.69</td> </tr> <tr> <td style="text-align: center;">2.38</td> <td style="text-align: center;">3.60</td> <td style="text-align: center;">6.60</td> <td style="text-align: center;">1.35</td> <td style="text-align: center;">&gt;15.0</td> <td style="text-align: center;">&gt;27.5</td> </tr> <tr> <td style="text-align: center;">1.40</td> <td style="text-align: center;">&gt;15.0</td> <td style="text-align: center;">&gt;27.5</td> <td></td> <td></td> <td></td> </tr> </tbody> </table> <p><sup>a</sup> Compiler</p>		at 24°C			at 37°C			pH	$mg\ cm^{-3}$	$10^3\ mol\ dm^{-3}^a$	pH	$mg\ cm^{-3}$	$10^3\ mol\ dm^{-3}^a$	3.50	1.13	2.07	3.60	1.56	2.85	2.78	2.00	3.67	3.30	1.90	3.48	2.70	3.25	5.95	2.73	3.65	6.69	2.38	3.60	6.60	1.35	>15.0	>27.5	1.40	>15.0	>27.5			
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	<b>REFERENCES:</b> (1) Brunner, R. <i>Monatsh.</i> <u>1955</u> , <b>86</b> , 767-95.																																										

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, compd with N-(phenylmethyl) benzene ethanamine (1:1) (benethamine penicillin G); <math>C_{16}H_{18}N_2O_4S \cdot C_{15}H_{17}N</math>; [751-84-8]</p> <p>(2) Sodium hydroxide; HNaO; [1310-73-2]</p> <p>(3) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Brunner, R.; Margreiter, H. <i>Monatsh.</i> <u>1955</u>, <b>86</b>, 958-85.</p>																												
<p>VARIABLES:</p> <p>pH at 24°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>																												
<p>EXPERIMENTAL VALUES:</p> <p style="text-align: center;">Solubility</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th rowspan="2">pH</th> <th colspan="2">at 24°C</th> <th rowspan="2">pH</th> <th colspan="2">at 37°C</th> </tr> <tr> <th>mg cm<sup>-3</sup></th> <th>10<sup>3</sup> mol dm<sup>-3</sup><sup>a</sup></th> <th>mg cm<sup>-3</sup></th> <th>10<sup>3</sup> mol dm<sup>-3</sup><sup>a</sup></th> </tr> </thead> <tbody> <tr> <td>7.07</td> <td>1.11</td> <td>2.03</td> <td>8.30</td> <td>1.69</td> <td>3.10</td> </tr> <tr> <td>7.80</td> <td>1.20</td> <td>2.20</td> <td></td> <td></td> <td></td> </tr> <tr> <td>8.78</td> <td>1.65</td> <td>3.03</td> <td></td> <td></td> <td></td> </tr> </tbody> </table> <p><sup>a</sup> Compiler</p>		pH	at 24°C		pH	at 37°C		mg cm <sup>-3</sup>	10 <sup>3</sup> mol dm <sup>-3</sup> <sup>a</sup>	mg cm <sup>-3</sup>	10 <sup>3</sup> mol dm <sup>-3</sup> <sup>a</sup>	7.07	1.11	2.03	8.30	1.69	3.10	7.80	1.20	2.20				8.78	1.65	3.03			
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	<p>REFERENCES:</p> <p>(1) Brunner, R. <i>Monatsh.</i> <u>1955</u>, <b>86</b>, 767-95.</p>																												

## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] complexed with 2-(diethylamino)ethyl-4-aminobenzoate (1:1), monohydrate (procaine penicillin G monohydrate);  $C_{16}H_{18}N_2O_4 \cdot S \cdot C_{13}H_{20}N_2O_2 \cdot H_2O$ ; [6130-64-9]
- (2) Water;  $H_2O$ ; [7732-18-5]

## EVALUATOR:

Eric Tomlinson  
Department of Pharmacy,  
University of Amsterdam,  
The Netherlands.  
December 1983

## CRITICAL EVALUATION:

The influence of pH (1.60 to 8.76) and temperature (297 K and 310 K) on the aqueous solubility of procaine penicillin G monohydrate have been studied by Brunner and Margreiter (1). The amount of penicillin dissolved in the solvent was determined by drying to constant weight. A precision of  $\pm 2\%$  is estimated for all the solubility values reported, (evaluator). It is not possible to estimate the precision in the reported temperature or pH values, though for the latter it is probably  $\pm 0.02$  pH units.

The solubilities of procaine penicillin G monohydrate at 297 K and 310 K are reported as  $8.41 \times 10^{-3}$  mol dm<sup>-3</sup> and  $12.8 \times 10^{-3}$  mol dm<sup>-3</sup>, respectively. (Values converted to SI units by compiler). The Table gives the aqueous solubility of procaine penicillin G monohydrate at various pH's and at 297 K and at 310 K. From this it is possible to see that the solubility increases sharply in strongly acid solutions, but only slightly in alkaline solutions. Brunner and Margreiter have made a detailed theoretical study concerning the calculation of the solubility of this solute using appropriate acid and base dissociation constants (2). At 297 K over the pH range 3.84 to 8.55, and at 310 K over the pH range 4.76 to 8.10, there was good agreement between results obtained experimentally and those obtained by calculation. However, at pH's above and below these, there was little agreement between the two, which could be indicative of degradation effects. Accordingly, all the values given in this evaluation are designated as being tentative, except for those determined at below pH 2.00 and above pH 8.6, which are rejected.

Solubility ( $10^3$ mol dm <sup>-3</sup> ) <sup>a</sup>			
pH <sup>b</sup>	at 297 K	pH <sup>b</sup>	at 310 K
1.60	35.9	2.30	34.9
1.92	24.0	3.08	17.8
2.30	14.8	4.76	13.1
3.84	8.83	6.20	12.7
4.55	8.68	7.35	13.1
6.52	8.53	8.10	13.7
7.05	8.66	8.76	17.8
8.07	9.60		
8.53	10.5		
8.90	12.2		

(<sup>a</sup> Calculated by compiler; <sup>b</sup> pH altered using either HCl or NaOH).

## REFERENCES

- (1) Brunner, R.; Margreiter, H. *Montash.* 1955, 86, 958.  
(2) Brunner, R.; Margreiter, H. *Montash.* 1955, 86, 767





<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2-(diethylamino)ethyl-4-aminobenzoate(1:1), monohydrate (procaine penicillin G); <math>C_{16}H_{18}N_2O_4 \cdot 5C_{13}H_{20}N_2O_2 \cdot H_2O</math>; [6130-64-9]</p> <p>(2) Sodium hydroxide; HNaO; [1310-73-2]</p> <p>(3) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Brunner, R.; Margreiter, H. <i>Montash</i> <u>1955</u>, 86, 958-85.</p>																																										
<p>VARIABLES:</p> <p>pH at 24 and 37°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>																																										
<p>EXPERIMENTAL VALUES:</p> <p style="text-align: center;">Solubility</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="3" style="text-align: center;">at 24°C</th> <th colspan="3" style="text-align: center;">at 37°C</th> </tr> <tr> <th style="text-align: center;">pH</th> <th style="text-align: center;">g. dm<sup>-3</sup></th> <th style="text-align: center;">10<sup>3</sup> mol dm<sup>-3</sup><sup>a</sup></th> <th style="text-align: center;">pH</th> <th style="text-align: center;">g. dm<sup>-3</sup></th> <th style="text-align: center;">10<sup>3</sup> mol dm<sup>-3</sup><sup>a</sup></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">6.52</td> <td style="text-align: center;">5.02</td> <td style="text-align: center;">8.53</td> <td style="text-align: center;">6.20</td> <td style="text-align: center;">7.50</td> <td style="text-align: center;">12.7</td> </tr> <tr> <td style="text-align: center;">7.05</td> <td style="text-align: center;">5.10</td> <td style="text-align: center;">8.66</td> <td style="text-align: center;">7.35</td> <td style="text-align: center;">7.72</td> <td style="text-align: center;">13.1</td> </tr> <tr> <td style="text-align: center;">8.07</td> <td style="text-align: center;">5.65</td> <td style="text-align: center;">9.60</td> <td style="text-align: center;">8.10</td> <td style="text-align: center;">8.08</td> <td style="text-align: center;">13.7</td> </tr> <tr> <td style="text-align: center;">8.53</td> <td style="text-align: center;">6.20</td> <td style="text-align: center;">10.5</td> <td style="text-align: center;">8.76</td> <td style="text-align: center;">10.5</td> <td style="text-align: center;">17.8</td> </tr> <tr> <td style="text-align: center;">8.90</td> <td style="text-align: center;">7.21</td> <td style="text-align: center;">12.2</td> <td></td> <td></td> <td></td> </tr> </tbody> </table> <p><sup>a</sup> Calculated by compiler</p>		at 24°C			at 37°C			pH	g. dm <sup>-3</sup>	10 <sup>3</sup> mol dm <sup>-3</sup> <sup>a</sup>	pH	g. dm <sup>-3</sup>	10 <sup>3</sup> mol dm <sup>-3</sup> <sup>a</sup>	6.52	5.02	8.53	6.20	7.50	12.7	7.05	5.10	8.66	7.35	7.72	13.1	8.07	5.65	9.60	8.10	8.08	13.7	8.53	6.20	10.5	8.76	10.5	17.8	8.90	7.21	12.2			
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<p>METHOD APPARATUS/PROCEDURE:</p> <p>To an accurately weighed sample of the antibiotic in a 50 cm<sup>3</sup> flask 20 cm<sup>3</sup> NaOH solution of the required pH was added and the suspension was shaken for about 1 hour at 24°C or 37°C. The suspension was then filtered and the pH of the clear filtrates accurately measured. The residue was quantitatively transferred into a tared glass crucible and dried in vacuum to constant weight. The solubilities found were compared with calculated values obtained in (1).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Source and purity of procaine penicillin G monohydrate were not specified. The water content of the sample was determined by Karl-Fischer titration.</p> <p>The purities of sodiumhydroxide and water were not specified.</p> <p>ESTIMATED ERROR:</p> <p>Nothing specified</p> <p>REFERENCES:</p> <p>(1) Brunner, R. <i>Montash</i> <u>1955</u>, 86, 767.</p>																																										

## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino], complexed with 2-(diethylamino)-ethyl-4-aminobenzoate (1:1) (procaine penicillin G);  $C_{16}H_{18}N_2O_4S \cdot C_{13}H_{20}N_2O_2$ ; [54-35-3]
- (2) Aqueous solvents

## EVALUATOR:

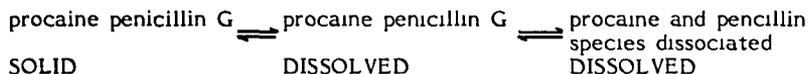
Eric Tomlinson, Department of Pharmacy, University of Amsterdam, The Netherlands.  
A. Regosz, Faculty of Pharmacy, Medical Academy, Gdansk, Poland.  
December 1983

## CRITICAL EVALUATION:

The solubility of procaine penicillin G in aqueous solutions has been reported in four studies (1-4). In 1953 Buckwalter et al (1) reported that procaine penicillin G exhibited enhanced stability in aqueous suspensions containing additives such as procaine hydrochloride [59-46-1] and sodium citrate. This increase in stability was attributed to a suppression of the solubility of procaine penicillin G. For example, the solubility in water at 298 K was reported as  $9.02 \times 10^{-3} \text{ mol dm}^{-3}$ , with this decreasing to  $2.61 \times 10^{-3} \text{ mol dm}^{-3}$  in the presence of procaine hydrochloride. For the purpose of this evaluation the values reported by Buckwalter et al are rejected since no information is given on the purity of the penicillin nor on the method of determination used.

Swintosky et al (2) have attempted to elucidate the above described behavior. To do so they determined the effects of various additives such as procaine hydrochloride, dextrose [50-99-7], sorbitol [50-70-4], sucrose [57-50-1], and various organic salts, on reducing the solubility of procaine penicillin G in water. The method used to determine the solubility is estimated to have a precision of  $\pm 5\%$  (evaluator). The following compilation sheets describe all the systems and values found. It is not proposed to reproduce these in this evaluation, though it is considered that all the values given may be regarded as tentative.

It is of interest to describe some of the findings of Swintosky et al. For example, the addition of 2% procaine hydrochloride to water reduced the solubility of procaine penicillin G at 298 K to about one fourth (from  $1.03 \times 10^{-2} \text{ mol dm}^{-3}$  to  $2.80 \times 10^{-3} \text{ mol dm}^{-3}$ ), though little further reduction could be seen with higher concentrations of procaine HCl. The authors suggested that the solubility data for procaine penicillin G in the presence of procaine HCl in aqueous phosphate buffer solutions had the following equilibrium



Most of the additives studied suppressed the solubility of procaine penicillin G. Its aqueous solubility was lowered from a reported  $1.03 \times 10^{-2} \text{ mol dm}^{-3}$  (phosphate buffer, pH 5.85, at  $298 \pm 2 \text{ K}$ ), to a minimum of  $6.31 \times 10^{-5} \text{ mol dm}^{-3}$  in an aqueous suspension containing 10% w/v sodium citrate, 0.2% w/v citric acid, 2% w/v procaine HCl, 40% w/v sorbitol and 25% w/v sodium gluconate. The authors suggested that this suspension (or a modification of it with a similarly effective suppression of solubility) might be used to prepare an oral dosage form of procaine penicillin G having a prolonged shelf life.

In a further paper, Swintosky et al prepared an aqueous suspension (pH 6.1) containing 2% w/v procaine HCl, 10% w/v sodium citrate, 0.20% w/v citric acid, 40% w/v sorbitol and 40% w/v sucrose. They report that the solubilities of procaine penicillin G in this suspension at  $298.2 \pm 0.1 \text{ K}$ ,  $310.2 \pm 0.1 \text{ K}$ ,  $318.2 \pm 0.1 \text{ K}$  and  $327.2 \pm 0.1 \text{ K}$  were  $1.68 \times 10^{-4} \text{ mol dm}^{-3}$ ,  $2.36 \times 10^{-4} \text{ mol dm}^{-3}$ ,  $3.99 \times 10^{-4} \text{ mol dm}^{-3}$  and  $9.72 \times 10^{-4} \text{ mol dm}^{-3}$ , respectively (3).

Weiss et al (4) have determined the solubility of procaine penicillin G in water at  $310 \pm 4 \text{ K}$  to be  $1.2 \times 10^{-2} \text{ mol dm}^{-3}$ . This is in good agreement with the values given by Swintosky et al (see above) and is to be regarded as a tentative value.

(All values in this evaluation have been converted to SI units by the evaluators).

## REFERENCES

- (1) Buckwalter, F.H.; Noel, R.H.; Walsh, E.A. *Antibiotics and Chemotherapy* 1955, 3, 292.
- (2) Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. *J. Am. Pharm. Assoc.* 1956, 45, 34.
- (3) Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. *J. Am. Pharm. Assoc.* 1956, 45, 37-40.
- (4) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* 1957, 7, 374.



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2-(diethylamino) ethyl-4-aminobenzoate(1:1) (procaine penicillin G); $C_{16}H_{18}N_2O_4S \cdot C_{13}H_{20}N_2O_2$ ; [54-35-3] (2) Benzoic acid, 4-amino-2-(diethyl-amino) ethyl ester, monohydrochloride (procaine hydrochloride); $C_{13}H_{20}N_2O_2 \cdot HCl$ ; [59-46-1] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Buckwalter, F.H.; Noel, R.H.; Walsh, E.A. <i>Antibiotics and Chemotherapy</i> , <u>1953</u> , <b>3</b> , 292-8.
<b>VARIABLES:</b> One temperature 25°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  The solubility of procaine penicillin G in aqueous solution containing 2% <sup>a</sup> procaine hydrochloride at 25°C was reported as: $1500 \text{ units cm}^{-3}$ , or $1.49 \text{ mg cm}^{-3}$ . ( $2.61 \times 10^{-3} \text{ mol dm}^{-3}$ - compiler) <sup>b</sup> .  <sup>a</sup> Probably w/v, (compiler) <sup>b</sup> According to U.S.P. one mg of procaine penicillin G represents 1009 penicillin units.	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Nothing specified	<b>SOURCE AND PURITY OF MATERIALS:</b> Procaine penicillin G was a product of Bristol Laboratories Inc., its purity was not specified. The source and purity of procaine hydrochloride was not given. Distilled water was used.
<b>ESTIMATED ERROR:</b> Nothing specified	
<b>REFERENCES:</b>	

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino)ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4S \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) Phosphoric acid, monosodium salt; <math>H_2NaO_4P</math>; [7558-80-7]</p> <p>(3) Phosphoric acid, disodium salt; <math>HNa_2O_4P</math>; [7558-79-4]</p> <p>(4) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. J. Am. Pharm. Assoc. <u>1956</u>, <u>45</u>, 34-40.</p>
<p>VARIABLES:</p> <p>One temperature: 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of procaine penicillin G in aqueous phosphate buffer pH 5.85 at <math>25 \pm 2^\circ C</math> was reported as:</p> <p style="text-align: center;"><math>5.9 \text{ mg cm}^{-3}</math>. (<math>10.3 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of antibiotic powder was added to an aqueous phosphate buffer solution (0.45 g <math>NaH_2PO_4 \cdot H_2O</math> and sufficient <math>Na_2HPO_4 \cdot 7H_2O</math> to give a pH of 5.85 at room temperature, <math>25 \pm 2^\circ C</math>). The suspension was agitated for 16 hours at room temperature, then filtered through a medium porosity sintered glass filter, and the filtrate dried in vacuum to constant weight at <math>60^\circ C</math>. The solid in each 1 cm<sup>3</sup> aliquot of filtrate were determined gravimetrically.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was of U.S.P. grade; its source was not described.</p> <p>The sources of <math>NaH_2PO_4 \cdot H_2O</math> and <math>Na_2HPO_4 \cdot 7H_2O</math> were not specified. Water was distilled.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 2^\circ C</math> (authors).</p> <p>REFERENCES.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino) ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4 \cdot S \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) Benzoic acid, 4-amino-2-(diethyl-amino) ethyl ester, monohydrochloride (procaine hydrochloride); <math>C_{13}H_{20}N_2O_2 \cdot HCl</math>; [59-46-1]</p> <p>(3) Phosphoric acid, monosodium salt; <math>NaH_2PO_4</math>; [7558-80-7]</p> <p>(4) Phosphoric acid, disodium salt; <math>Na_2HPO_4</math>; [7558-79-4]</p> <p>(5) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. J. Am. Pharm. Assoc. 1956, 45, 34-40.</p>															
<p>VARIABLES:</p> <p>Concentration of procaine hydrochloride</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>															
<p>EXPERIMENTAL VALUES:</p> <p style="text-align: center;">Solubility</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;">Procaine . HCl added to buffer solution pH 5.85 % w/v</th> <th style="text-align: center;">mg cm<sup>-3</sup></th> <th style="text-align: center;">10<sup>3</sup> mol dm<sup>-3</sup><sup>a</sup> solution</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">0.50</td> <td style="text-align: center;">3.4</td> <td style="text-align: center;">5.9</td> </tr> <tr> <td style="text-align: center;">1.00</td> <td style="text-align: center;">2.1</td> <td style="text-align: center;">3.7</td> </tr> <tr> <td style="text-align: center;">2.00</td> <td style="text-align: center;">1.6</td> <td style="text-align: center;">2.8</td> </tr> <tr> <td style="text-align: center;">3.00</td> <td style="text-align: center;">1.5</td> <td style="text-align: center;">2.6</td> </tr> </tbody> </table> <p><sup>a</sup>Calculated by compiler</p>		Procaine . HCl added to buffer solution pH 5.85 % w/v	mg cm <sup>-3</sup>	10 <sup>3</sup> mol dm <sup>-3</sup> <sup>a</sup> solution	0.50	3.4	5.9	1.00	2.1	3.7	2.00	1.6	2.8	3.00	1.5	2.6
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<p>AUXILIARY INFORMATION</p>																
<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of antibiotic powder was added to an aqueous phosphate buffer solution (0.45 g <math>NaH_2PO_4 \cdot H_2O</math> and sufficient <math>Na_2HPO_4 \cdot 7H_2O</math> to give a pH of 5.85 at room temperature, <math>25 \pm 2^\circ C</math>) containing either 0.50, 1.00, 2.00 or 3.00 % w/v procaine HCl. The suspension was agitated for 16 hours at room temperature, then filtered through a medium porosity sintered glass filter, and the filtrate dried in vacuum to constant weight at <math>60^\circ C</math>. The solid in each 1 cm<sup>3</sup> aliquot of filtrate were determined gravimetrically.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was of U.S.P. grade; its source was not described.</p> <p>The sources of <math>NaH_2PO_4 \cdot H_2O</math> and <math>Na_2HPO_4 \cdot 7H_2O</math> were not specified. Water was distilled.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 2^\circ C</math> (authors).</p> <p>REFERENCES.</p>															

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino)ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4 \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) 1,2,3-Propanetricarboxylic acid, 2-hydroxy- (citric acid); <math>C_6H_8O_7</math>; [77-92-9]</p> <p>(3) 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, trisodium salt (sodium citrate); <math>C_6H_5Na_3O_7</math>; [68-04-2]</p> <p>(4) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. J. Am. Pharm. Assoc. 1956, 45, 34-40.</p>																								
<p>VARIABLES:</p> <p>Concentration of citric acid and sodium citrate</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>																								
<p>EXPERIMENTAL VALUES:</p> <table border="1" data-bbox="266 637 1169 879" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th colspan="4" style="text-align: center;">Solubility</th> </tr> <tr> <th style="text-align: center;">Citric acid</th> <th style="text-align: center;">Sodium citrate</th> <th style="text-align: center;"><math>mg\ cm^{-3}</math></th> <th style="text-align: center;"><math>10^3\ mol\ dm^{-3}{}^a</math> solution</th> </tr> <tr> <th style="text-align: center;">Added</th> <th style="text-align: center;">Added</th> <th></th> <th></th> </tr> <tr> <th style="text-align: center;">% w/v</th> <th style="text-align: center;">% w/v</th> <th></th> <th></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">0.1</td> <td style="text-align: center;">5</td> <td style="text-align: center;">5.71</td> <td style="text-align: center;">10.00</td> </tr> <tr> <td style="text-align: center;">0.2</td> <td style="text-align: center;">10</td> <td style="text-align: center;">4.04</td> <td style="text-align: center;">7.08</td> </tr> </tbody> </table> <p style="margin-left: 20px;"><sup>a</sup>Calculated by compiler</p>		Solubility				Citric acid	Sodium citrate	$mg\ cm^{-3}$	$10^3\ mol\ dm^{-3}{}^a$ solution	Added	Added			% w/v	% w/v			0.1	5	5.71	10.00	0.2	10	4.04	7.08
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<p>METHOD APPARATUS/PROCEDURE:</p> <p>Suspensions of procaine penicillin G were agitated in vehicles containing variable amounts of citric acid and sodium citrate for 16 hours at room temperature (<math>25 \pm 2^\circ C</math>), then were filtered using a medium porosity glass filter. The filtrates were diluted and the amounts of procaine penicillin G dissolved in them, determined spectrophotometrically.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was of U.S.P. grade; its source was not described.</p> <p>Sources and purities of citric acid and sodium citrate were not specified. Water was distilled.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 2^\circ C</math> (authors).</p> <p>REFERENCES.</p>																								



<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino)ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4S.C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, trisodium salt (sodium citrate); <math>C_6H_5Na_3O_7</math>; [68-04-2]</p> <p>(3) D-Glucitol (D-Sorbitol); <math>C_6H_{14}O_6</math>; [50-70-4]</p> <p>(4) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. <i>J. Am. Pharm. Assoc.</i> 1956, 45, 34-40.</p>									
<p>VARIABLES:</p> <p>Concentration of sodium citrate</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>									
<p>EXPERIMENTAL VALUES:</p> <p style="text-align: center;">Solubility</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;">Sodium citrate in Sorbo<sup>a</sup> Added % w/v</th> <th style="text-align: center;">mg cm<sup>-3</sup></th> <th style="text-align: center;">10<sup>3</sup> mol dm<sup>-3</sup> solution<sup>b</sup></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">5</td> <td style="text-align: center;">1.85</td> <td style="text-align: center;">3.24</td> </tr> <tr> <td style="text-align: center;">10</td> <td style="text-align: center;">1.10</td> <td style="text-align: center;">1.93</td> </tr> </tbody> </table> <p><sup>a</sup>Sorbo is a product of Atlas Powder Co. Wilmington 99, Del, containing 70% D-sorbitol in water (authors).</p> <p><sup>b</sup>Calculated by compiler</p>		Sodium citrate in Sorbo <sup>a</sup> Added % w/v	mg cm <sup>-3</sup>	10 <sup>3</sup> mol dm <sup>-3</sup> solution <sup>b</sup>	5	1.85	3.24	10	1.10	1.93
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AUXILIARY INFORMATION										
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Suspensions of procaine penicillin G were agitated in vehicles containing variable amounts of sodium citrate in Sorbo for 16 hours at room temperature (25±2°C), then were filtered using a medium porosity glass filter. The filtrates were diluted and the content of antibiotic determined spectrophotometrically.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was of U.S.P. grade; its source was not described.</p> <p>Sources and purities of sodium citrate and sorbitol were not specified. Water was distilled.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: ±2°C (authors).</p> <p>REFERENCES:</p>									

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino)ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4 \cdot S \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, trisodium salt (sodium citrate); <math>C_6H_5Na_3O_7</math>; [68-04-2]</p> <p>(3) <math>\alpha</math>-D-Glucopyranoside, <math>\beta</math>-D-fructofuranosyl (Sucrose); <math>C_{12}H_{22}O_{11}</math>; [57-50-1]</p> <p>(4) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. <i>J. Am. Pharm. Assoc.</i> <u>1956</u>, <b>45</b>, 34-40.</p>															
<p>VARIABLES:</p> <p>Concentration of sodium citrate</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>															
<p>EXPERIMENTAL VALUES:</p> <table border="1" data-bbox="266 642 1131 944" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th colspan="3" style="text-align: center;">Solubility</th> </tr> <tr> <th style="text-align: center;">Sodium citrate in Sorbo<sup>a</sup> Added % w/v</th> <th style="text-align: center;">mg cm<sup>-3</sup></th> <th style="text-align: center;">10<sup>3</sup> mol dm<sup>-3</sup> solution<sup>b</sup></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">5</td> <td style="text-align: center;">4.55</td> <td style="text-align: center;">7.97</td> </tr> <tr> <td style="text-align: center;">10</td> <td style="text-align: center;">3.12</td> <td style="text-align: center;">5.47</td> </tr> <tr> <td style="text-align: center;">15</td> <td style="text-align: center;">2.66</td> <td style="text-align: center;">4.66</td> </tr> </tbody> </table> <p><sup>a</sup>Sorbo is a product of Atlas Powder Co. Wilmington 99, Del, containing 70% D-sorbitol in water (authors).</p> <p><sup>b</sup>Calculated by compiler</p>		Solubility			Sodium citrate in Sorbo <sup>a</sup> Added % w/v	mg cm <sup>-3</sup>	10 <sup>3</sup> mol dm <sup>-3</sup> solution <sup>b</sup>	5	4.55	7.97	10	3.12	5.47	15	2.66	4.66
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<p>METHOD APPARATUS/PROCEDURE:</p> <p>Suspensions of procaine penicillin G were agitated in vehicles containing variable amounts of sodium citrate in syrup for 16 hours at room temperature (<math>25 \pm 2^\circ\text{C}</math>), then were filtered using a medium porosity glass filter. The filtrates were diluted and the content of antibiotic determined spectrophotometrically.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was of U.S.P. grade; its source was not described.</p> <p>Source and purity of sodium citrate were not specified. The sucrose used was probably of U.S.P. grade. Water was distilled.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 2^\circ\text{C}</math> (authors).</p> <p>REFERENCES.</p>															

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino) ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4S \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, trisodium salt (sodium citrate); <math>C_6H_5Na_3O_7</math>; [68-04-2]</p> <p>(3) D-Glucitol (D-Sorbitol); <math>C_6H_{14}O_6</math>; [50-70-4]</p> <p>(4) <math>\alpha</math>-D-Glucopyranoside, <math>\beta</math>-D-fructofuranosyl (Sucrose); <math>C_{12}H_{22}O_{11}</math>; [57-50-1]</p> <p>(5) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS: Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. <i>J. Am. Pharm. Assoc.</i> <u>1956</u>, <i>45</i>, 34-40.</p>
<p>VARIABLES:</p> <p>One temperature: 25°C</p>	<p>PREPARED BY: A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of procaine penicillin G in aqueous solution at <math>25 \pm 2^\circ C</math> containing 10% w/v of sodium citrate in equal parts of Sorbo<sup>a</sup> and Syrup<sup>b</sup> was reported as:</p> <p style="text-align: center;"><math>1.79 \text{ mg cm}^{-3}</math>. (<math>3.14 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p> <p><sup>a</sup>Sorbo is a product of Atlas Powder Co. Wilmington 99, Del, containing 70% D-sorbitol in water (authors).</p> <p><sup>b</sup>Syrup refers to the official U.S.P. product containing 85% w/v sucrose in distilled water - (authors).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Suspensions of procaine penicillin G were agitated in vehicles containing 10% w/v of sodium citrate in equal parts of Sorbo and Syrup for 16 hours at room temperature (<math>25 \pm 2^\circ C</math>), then were filtered using a medium porosity glass filter. The filtrates were diluted and the content of antibiotic determined spectrophotometrically.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was of U.S.P. grade; its source was not described.</p> <p>Sources and purities of sodium citrate and sorbitol were not specified. Water was distilled.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 2^\circ C</math> (authors).</p> <p>REFERENCES.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino)ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4 \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, trisodium salt (sodium citrate); <math>C_6H_5Na_3O_7</math>; [68-04-2]</p> <p>(3) D-Glucose (dextrose); <math>C_6H_{12}O_6</math>; [50-99-7]</p> <p>(4) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. <i>J. Am. Pharm. Assoc.</i> <u>1956</u>, <i>45</i>, 34-40.</p>
<p>VARIABLES:</p> <p>One temperature: 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of procaine penicillin G in aqueous solution at <math>25 \pm 2^\circ C</math> containing 5% w/v of sodium citrate in 100% w/v of dextrose solution was reported as:</p> <p style="text-align: center;"><math>7.06 \text{ mg cm}^{-3}</math>. (<math>12.37 \times 10^{-3} \text{ mol dm}^{-3}</math> - compiler)</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Suspensions of procaine penicillin G were agitated in vehicles containing 5% w/v of sodium citrate in 100% w/v of dextrose solution for 16 hours at room temperature (<math>25 \pm 2^\circ C</math>), then were filtered using a medium porosity glass filter. The filtrates were diluted and the content of antibiotic determined spectrophotometrically.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was of U.S.P. grade; its source was not described.</p> <p>Sources and purities of sodium citrate and dextrose were not specified. Water was distilled.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 2^\circ C</math> (authors).</p> <p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino)ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4 \cdot S \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) Butanedioic acid, 2,3-dihydroxy- (L-(+)-tartaric acid); <math>C_4H_6O_6</math>; [87-69-4]</p> <p>(3) Butanedioic acid, 2,3-dihydroxy-, disodium salt (L-(+)-sodium tartrate); <math>C_4H_4Na_2O_6</math>; [868-18-8]</p> <p>(4) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. J. Am. Pharm. Assoc. <u>1956</u>, 45, 34-40.</p>
<p>VARIABLES:</p> <p>One temperature: 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of procaine penicillin G in aqueous solution at <math>25 \pm 2^\circ C</math> containing 20% w/v of sodium tartrate with tartaric acid to pH 6.15 was reported as:</p> <p style="text-align: center;"><math>2.36 \text{ mg cm}^{-3}</math>. (<math>4.13 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p style="text-align: center;">AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Suspensions of procaine penicillin G were agitated in vehicles containing 20% w/v of sodium tartrate with tartaric acid to pH 6.15 for 16 hours at room temperature (<math>25 \pm 2^\circ C</math>), then were filtered using a medium porosity glass filter. The filtrates were diluted and the content of antibiotic determined spectrophotometrically.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was of U.S.P. grade; its source was not described.</p> <p>Tartrates were dextrorotatory. Water was distilled.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 2^\circ C</math> (authors).</p> <p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino)ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4S \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) Butanedioic acid, 2,3-dihydroxy- (tartaric acid); <math>C_4H_6O_6</math>; [133-37-9]</p> <p>(3) Butanedioic acid, 2,3-dihydroxy-, disodium salt (L-(+)-sodium tartrate); <math>C_4H_4Na_2O_6</math>; [868-18-8]</p> <p>(4) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. <i>J. Am. Pharm. Assoc.</i> 1956, 45, 34-40.</p>
<p>VARIABLES:</p> <p>One temperature: 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of procaine penicillin G in aqueous solution at <math>25 \pm 2^\circ C</math> containing 15% w/v of sodium tartrate with dl-tartaric acid to pH 6.1 was reported as:</p> <p style="text-align: center;"><math>3.15 \text{ mg cm}^{-3}</math>. (<math>5.52 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Suspensions of procaine penicillin G were agitated in vehicles containing 20% w/v of sodium tartrate with dl-tartaric acid to pH 6.1 for 16 hours at room temperature (<math>25 \pm 2^\circ C</math>), then were filtered using a medium porosity glass filter. The filtrates were diluted and the content of antibiotic determined spectrophotometrically.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was of U.S.P. grade; its source was not described.</p> <p>dl-Tartaric acid was used. Sodium tartrate was dextrorotatory. Water was distilled.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 2^\circ C</math> (authors).</p> <p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino) ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4S \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) D-Gluconic acid, monosodium salt (sodium gluconate); <math>C_6H_{11}NaO_7</math>; [527-07-1]</p> <p>(3) D-Gluconic acid, <math>\delta</math>-lactone (glucono <math>\Delta</math> lactone); <math>C_6H_{10}O_6</math>; [90-80-2]</p> <p>(4) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. J. Am. Pharm. Assoc. <u>1956</u>, 45, 34-40.</p>
<p>VARIABLES:</p> <p>One temperature: 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of procaine penicillin G in aqueous solution at <math>25 \pm 2^\circ C</math> containing 25% w/v of sodium gluconate with glucono <math>\Delta</math> lactone to pH 6.1 was reported as:</p> <p style="text-align: center;"><math>3.88 \text{ mg cm}^{-3}</math>. (<math>6.80 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Suspensions of procaine penicillin G were agitated in vehicles containing 25% w/v of sodium gluconate with glucono <math>\Delta</math> lactone to pH 6.1 for 16 hours at room temperature (<math>25 \pm 2^\circ C</math>), then were filtered using a medium porosity glass filter. The filtrates were diluted and the content of antibiotic determined spectrophotometrically.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was of U.S.P. grade; its source was not described.</p> <p>Sources and purities of sodium gluconate and glucono <math>\Delta</math> lactone were not specified. Water was distilled.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 2^\circ C</math> (authors).</p> <p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino) ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4S \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) 1,2,3-Propanetricarboxylic acid, 2-hydroxy- (citric acid); <math>C_6H_8O_7</math>; [77-92-9]</p> <p>(3) 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, trisodium salt (sodium citrate); <math>C_6H_5Na_3O_7</math>; [68-04-2]</p> <p>(4) Butanedioic acid, 2,3-dihydroxy-, disodium salt (L-(+)-sodium tartrate); <math>C_4H_4Na_2O_6</math>; [868-18-8]</p> <p>(5) D-Glucitol (D-Sorbitol); <math>C_6H_{14}O_6</math>; [50-70-4]</p> <p>(6) <math>\alpha</math>-D-Glucopyranoside, <math>\beta</math>-D-fructofuranosyl (Sucrose); <math>C_{12}H_{22}O_{11}</math>; [57-50-1]</p> <p>(7) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. <i>J. Am. Pharm. Assoc.</i> 1956, 45, 34-40.</p>
<p>VARIABLES:</p> <p>One temperature: 25°C</p>	<p>PREPARED BY</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of procaine penicillin G in aqueous solution at <math>25 \pm 2^\circ C</math> containing 10% w/v of sodium citrate, 5% w/v sodium tartrate, 40% w/v sorbitol, 40% w/v sucrose and 0.25% w/v citric acid was reported as:</p> <p style="text-align: center;"><math>1.38 \text{ gm cm}^{-3}</math>. (<math>2.42 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Suspensions of procaine penicillin G were agitated in vehicles containing 10% w/v sodium citrate, 5% w/v sodium tartrate 4% w/v sorbitol, 40% w/v sucrose and 0.25% w/v citric acid for 16 hours at room temperature (<math>25 \pm 2^\circ C</math>), then were filtered using a medium porosity glass filter. The filtrates were diluted and the content of antibiotic determined spectrophotometrically.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was of U.S.P. grade; its source was not described.</p> <p>Sources and purities of citric acid, sodium citrate, sorbitol and sucrose were not specified. Sodium tartrate used was dextrorotatory. Water was distilled.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 2^\circ C</math> (authors).</p> <p>REFERENCES.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino)ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4 \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) Butanedioic acid, 2,3-dihydroxy- (L-(+)-tartaric acid); <math>C_4H_6O_6</math>; [87-69-4]</p> <p>(3) Butanedioic acid, 2,3-dihydroxy-, disodium salt (L-(+)-sodium tartrate); <math>C_4H_4Na_2O_6</math>; [868-18-8]</p> <p>(4) D-Gluconic acid, monosodium salt (sodium gluconate); <math>C_6H_{11}NaO_7</math>; [527-07-1]</p> <p>(5) D-Glucitol (D-Sorbitol); <math>C_6H_{14}O_6</math>; [50-70-4]</p> <p>(6) <math>\alpha</math>-D-Glucopyranoside, <math>\beta</math>-D-fructofuranosyl (Sucrose); <math>C_{12}H_{22}O_{11}</math>; [57-50-1]</p> <p>(7) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. J. Am. Pharm. Assoc. 1956, 45, 34-40.</p>
<p>VARIABLES:</p> <p>One temperature: 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of procaine penicillin G in aqueous solution at <math>25 \pm 2^\circ\text{C}</math> containing 10% w/v sodium tartrate, 15% w/v sodium gluconate, 40% w/v sorbitol, 40% w/v sucrose and 0.25% w/v tartaric acid was reported as:</p> <p style="text-align: center;"><math>1.42 \text{ mg cm}^{-3}</math>. (<math>2.49 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Suspensions of procaine penicillin G were agitated in vehicles containing 10% w/v Sodium tartrate, 15% w/v sodium gluconate, 40% w/v sorbitol, 40% w/v sucrose and 0.25% w/v tartaric acid for 16 hours at room temperature (<math>25 \pm 2^\circ\text{C}</math>), then were filtered using a medium porosity glass filter. The filtrates were diluted and the content of antibiotic determined spectrophotometrically.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was of U.S.P. grade; its source was not described.</p> <p>Sources and purities of sodium gluconate, sorbitol and sucrose were not specified. Tartrates were dextrorotatory. Water was distilled.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 2^\circ\text{C}</math> (authors).</p>
	<p>REFERENCES.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino) ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4 \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) Benzoic acid, 4-amino-2-(diethyl-amino) ethyl ester, monohydrochloride (procaine hydrochloride); <math>C_{13}H_{20}N_2O_2 \cdot HCl</math>; [59-46-1]</p> <p>(3) 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, trisodium salt (sodium citrate); <math>C_6H_5Na_3O_7</math>; [68-04-2]</p> <p>(4) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. <i>J. Am. Pharm. Assoc.</i> <u>1956</u>, <i>45</i>, 34-40.</p>
<p>VARIABLES:</p> <p>One temperature: 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of procaine penicillin G in aqueous solution at <math>25 \pm 2^\circ C</math> containing 5% w/v sodium citrate and 2% w/v procaine hydrochloride was reported as:</p> <p style="text-align: center;"><math>0.94 \text{ mg cm}^{-3}</math>. (<math>1.65 \times 10^{-3} \text{ mol dm}^{-3}</math> - compiler).</p>	
<p style="text-align: center;">AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Suspensions of procaine penicillin G were agitated in vehicles containing 5% w/v sodium citrate and 2% w/v procaine HCl for 16 hours at room temperature (<math>25 \pm 2^\circ C</math>), then were filtered using a medium porosity glass filter. The filtrate was diluted and the content of antibiotic assayed microbiologically (1).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was of U.S.P. grade; its source was not described.</p> <p>Sources and purities of procaine.HCl and sodium citrate were not specified. Water was distilled.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 2^\circ C</math> (authors).</p> <p>REFERENCES.</p> <p>(1) "Compilation of Regulations for Tests and Methods of Assay and Certification of Antibiotics and Antibiotic-Containing Drugs", U.S. Department of Health, Education and Welfare, Food and Drug Administration, Section 141 a.1, page A-1.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino)ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4S \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) Benzoic acid, 4-amino-2-(diethyl amino)ethyl ester, monohydrochloride (procaine hydrochloride); <math>C_{13}H_{20}N_2O_2 \cdot HCl</math>; [59-46-1]</p> <p>(3) 1,2,3-Propanetricarboxylic acid, 2-hydroxy-trisodium salt (sodium citrate); <math>C_6H_5Na_3O_7</math>; [68-04-2]</p> <p>(4) <math>\alpha</math>-D-Glucopyranoside, <math>\beta</math>-D-fructofuranosyl (Sucrose); <math>C_{12}H_{22}O_{11}</math>; [57-50-1]</p> <p>(5) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. <i>J. Am. Pharm. Assoc.</i> <u>1956</u>, <i>45</i>, 34-40.</p>									
<p>VARIABLES:</p> <p>Concentration of sodium citrate</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>									
<p>EXPERIMENTAL VALUES:</p> <p style="text-align: center;">Solubility</p> <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th style="text-align: left;">Sodium citrate Added % w/v</th> <th style="text-align: center;"><math>mg\ cm^{-3}</math></th> <th style="text-align: center;"><math>10^4\ mol\ dm^{-3}\ solution^a</math></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">10</td> <td style="text-align: center;">0.16</td> <td style="text-align: center;">2.80</td> </tr> <tr> <td style="text-align: center;">15</td> <td style="text-align: center;">0.25</td> <td style="text-align: center;">4.38</td> </tr> </tbody> </table> <p><sup>a</sup> Calculated by compiler</p>		Sodium citrate Added % w/v	$mg\ cm^{-3}$	$10^4\ mol\ dm^{-3}\ solution^a$	10	0.16	2.80	15	0.25	4.38
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<p>AUXILIARY INFORMATION</p>										
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Suspensions of procaine penicillin G were agitated in vehicles containing 2% w/v procaine.HCl in syrup and variable amounts of sodium citrate for 16 hours at room temperature (<math>25 \pm 2^\circ C</math>), then were filtered using a medium porosity glass filter. The filtrates were diluted and the content of antibiotic assayed microbiologically (1).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was of U.S.P. grade; its source was not described.</p> <p>Sources and purities of procaine.HCl, and sodium citrate were not specified. Sucrose was probably of U.S.P. grade. Water was distilled.</p> <p>Syrup refers to the official U.S.P. product containing 85% w/v of sucrose in distilled water (authors).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 2^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) "Compilation of Regulations for Tests and Methods of Assay and Certification of Antibiotics and Antibiotic-Containing Drugs", U.S. Department of Health, Education and Welfare, Food and Drug Administration, Section 141 a.1, page A-1.</p>									

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino)ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4 \cdot S \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) 1,2,3-Propanetricarboxylic acid, 2-hydroxy- (citric acid); <math>C_6H_8O_7</math>; [77-92-9]</p> <p>(3) 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, trisodium salt (sodium citrate); <math>C_6H_5Na_3O_7</math>; [68-04-2]</p> <p>(4) D-Glucitol (D-Sorbitol); <math>C_6H_{14}O_6</math>; [50-70-4]</p> <p>(5) <math>\alpha</math>-D-Glucopyranoside, <math>\beta</math>-D-fructofuranosyl (Sucrose); <math>C_{12}H_{22}O_{11}</math>; [57-50-1]</p> <p>(6) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. <i>J. Am. Pharm. Assoc.</i> <u>1956</u>, 45, 34-40.</p>
<p>VARIABLES:</p> <p>One temperature: 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of procaine penicillin G in aqueous solution at <math>25 \pm 2^\circ\text{C}</math> containing 10% w/v sodium citrate, 0.2% w/v citric acid, 40% w/v sorbitol and 40% w/v sucrose was reported as:</p> <p style="text-align: center;"><math>1.2 \text{ mg cm}^{-3}</math>. (<math>2.10 \times 10^{-3} \text{ mol dm}^{-3}</math> - compiler).</p>	
<p style="text-align: center;">AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Suspensions of procaine penicillin G were agitated in vehicles containing 10% w/v sodium citrate, 0.2% citric acid, 40% w/v sorbitol and 40% w/v sucrose for 16 hours at room temperature (<math>25 \pm 2^\circ\text{C}</math>), then were filtered using a medium porosity glass filter. The filtrates were diluted and the content of antibiotic determined spectrophotometrically.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was of U.S.P. grade; its source was not described.</p> <p>Sources and purities of citric acid, sodium citrate, sorbitol and sucrose were not specified. Water was distilled.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 2^\circ\text{C}</math> (authors).</p> <p>REFERENCES.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino)ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4 \cdot S \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) Benzoic acid, 4-amino-2-(diethyl-amino)ethyl ester, monohydrochloride (procaine hydrochloride); <math>C_{13}H_{20}N_2O_2 \cdot HCl</math>; [59-46-1]</p> <p>(3) 1,2,3-Propanetricarboxylic acid, 2-hydroxy-trisodium salt (sodium citrate); <math>C_6H_5Na_3O_7</math>; [68-04-2]</p> <p>(4) D-Glucitol (D-Sorbitol); <math>C_6H_{14}O_6</math>; [50-70-4]</p> <p>(5) <math>\alpha</math>-D-Glucopyranoside, <math>\beta</math>-D-fructofuranosyl (Sucrose); <math>C_{12}H_{22}O_{11}</math>; [57-50-1]</p> <p>(6) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. <i>J. Am. Pharm. Assoc.</i> <u>1956</u>, <i>45</i>, 34-40.</p>
<p>VARIABLES:</p> <p>One temperature: 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of procaine penicillin G in aqueous solution at <math>25 \pm 2^\circ C</math> containing 10% w/v sodium citrate and 2% w/v procaine hydrochloride in equal parts of syrup<sup>a</sup> and Sorbo<sup>b</sup> was reported as: <math>0.09 \text{ mg cm}^{-3}</math>. (<math>1.58 \times 10^{-4} \text{ mol dm}^{-3}</math> - compiler).</p> <p><sup>a</sup>Syrup refers to the official U.S.P. product containing 85% w/v sucrose in distilled water - authors.</p> <p><sup>b</sup>Sorbo is a product of Atlas Powder Co. Wilmington 99, Del, containing 70% w/v D-sorbitol in water - authors.</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Suspensions of procaine penicillin G were agitated in vehicles containing 10% w/v of sodium citrate and 2% w/v of procaine.HCl in equal parts of syrup and Sorbo for 16 hours at room temperature (<math>25 \pm 2^\circ C</math>), then were filtered using a medium porosity glass filter. The filtrate was diluted and the content of antibiotic assayed microbiologically (1).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was of U.S.P. grade; its source was not described.</p> <p>Sources and purities of procaine.HCl, sodium citrate and sorbitol were not specified. Sucrose was probably of U.S.P. grade. Water was distilled.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 2^\circ C</math> (authors).</p>
<p>REFERENCES:</p> <p>(1) "Compilation of Regulations for Tests and Methods of Assay and Certification of Antibiotics and Antibiotic-Containing Drugs", U.S. Department of Health, Education and Welfare, Food and Drug Administration, Section 141 a.1, page A-1.</p>	

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino)ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4S \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) Benzoic acid, 4-amino-2-(diethyl-amino) ethylester, monohydrochloride (procaine hydrochloride); <math>C_{13}H_{20}N_2O_2 \cdot HCl</math>; [59-46-1]</p> <p>(3) 1,2,3-Propanetricarboxylic acid, 2-hydroxy- (citric acid); <math>C_6H_8O_7</math>; [77-92-9]</p> <p>(4) 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, trisodium salt (sodium citrate); <math>C_6H_5Na_3O_7</math>; [68-04-2]</p> <p>(5) D-Glucitol (D-Sorbitol); <math>C_6H_{14}O_6</math>; [50-70-4]</p> <p>(6) <math>\alpha</math>-D-Glucopyranoside, <math>\beta</math>-D-fructofuranosyl (Sucrose); <math>C_{12}H_{22}O_{11}</math>; [57-50-1]</p> <p>(7) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS: Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. J. Am. Pharm. Assoc. <u>1956</u>, 45, 34-40.</p>																		
<p>VARIABLES: Concentration of procaine hydrochloride</p>	<p>PREPARED BY: A. Regosz</p>																		
<p>EXPERIMENTAL VALUES:</p> <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th colspan="3" style="text-align: center;">Solubility</th> </tr> <tr> <th style="text-align: left;">Procaine hydrochloride Added % w/v</th> <th style="text-align: center;"><math>mg\ cm^{-3}</math></th> <th style="text-align: center;"><math>10^4\ mol\ dm^{-3}\ solution^a</math></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">0.5</td> <td style="text-align: center;">0.23</td> <td style="text-align: center;">4.03</td> </tr> <tr> <td style="text-align: center;">1.0</td> <td style="text-align: center;">0.13</td> <td style="text-align: center;">2.28</td> </tr> <tr> <td style="text-align: center;">1.5</td> <td style="text-align: center;">0.11</td> <td style="text-align: center;">1.93</td> </tr> <tr> <td style="text-align: center;">2.0</td> <td style="text-align: center;">0.10</td> <td style="text-align: center;">1.70</td> </tr> </tbody> </table> <p><sup>a</sup> Calculated by compiler</p>		Solubility			Procaine hydrochloride Added % w/v	$mg\ cm^{-3}$	$10^4\ mol\ dm^{-3}\ solution^a$	0.5	0.23	4.03	1.0	0.13	2.28	1.5	0.11	1.93	2.0	0.10	1.70
Solubility																			
Procaine hydrochloride Added % w/v	$mg\ cm^{-3}$	$10^4\ mol\ dm^{-3}\ solution^a$																	
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<p>AUXILIARY INFORMATION</p>																			
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Suspensions of procaine penicillin G were agitated in vehicles containing 10% w/v Sodium citrate, 0.2% w/v citric acid, 40% w/v sorbitol, 40% w/v sucrose and variable amounts of procaine.HCl for 16 hours at room temperature (<math>25 \pm 2^\circ C</math>), then were filtered using a medium porosity glass filter. The filtrates were diluted and the content of antibiotic assayed microbiologically (1).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was of U.S.P. grade; its source was not described.</p> <p>Sources and purities of procaine.HCl, citric acid, sodium citrate, sorbitol and sucrose were not specified. Water was distilled.</p> <p>ESTIMATED ERROR: Solubility precision: none specified Temperature precision: <math>\pm 2^\circ C</math> (authors).</p> <p>REFERENCES: (1) "Compilation of Regulations for Tests and Methods of Assay and Certification of Antibiotics and Antibiotic-Containing Drugs", U.S. Department of Health, Education and Welfare, Food and Drug Administration, Section 141 a.1, page A-1.</p>																		

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino) ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4S \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) 1,2,3-Propanetricarboxylic acid, 2-hydroxy- (citric acid); <math>C_6H_8O_7</math>; [77-92-9]</p> <p>(3) 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, trisodium salt (sodium citrate); <math>C_6H_5Na_3O_7</math>; [68-04-2]</p> <p>(4) Butanedioic acid, 2,3-dihydroxy-, disodium salt (L-(+)-sodium tartrate); <math>C_4H_4Na_2O_6</math>; [868-18-8]</p> <p>(5) D-Glucitol (D-Sorbitol); <math>C_6H_{14}O_6</math>; [50-70-4]</p> <p>(6) <math>\alpha</math>-D-Glucopyranoside, <math>\beta</math>-D-fructofuranosyl (Sucrose); <math>C_{12}H_{22}O_{11}</math>; [57-50-1]</p> <p>(7) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. J. Am. Pharm. Assoc. <u>1956</u>, 45, 34-40.</p>
<p>VARIABLES:</p> <p>One temperature: 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of procaine penicillin G in aqueous solution at <math>25 \pm 2^\circ\text{C}</math> containing 10% w/v sodium citrate, 5% w/v sodium tartrate, 0.25% w/v citric acid, 40% w/v sorbitol and 40% w/v sucrose was reported as:</p> <p style="text-align: center;"><math>0.9 \text{ mg cm}^{-3}</math>. (<math>1.6 \times 10^{-3} \text{ mol dm}^{-3}</math> - compiler).</p>	
<p style="text-align: center;">AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Suspensions of procaine penicillin G were agitated in vehicles containing 10% w/v Sodium citrate, 5% w/v sodium tartrate, 0.25% citric acid, 40% w/v sorbitol and 40% w/v sucrose for 16 hours at room temperature (<math>25 \pm 2^\circ\text{C}</math>), then were filtered using a medium porosity glass filter. The filtrates were diluted and the content of antibiotic determined spectrophotometrically.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was of U.S.P. grade; its source was not described.</p> <p>Sources and purities of citric acid, sodium citrate, sorbitol and sucrose were not specified. Sodium tartrate was dextrorotatory. Water was distilled.</p>
	<p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 2^\circ\text{C}</math> (authors).</p>
	<p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino) ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4S \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) Benzoic acid, 4-amino-2-(diethyl-amino) ethyl ester, monohydrochloride (procaine hydrochloride); <math>C_{13}H_{20}N_2O_2 \cdot HCl</math>; [59-46-1]</p> <p>(3) 1,2,3-Propanetricarboxylic acid, 2-hydroxy- (citric acid); <math>C_6H_8O_7</math>; [77-92-9]</p> <p>(4) 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, trisodium salt (sodium citrate); <math>C_6H_5Na_3O_7</math>; [68-04-2]</p> <p>(5) D-Glucitol (D-Sorbitol); <math>C_6H_{14}O_6</math>; [50-70-4]</p> <p>(6) D-Gluconic acid, monoosodium salt (sodium gluconate); <math>C_6H_{11}NaO_7</math>; [527-07-1]</p> <p>(7) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. <i>J. Am. Pharm. Assoc.</i> <u>1956</u>, <i>45</i>, 34-40.</p>
<p>VARIABLES:</p> <p>One temperature: 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of procaine penicillin G in aqueous solution at <math>25 \pm 2^\circ C</math> containing 10% w/v sodium citrate, 0.2% w/v citric acid, 2% w/v procaine.HCl, 40% w/v sorbitol and 25% w/v sodium gluconate was reported as:</p> <p style="text-align: center;"><math>0.036 \text{ mg cm}^{-3}</math>. (<math>6.31 \times 10^{-5} \text{ mol dm}^{-3}</math> - compiler).</p>	
<p style="text-align: center;">AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Suspensions of procaine penicillin G were agitated in vehicles containing 10% w/v sodium citrate, 0.2% w/v citric acid, 2% w/v procaine HCl, 40% w/v sorbitol and 25% w/v sodium gluconate for 16 hours at room temperature (<math>25 \pm 2^\circ C</math>), then were filtered using a medium porosity glass filter. The filtrates were diluted and the content of antibiotic assayed microbiologically (1).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was of U.S.P. grade; its source was not described.</p> <p>Sources and purities of procaine.HCl, citric acid, sodium citrate, sorbitol and sodium gluconate were not specified. Water was distilled.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 2^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) "Compilation of Regulations for Tests and Methods of Assay and Certification of Antibiotics and Antibiotic-Containing Drugs", U.S. Department of Health, Education and Welfare, Food and Drug Administration, Section 141 a.1, page A-1.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino) ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4 \cdot S \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) Benzoic acid, 4-amino-2-(diethyl-amino) ethyl ester, monohydrochloride (procaine hydrochloride); <math>C_{13}H_{20}N_2O_2 \cdot HCl</math>; [59-46-1]</p> <p>(3) 1,2,3-Propanetricarboxylic acid, 2-hydroxy-(citric acid); <math>C_6H_8O_7</math>; [77-92-9]</p> <p>(4) 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, trisodium salt (sodium citrate); <math>C_6H_5Na_3O_7</math>; [68-04-2]</p> <p>(5) D-Glucitol (D-Sorbitol); <math>C_6H_{14}O_6</math>; [50-70-4]</p> <p>(6) <math>\alpha</math>-D-Glucopyranoside, <math>\beta</math>-D-fructofuranosyl (Sucrose); <math>C_{12}H_{22}O_{11}</math>; [57-50-1]</p> <p>(7) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Swintosky, J.V.; Rosen, E.; Robinson, M.J.; Chamberlain, R.E.; Guarini, J.R. <i>J. Am. Pharm. Assoc.</i> <u>1956</u>, <u>45</u>,</p>																								
<p>VARIABLES:</p> <p>Temperature</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>																								
<p>EXPERIMENTAL VALUES:</p> <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th colspan="4" style="text-align: center;">Solubility</th> </tr> <tr> <th style="text-align: center;"><math>t/^\circ C</math></th> <th style="text-align: center;">Units <math>cm^{-3}{}^b</math></th> <th style="text-align: center;"><math>mg\ cm^{-3}{}^a</math></th> <th style="text-align: center;"><math>10^4\ mol\ dm^{-3}{}^a</math></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">25</td> <td style="text-align: center;">97</td> <td style="text-align: center;">0.10</td> <td style="text-align: center;">1.68</td> </tr> <tr> <td style="text-align: center;">37</td> <td style="text-align: center;">136</td> <td style="text-align: center;">0.14</td> <td style="text-align: center;">2.36</td> </tr> <tr> <td style="text-align: center;">43</td> <td style="text-align: center;">230</td> <td style="text-align: center;">0.23</td> <td style="text-align: center;">3.99</td> </tr> <tr> <td style="text-align: center;">54</td> <td style="text-align: center;">560</td> <td style="text-align: center;">0.56</td> <td style="text-align: center;">9.72</td> </tr> </tbody> </table> <p><sup>a</sup> Calculated by compiler</p> <p><sup>b</sup> According to U.S.P. one mg of procaine penicillin G represents 1009 penicillin units - (compiler).</p>		Solubility				$t/^\circ C$	Units $cm^{-3}{}^b$	$mg\ cm^{-3}{}^a$	$10^4\ mol\ dm^{-3}{}^a$	25	97	0.10	1.68	37	136	0.14	2.36	43	230	0.23	3.99	54	560	0.56	9.72
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$t/^\circ C$	Units $cm^{-3}{}^b$	$mg\ cm^{-3}{}^a$	$10^4\ mol\ dm^{-3}{}^a$																						
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<p>AUXILIARY INFORMATION</p>																									
<p>METHOD APPARATUS/PROCEDURE:</p> <p>An aqueous vehicle of pH 6.1 containing 2.0% w/v of procaine HCl, 10% w/v of sodium citrate, 0.20% w/v of citric acid, 40% w/v of sorbitol and 40% of sucrose was prepared. Suspension of procaine penicillin G in this vehicle were maintained at 37°C, 43°C and 54°C (<math>\pm 0.1</math>) for 16 hours with constant agitation. They were then filtered through a medium porosity sintered glass filter. The penicillin content of these solutions was determined microbiologically (1).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was of U.S.P. grade; its source was not described.</p> <p>Sources and purities of procaine HCl, citric acid, sodium citrate, sorbitol and sucrose were not specified. Water was distilled.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 0.1^\circ C</math> (authors).</p> <p>REFERENCES.</p> <p>(1) "Compilation of Regulations for Tests and Methods of Assay and Certification of Antibiotics and Antibiotic-Containing Drugs", U.S. Department of Health, Education and Welfare, Food and Drug Administration, Section 141 a.1, page A-1.</p>																								

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino) ethyl-4-aminobenzoate(1:1) (procaine penicillin G); $C_{16}H_{18}N_2O_4S \cdot C_{13}H_{20}N_2O_2$ ; [54-35-3] (2) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of procaine penicillin G in water at <math>28 \pm 4^\circ C</math> was reported as:  <math>6.8 \text{ mg cm}^{-3}</math>. (<math>1.2 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD / APPARATUS / PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a 15 $\text{cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $28 \pm 4^\circ C$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 $\text{cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ C$ . The residue was further dried for 3 hr at $60^\circ C$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b>  Procaine penicillin G was a pooled commercial product of high purity (95 to 100%).  Water was of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 4^\circ C$ (authors).  <b>REFERENCES:</b>

## COMPONENTS:

(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,3,-dimethyl-7-oxo-6-[(phenylacetyl)amino] complexed with 2-(diethylamino)ethyl-4-aminobenzoate (1:1) (procaine penicillin G);  $C_{16}H_{18}N_2O_4S.C_{13}H_{20}N_2O_2$ ; [54-35-3]

(2) All non aqueous solvents.

## EVALUATOR:

Eric Tomlinson,  
Department of Pharmacy,  
University of Amsterdam,  
The Netherlands.

December 1983

## CRITICAL EVALUATION:

Values for the solubility of procaine penicillin G in 23 non aqueous solvents at  $301 \pm 4$  K have been reported by Weiss et al (1). These workers used a pooled commercial sample of high purity (95-100%). The amount of penicillin dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than  $20 \text{ mg cm}^{-3}$ . All values reported were uncorrected for solvent blank, which was generally less than 0.05 mg total. All data according to Weiss et al have been recalculated to SI units (compiler), and are given in the Table.

Solvent	Solubility <sub>3</sub> (at $301 \pm 4$ K) ( $\text{mol dm}^{-3}$ )	
methanol	a	
ethanol	a	
isopropanol	$1.1 \times 10^{-2}$	
isoamyl alcohol	$4.6 \times 10^{-3}$	
cyclohexane	$1.3 \times 10^{-4}$	
benzene	$1.3 \times 10^{-3}$	
toluene	$1.84 \times 10^{-3}$	
ligroin	$2.1 \times 10^{-4}$	
isooctane	0	
carbon tetrachloride	$2.10 \times 10^{-4}$	
ethyl acetate	$5.87 \times 10^{-3}$	( <sup>a</sup> solubility greater than $3.5 \times 10^{-2} \text{ mol dm}^{-3}$ )
isoamyl acetate	$2.1 \times 10^{-3}$	
acetone	$2.62 \times 10^{-2}$	
methyl ethyl ketone	$2.40 \times 10^{-2}$	
diethylether	$1.05 \times 10^{-3}$	
ethylene chloride	$3.5 \times 10^{-3}$	
1,4-dioxane	$1.7 \times 10^{-2}$	
chloroform	a	
carbon disulfide	$8.9 \times 10^{-4}$	
pyridine	a	
formamide	a	
ethylene glycol	a	
benzyl alcohol	a	

(All solvents are U.S.P. or A.C.S. grade)

All these values have an estimated precision of  $\pm 5\%$  (evaluator). However they are unconfirmed findings, and must be designated as tentative, except for (i) where the solubility is reported as being greater than  $3.5 \times 10^{-2} \text{ mol dm}^{-3}$ , (which are regarded as doubtful), and (ii) the value for solubility in isooctane, (which is rejected since the assay procedure used is not sufficiently sensitive for this value to have any meaning).

## REFERENCE

(1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* 1957, 7, 374.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino)ethyl-4-aminobenzoate(1:1) (procaine penicillin G); $C_{16}H_{18}N_2O_4 \cdot S \cdot C_{13}H_{20}N_2O_2$ ; [54-35-3] (2) Methanol; $CH_4O$ ; [67-56-1]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of procaine penicillin G in methanol at $28 \pm 4^\circ C$ was reported as greater than: $20 \text{ mg cm}^{-3}$ . (Greater than $3.5 \times 10^{-2} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ C$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b> Procaine penicillin G was a pooled commercial product of high purity (95 to 100%). Methanol was of A.C.S. or U.S.P. grade.
	<b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 4^\circ C$ (authors).
	<b>REFERENCES:</b>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino) ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4 \cdot S \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) Ethanol; <math>C_2H_6O</math>; [64-17-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of procaine penicillin G in ethanol at <math>28 \pm 4^\circ\text{C}</math> was reported as greater than: <math>20 \text{ gm cm}^{-3}</math>. (Greater than <math>3.5 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ\text{C}</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was a pooled commercial product of high purity (95 to 100%).</p> <p>Ethanol was of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified</p> <p>Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino)ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4 \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) 2-Propanol (isopropanol); <math>C_3H_8O</math>; [67-63-0]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of procaine penicillin G in isopropanol at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>6.5 \text{ mg cm}^{-3}</math>. (<math>1.1 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was a pooled commercial product of high purity (95 to 100%).</p> <p>Isopropanol was of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino)ethyl-4-aminobenzoate(1:1) (procaine penicillin G); $C_{16}H_{18}N_2O_4 \cdot S \cdot C_{13}H_{20}N_2O_2$ ; [54-35-3] (2) Cyclohexane; $C_6H_{12}$ ; [110-82-7]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of procaine penicillin G in cyclohexane at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.08 \text{ mg cm}^{-3}</math>. (<math>1.3 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Procaine penicillin G was a pooled commercial product of high purity (95 to 100%).          Cyclohexane was of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <b>REFERENCES.</b>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino) ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4 \cdot S \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) Benzene; <math>C_6H_6</math>; [71-43-2]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> 1957, 7, 374-7.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of procaine penicillin G in benzene at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.08 \text{ mg cm}^{-3}</math>. (<math>1.3 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was a pooled commercial product of high purity (95 to 100%).</p> <p>Benzene was of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p>



<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino)ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4 \cdot S \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) Petroleum ether (ligroin)</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> 1957, 7, 374-7.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of procaine penicillin G in ligroin at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.12 \text{ mg cm}^{-3}</math>. (<math>2.1 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was a pooled commercial product of high purity (95 to 100%).</p> <p>Ligroin was of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino) ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4 \cdot S \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) Pentane, 2,2,4-trimethyl- (isooctane); <math>C_8H_{18}</math>; [540-84-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of procaine penicillin G in isooctane at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.0 \text{ mg cm}^{-3}</math>. (<math>0.0 \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was a pooled commercial product of high purity (95 to 100%).</p> <p>Isooctane was of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino) ethyl-4-aminobenzoate(1:1) (procaine penicillin G); $C_{16}H_{18}N_2O_4S \cdot C_{13}H_{20}N_2O_2$ ; [54-35-3] (2) Acetic acid, ethyl ester (ethyl acetate); $C_4H_8O_2$ ; [141-78-6]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of procaine penicillin G in ethyl acetate at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>3.35 \text{ mg cm}^{-3}</math>. (<math>5.87 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Procaine penicillin G was a pooled commercial product of high purity (95 to 100%).           Ethyl acetate was used of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b>





<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino) ethyl-4-aminobenzoate(1:1) (procaine penicillin G); $C_{16}H_{18}N_2O_4S \cdot C_{13}H_{20}N_2O_2$ ; [54-35-3] (2) 2-Butanone; $C_4H_8O$ ; [78-93-3]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of procaine penicillin G in 2-butanone at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>13.7 \text{ mg cm}^{-3}</math>. (<math>2.4 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Procaine penicillin G was a pooled commercial product of high purity (95 to 100%).          2-Butanone was of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b>













<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] compd with 2(diethylamino)ethyl-4-aminobenzoate(1:1) (procaine penicillin G); <math>C_{16}H_{18}N_2O_4 \cdot S \cdot C_{13}H_{20}N_2O_2</math>; [54-35-3]</p> <p>(2) Formamide; <math>CH_3NO</math>; [75-12-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of procaine penicillin G in formamide at <math>28 \pm 4^\circ C</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>3.5 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Procaine penicillin G was a pooled commercial product of high purity (95 to 100%).</p> <p>Formamide was of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 4^\circ C</math> (authors).</p>
	<p>REFERENCES.</p>





## COMPONENTS:

(1) 4-Thia -1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, complexed with (-)-2-(methylamino)-1,2-diphenylethanol (1:1) (1-ephenamine penicillin G);  $C_{16}H_{18}N_2O_4S \cdot C_{15}H_{17}NO$ ; [7177-43-7]

(2) All solvents

## EVALUATOR:

Eric Tomlinson.  
Department of Pharmacy,  
University of Amsterdam,  
The Netherlands.

December 1983.

## CRITICAL EVALUATION:

Values for the solubility of 1-ephenamine penicillin G in 24 different solvents at  $301 \pm 4$  K have been reported by Weiss et al (1). These workers used a pooled commercial sample of high purity (95-100%). The amount of penicillin dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than  $20 \text{ mg cm}^{-3}$ . All values reported were uncorrected for solvent blank, which was generally less than 0.05 mg total. All data according to Weiss et al have been recalculated to SI units (compiler), and are given in the Table.

Solvent	Solubility <sub>2,3</sub> (at $301 \pm 4$ K) ( $\text{mol dm}^{-3}$ )
water	$2.1 \times 10^{-3}$
methanol	$3.5 \times 10^{-2}$
ethanol	$4.4 \times 10^{-3}$
isopropanol	$8.0 \times 10^{-4}$
isoamyl alcohol	$1.8 \times 10^{-4}$
cyclohexane	$1.5 \times 10^{-4}$
benzene	$2.1 \times 10^{-4}$
toluene	$1.5 \times 10^{-4}$
ligroin	0
isooctane	$5.7 \times 10^{-5}$
carbon tetrachloride	$2.2 \times 10^{-4}$
ethyl acetate	$1.4 \times 10^{-4}$
isoamyl acetate	$4.6 \times 10^{-4}$
acetone	$1.3 \times 10^{-3}$
methyl ethyl ketone	$1.5 \times 10^{-3}$
diethylether	$8.6 \times 10^{-3}$
ethylene chloride	$1.3 \times 10^{-3}$
1,4-dioxane	$8.1 \times 10^{-3}$
chloroform	$2.8 \times 10^{-3}$
carbon disulfide	$1.2 \times 10^{-4}$
pyridine	a
formamide	a
ethylene glycol	$1.6 \times 10^{-2}$
benzyl alcohol	$1.8 \times 10^{-2}$

(<sup>a</sup> solubility greater than  $3.6 \times 10^{-2} \text{ mol dm}^{-3}$ )

(All solvents are U.S.P. or A.C.S. grade)

All these values have an estimated precision of  $\pm 5\%$  (evaluator). However they are unconfirmed findings, and must be designated as **tentative**, except for (i) where the solubility is reported as being greater than  $3.6 \times 10^{-2} \text{ mol dm}^{-3}$ , (which are regarded as **doubtful**), and (ii) the value for solubility in ligroin, (which is **rejected** since the assay procedure used is not sufficiently sensitive for this value to have any meaning).

## REFERENCE

(1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* 1957, 7, 374.











<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, compd with (-)-2-(methylamino)-1,2-diphenylethanol (1:1) (l-ephenamine penicillin G); $C_{16}H_{18}N_2O_4S \cdot C_{15}H_{17}NO$ ; [7177-43-7] (2) Cyclohexane; $C_6H_{12}$ ; [110-82-7]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of l-ephenamine penicillin G in cyclohexane at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.085 \text{ mg cm}^{-3}</math>. (<math>1.5 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>l-Ephenamine penicillin G was a pooled commercial product of high purity (95 to 100%).          Cyclohexane was of A.C.S. or U.S.P. grade.</p>
	<b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).
	<b>REFERENCES:</b>





<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, compd with (-)-2-(methylamino)-1,2-diphenylethanol (1:1)(1-ephenamine penicillin G); $C_{16}H_{18}N_2O_4S \cdot C_{15}H_{17}NO$ ; [7177-43-7] (2) Petroleum ether (Ilgroin)	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright W.W. <i>Antibiotics and Chemotherapy</i> 1957, 7, 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of 1-ephenamine penicillin G in Ilgroin at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.0 \text{ mg cm}^{-3}</math>. (<math>0.0 \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>1-Ephenamine penicillin G was a pooled commercial product of high purity (95 to 100%).          Ilgroin was of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).  <b>REFERENCES:</b>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, compd with (-)-2-(methylamino)-1,2-diphenylethanol (1:1)(1-ephenamine penicillin G); $C_{16}H_{18}N_2O_4S \cdot C_{15}H_{17}NO$ ; [7177-43-7] (2) Pentane, 2,2,4,-trimethyl- (isooctane); $C_8H_{18}$ ; [540-84-1]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright W.W. <b>Antibiotics and Chemotherapy</b> <u>1957</u> , 7, 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of 1-ephenamine penicillin G in isooctane at <math>28 \pm 4^\circ C</math> was reported as:  <math>0.032 \text{ mg cm}^{-3}</math>. (<math>5.7 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $28 \pm 4^\circ C$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ C$ . The residue was further dried for 3 hr at $60^\circ C$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b>  1-Ephenamine penicillin G was a pooled commercial product of high purity (95 to 100%).  Isooctane was of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ C$ (authors).  <b>REFERENCES:</b>





















<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, compd with (-)-2-(methylamino)-1,2-diphenylethanol (1:1) (1-ephenamine penicillin G); $C_{16}H_{18}N_2O_4S \cdot C_{15}H_{17}NO$ ; [7177-43-7] (2) Pyridine; $C_5H_5N$ ; [110-86-1]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of 1-ephenamine penicillin G in pyridine at <math>28 \pm 4^\circ C</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>3.6 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $28 \pm 4^\circ C$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b>  1-Ephenamine penicillin G was a pooled commercial product of high purity (95 to 100%).  Pyridine was of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ C$ (authors).  <b>REFERENCES:</b>







<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, complexed with 1-(p-chlorobenzyl)-2-(1-pyrrolidinylmethyl) benzimidazole (1:1) (clemizole penicillin G); $C_{16}H_{18}N_2O_4 \cdot C_{19}H_{20}ClN_3$ ; [6011-39-8] (2) Allsolvents	<b>EVALUATOR:</b> Eric Tomlinson. Department of Pharmacy, University of Amsterdam, The Netherlands. December 1983
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**CRITICAL EVALUATION:**

The solubilities of clemizole penicillin G in 24 different solvents at  $294 \pm 1$  K have been reported by Marsh et al (1). These workers used a sample of penicillin provided by Pfizer Inc. (one of the largest producers of the solute at that time). The amount of penicillin dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than  $20 \text{ mg cm}^{-3}$ . All values reported were uncorrected for solvent blank, which was generally less than  $0.05 \text{ mg total}$ . All data according to Marsh et al have been recalculated to SI units (compiler), and are given in the Table.

Solvent	Solubility <sub>23</sub> (at $294 \pm 1$ K) ( $\text{mol dm}^{-3}$ )	
water	$1.80 \times 10^{-3}$	
methanol	a	
ethanol	a	
isopropanol	$8.65 \times 10^{-3}$	
isoamyl alcohol	$1.24 \times 10^{-2}$	
cyclohexane	$8.56 \times 10^{-4}$	
benzene	$4.87 \times 10^{-3}$	
ligroin	$9.01 \times 10^{-4}$	
isooctane	$1.01 \times 10^{-3}$	
carbon tetrachloride	$1.69 \times 10^{-3}$	
ethyl acetate	$6.89 \times 10^{-3}$	( <sup>a</sup> solubility greater than $3.0 \times 10^{-2} \text{ mol dm}^{-3}$ )
isoamyl acetate	$3.65 \times 10^{-2}$	
acetone	$1.82 \times 10^{-2}$	
methyl ethyl ketone	$1.45 \times 10^{-2}$	
diethylether	$2.70 \times 10^{-3}$	
ethylene chloride	a	
1,4-dioxane	a	
chloroform	a	
carbon disulfide	$2.42 \times 10^{-3}$	
pyridine	a	
formamide	a	
ethylene glycol	a	
propylene glycol	$2.01 \times 10^{-2}$	
dimethyl sulfoxide	a	

(All solvents are probably of U.S.P. or A.C.S. grade as in previous studies by this group (ref. 2)).

All these values have an estimated precision of  $\pm 5\%$  (evaluator). However they are unconfirmed findings and have been determined for a sample of unstated purity. Normally these data should be rejected, however consideration of the previous publications from this group (2), and the fact that the supplier of the sample is a highly reputable drug company, allows these values to be regarded as **highly tentative**, except for where the solubility is reported as being greater than  $3.0 \times 10^{-2} \text{ mol dm}^{-3}$ , (which are regarded as being **doubtful**).

The authors report an increase in solubility of clemizole penicillin G in acid (0.1 N HCl) and in alkali (0.1 N NaOH) to  $1.86 \times 10^{-2} \text{ mol dm}^{-3}$  and  $2.45 \times 10^{-2} \text{ mol dm}^{-3}$ , respectively. This is in line with the ampholytic nature of clemizole penicillin G, and these latter values are also designated as being **tentative**. (The value in 0.1 N NaOH was corrected for a solvent blank of 0.58 mg (total) by the authors - it was not found necessary to do so for the acid solution where the blank value was less than 0.5 % of the total weight found).

**REFERENCES**

- (1) Marsh, J.R.; Weiss, P.J.; *J. Ass. Offic. Anal. Chem.* **1967**, *50*, 457.
- (2) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* **1957**, *7*, 374.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, compd with 1-(p-chlorobenzyl)-2-(1-pyrrolidinylmethyl) benzimidazole(1:1) clemizole penicillin G; $C_{16}H_{18}N_2O_4S \cdot C_{19}H_{20}ClN_3$ ; [6011-39-8] (2) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of clemizole penicillin G in water at <math>21 \pm 1^\circ C</math> was reported as:  <math>1.19 \text{ mg cm}^{-3}</math>. (<math>1.80 \times 10^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube. The tube was thoroughly shaken by hand for about 2 minutes at room temperature (<math>21 \pm 1^\circ C</math>). If any insoluble material was visible, the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel, and the clear filtrate was collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ C</math>. The residue was further dried for 3 hours at <math>60^\circ C</math> in a vacuum oven. After cooling, the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Clemizole penicillin G was provided by Pfizer Inc. Its purity was not specified.</p> <p>Water was probably of U.S.P. grade (1).</p>
	<b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p>
	<b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, compd with 1-(p-chlorobenzyl)-2-(1-pyrrolidinylmethyl) benzimidazole(1:1) clemizole penicillin G; $C_{16}H_{18}N_2O_4S.C_{19}H_{20}ClN_3$ ; [6011-39-8] (2) Hydrochloric acid; HCl; [7647-01-0] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. 1967, 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of clemizole penicillin G in 0.1 N hydrochloric acid at <math>21 \pm 1^\circ C</math> was reported as:  <math>12.26 \text{ mg cm}^{-3}</math>. (<math>1.86 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube. The tube was thoroughly shaken by hand for about 2 minutes at room temperature (<math>21 \pm 1^\circ C</math>). If any insoluble material was visible, the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel, and the clear filtrate was collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ C</math>. The residue was further dried for 3 hours at <math>60^\circ C</math> in a vacuum oven. After cooling, the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Clemizole penicillin G was provided by Pfizer Inc. Its purity was not specified.</p> <p>The purity of hydrochloric acid was not specified.</p> <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, compd with 1-(p-chlorobenzyl)-2-(1-pyrrolidinylmethyl) benzimidazole(1:1) clemizole penicillin G; $C_{16}H_{18}N_2O_4S.C_{19}H_{20}ClN_3$ ; [6011-39-8] (2) Sodium hydroxide; NaOH; [1310-73-2] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. 1967, 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of clemizole penicillin G in 0.1 N sodium hydroxide at <math>21 \pm 1^\circ C</math> was reported as:  <math>16.14 \text{ mg cm}^{-3}</math>. (<math>2.45 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube. The tube was thoroughly shaken by hand for about 2 minutes at room temperature (<math>21 \pm 1^\circ C</math>). If any insoluble material was visible, the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel, and the clear filtrate was collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ C</math>. The residue was further dried for 3 hours at <math>60^\circ C</math> in a vacuum oven. After cooling, the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Clemizole penicillin G was provided by Pfizer Inc. Its purity was not specified.</p> <p>The purity of sodium hydroxide and water were not specified.</p> <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b>





















<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, compd with 1-(p-chlorobenzyl)-2-(1-pyrrolidinylmethyl) benzimidazole(1:1) clemizole penicillin G; $C_{16}H_{18}N_2O_4S.C_{19}H_{20}ClN_3$ ; [6011-39-8] (2) 1-Butanol, 3-methyl acetate (isoamyl acetate); $C_7H_{14}O_2$ ; [123-92-2]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u> , 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of clemizole penicillin G in isoamyl acetate at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>2.41 \text{ mg cm}^{-3}</math>. (<math>3.65 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube. The tube was thoroughly shaken by hand for about 2 minutes at room temperature (<math>21 \pm 1^\circ\text{C}</math>). If any insoluble material was visible, the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel, and the clear filtrate was collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hours at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Clemizole penicillin G was provided by Pfizer Inc. Its purity was not specified.</p> <p>Isoamyl acetate was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p>
	<b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <u>Antibiotics and Chemotherapy</u> 1957, 7, 374

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, compd with 1-(p-chlorobenzyl)-2-(1-pyrrolidinylmethyl) benzimidazole(1:1) clemizole penicillin G; $C_{16}H_{18}N_2O_4S \cdot C_{19}H_{20}ClN_3$ ; [6011-39-8] (2) 2-Propanone (acetone); $C_3H_6O$ ; [67-64-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of clemizole penicillin G in acetone at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>11.99 \text{ mg cm}^{-3}</math>. (<math>1.82 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube. The tube was thoroughly shaken by hand for about 2 minutes at room temperature (<math>21 \pm 1^\circ\text{C}</math>). If any insoluble material was visible, the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel, and the clear filtrate was collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hours at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Clemizole penicillin G was provided by Pfizer Inc. Its purity was not specified.</p> <p>Acetone was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b>  <p>Solubility: None specified.          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <i>7</i> , 374

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, compd with 1-(p-chlorobenzyl)-2-(1-pyrrolidinylmethyl) benzimidazole(1:1) clemizole penicillin G; $C_{16}H_{18}N_2O_4S \cdot C_{19}H_{20}ClN_3$ ; [6011-39-8] (2) 2-Butanone (methyl ethyl ketone); $C_4H_8O$ ; [78-93-3]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u> , 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of clemizole penicillin G in methyl ethyl ketone at <math>21 \pm 1^\circ C</math> was reported as:  <math>9.58 \text{ mg cm}^{-3}</math>. (<math>1.45 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube. The tube was thoroughly shaken by hand for about 2 minutes at room temperature (<math>21 \pm 1^\circ C</math>). If any insoluble material was visible, the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel, and the clear filtrate was collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ C</math>. The residue was further dried for 3 hours at <math>60^\circ C</math> in a vacuum oven. After cooling, the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Clemizole penicillin G was provided by Pfizer Inc. Its purity was not specified.</p> <p>Methyl ethyl ketone was probably of A.C.S. or U.S.P. grade (1).</p> <hr/> <b>ESTIMATED ERROR:</b>  <p>Solubility: None specified.          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <hr/> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <u>Antibiotics and Chemotherapy</u> <u>1957</u>, 7, 374</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, compd with 1-(p-chlorobenzyl)-2-(1-pyrrolidinylmethyl) benzimidazole(1:1) clemizole penicillin G; $C_{16}H_{18}N_2O_4S \cdot C_{19}H_{20}ClN_3$ ; [6011-39-8] (2) Ethane, 1,1'-oxybis- (diethyl ether); $C_4H_{10}O$ ; [60-29-7]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u> , 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of clemizole penicillin G in diethyl ether at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>1.79 \text{ mg cm}^{-3}</math>. (<math>2.70 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube. The tube was thoroughly shaken by hand for about 2 minutes at room temperature ( $21 \pm 1^\circ\text{C}$ ). If any insoluble material was visible, the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel, and the clear filtrate was collected in a test tube. Four $\text{cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle and evaporated by heating at $100^\circ\text{C}$ . The residue was further dried for 3 hours at $60^\circ\text{C}$ in a vacuum oven. After cooling, the bottle was reweighed ( $\pm 0.01 \text{ mg}$ ).	<b>SOURCE AND PURITY OF MATERIALS:</b>  Clemizole penicillin G was provided by Pfizer Inc. Its purity was not specified.  Diethyl ether was probably of A.C.S. or U.S.P. grade (1).  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 1^\circ\text{C}$ (authors).
	<b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374







<p><b>COMPONENTS:</b></p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, compd with 1-(p-chlorobenzyl)-2-(1-pyrrolidinylmethyl) benzimidazole(1:1) clemizole penicillin G; <math>C_{16}H_{18}N_2O_4S.C_{19}H_{20}ClN_3</math>; [6011-39-8]</p> <p>(2) Carbon disulfide; <math>CS_2</math> [75-15-0]</p>	<p><b>ORIGINAL MEASUREMENTS:</b></p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p><b>VARIABLES:</b></p> <p>One temperature: 21°C</p>	<p><b>PREPARED BY:</b></p> <p>A. Regosz</p>
<p><b>EXPERIMENTAL VALUES:</b></p> <p>Solubility of clemizole penicillin G in carbon disulfide at <math>21 \pm 1^\circ C</math> was reported as:  <math>1.60 \text{ mg cm}^{-3}</math>. (<math>2.42 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p style="text-align: center;"><b>AUXILIARY INFORMATION</b></p>	
<p><b>METHOD/APPARATUS/PROCEDURE:</b></p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube. The tube was thoroughly shaken by hand for about 2 minutes at room temperature (<math>21 \pm 1^\circ C</math>). If any insoluble material was visible, the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel, and the clear filtrate was collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ C</math>. The residue was further dried for 3 hours at <math>60^\circ C</math> in a vacuum oven. After cooling, the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<p><b>SOURCE AND PURITY OF MATERIALS:</b></p> <p>Clemizole penicillin G was provided by Pfizer Inc. Its purity was not specified.</p> <p>Carbon disulfide was probably of A.C.S. or U.S.P. grade (1).</p> <p><b>ESTIMATED ERROR:</b></p> <p>Solubility: None specified.  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p><b>REFERENCES:</b></p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374</p>





<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, compd with 1-(p-chlorobenzyl)-2-(1-pyrrolidinylmethyl) benzimidazole(1:1) clemizole penicillin G; $C_{16}H_{18}N_2O_4S \cdot C_{19}H_{20}ClN_3$ ; [6011-39-8] (2) 1,2-Ethanediol (ethylene glycol); $C_2H_6O_2$ ; [107-21-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u> , 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of clemizole penicillin G in ethylene glycol at <math>21 \pm 1^\circ\text{C}</math> is greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>3.0 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the test sample in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 minutes at room temp ( $21 \pm 1^\circ\text{C}$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b>  Clemizole penicillin G was provided by Pfizer Inc. Its purity was not specified.  Ethylene glycol was probably of A.C.S. or U.S.P. grade (1).  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 1^\circ\text{C}$ (authors).  <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <u>Antibiotics and Chemotherapy</u> <u>1957</u> , 7, 374

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, compd with 1-(p-chlorobenzyl)-2-(1-pyrrolidinylmethyl) benzimidazole(1:1) clemizole penicillin G; $C_{16}H_{18}N_2O_4S \cdot C_{19}H_{20}ClN_3$ ; [6011-39-8] (2) 1,2-Propanediol (propylene glycol); $C_3H_8O_2$ ; [57-55-6]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of clemizole penicillin G in propylene glycol at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>13.28 \text{ mg cm}^{-3}</math>. (<math>2.01 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube. The tube was thoroughly shaken by hand for about 2 minutes at room temperature (<math>21 \pm 1^\circ\text{C}</math>). If any insoluble material was visible, the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel, and the clear filtrate was collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hours at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Clemizole penicillin G was provided by Pfizer Inc. Its purity was not specified.</p> <p>Propylene glycol was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <b>7</b> , 374

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, compd with 1-(p-chlorobenzyl)-2-(1-pyrrolidinylmethyl) benzimidazole(1:1) clemizole penicillin G; $C_{16}H_{18}N_2O_4S \cdot C_{19}H_{20}ClN_3$ ; [6011-39-8] (2) Methane,sulfinylbis- (dimethyl sulfoxide); $C_2H_6OS$ ; [67-68-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u> , 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of clemizole penicillin G in dimethyl sulfoxide at <math>21 \pm 1^\circ C</math> is greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>3.0 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the test sample in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 minutes at room temp (<math>21 \pm 1^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Clemizole penicillin G was provided by Pfizer Inc. Its purity was not specified.</p> <p>Dimethyl sulfoxide was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <u>Antibiotics and Chemotherapy</u> <u>1957</u> , 7, 374

COMPONENTS:	EVALUATOR:
(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, compd with N,N'-bis[(1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenyl)methyl]-1,2-ethanediamine (2:1) (hydrabamine penicillin G); $C_{16}H_{18}N_2O_4S \cdot 1/2C_{42}H_{64}N_2$ ; [3344-16-9] (2) All solvents	Eric Tomlinson. Department of Pharmacy, University of Amsterdam, The Netherlands. December 1983
CRITICAL EVALUATION:	
<p>The solubilities of hydrabamine penicillin G in 24 different solvents at <math>301 \pm 4</math> K have been reported by Weiss et al (1). These workers used a pooled commercial product sample of high purity (95 to 100%). The amount of penicillin dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than <math>20 \text{ mg cm}^{-3}</math>. All values reported were uncorrected for solvent blank, which was generally less than <math>0.05 \text{ mg total}</math>. All data according to Weiss et al have been recalculated to SI units (compiler), and are given in the Table.</p>	
Solvent	Solubility (at $301 \pm 4$ K) ( $\text{mol dm}^{-3}$ )
water methanol ethanol isopropanol isoamyl alcohol cyclohexane benzene toluene ligroin isooctane carbon tetrachloride ethyl acetate isoamyl acetate acetone methyl ethyl ketone diethylether ethylene chloride 1,4-dioxane chloroform carbon disulfide pyridine formamide ethylene glycol benzyl alcohol	$1.2 \times 10^{-4}$ $1.1 \times 10^{-2}$ $8.2 \times 10^{-3}$ $2.7 \times 10^{-3}$ $4.9 \times 10^{-3}$ $1.8 \times 10^{-4}$ $9.5 \times 10^{-4}$ $6.2 \times 10^{-4}$ 0 $8.7 \times 10^{-5}$ $7.9 \times 10^{-4}$ $2.6 \times 10^{-3}$ $2.2 \times 10^{-3}$ $5.4 \times 10^{-3}$ $5.8 \times 10^{-3}$ $1.1 \times 10^{-3}$ a $2.3 \times 10^{-2}$ a $2.2 \times 10^{-3}$ a a a a
	( <sup>a</sup> solubility greater than $3.2 \times 10^{-2} \text{ mol dm}^{-3}$ )
(All solvents are of U.S.P. or A.C.S. grade).	
All these values have an estimated precision of $\pm 5\%$ (evaluator). However they are unconfirmed findings and must be designated as being <b>tentative</b> , except for where (i) the solubility is reported as being greater than $3.2 \times 10^{-2} \text{ mol dm}^{-3}$ , (which are regarded as being <b>doubtful</b> ), and (ii) the value for solubility in ligroin, (which is rejected since the assay procedure used is not sufficiently sensitive for this value to have any significance).	
REFERENCE	
(1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> 1957, 7, 374.	













<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, compd with N,N'-bis[(1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenyl)methyl]-1,2-ethanediamine (2:1) (hydrabamine penicillin G); $C_{16}H_{18}N_2O_4S \cdot 1/2C_{42}H_{64}N_2$ ; [3344-16-9] (2) Benzene; $C_6H_6$ ; [71-43-2]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of hydrabamine penicillin G in benzene at <math>28 \pm 4^\circ\text{C}</math> was reported as:</p> <p style="text-align: center;"><math>0.60 \text{ mg cm}^{-3}</math>. (<math>9.48 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent was added to about 200 mg of the antibiotic in a 15 $\text{cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $28 \pm 4^\circ\text{C}$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 $\text{cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ\text{C}$ . The residue was further dried for 3 hr at $60^\circ\text{C}$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b>  Hydrabamine penicillin G was a pooled commercial product of high purity (95 to 100%).  Benzene was of A.C.S. or U.S.P. grade.
	<b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).
	<b>REFERENCES:</b>























<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, compd with N,N'-bis[(1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenyl)methyl]-1,2-ethanediamine (2:1) (hydrabamine penicillin G); $C_{16}H_{18}N_2O_4S \cdot 1/2 C_{42}H_{64}N_2$ ; [3344-16-9] (2) Methane, trichloro- (chloroform); $CHCl_3$ ; [67-66-3]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <b>7</b> , 374-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of hydrabamine penicillin G in chloroform at <math>28 \pm 4^\circ C</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>3.2 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent was added to about 200 mg of the antibiotic in a 15 $\text{cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ C$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg. cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b>  Hydrabamine penicillin G was a pooled commercial product of high purity (95 to 100%).  Chloroform was of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ C$ (authors).  <b>REFERENCES:</b>









<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, compd with N,N'-bis[(1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenyl)methyl]-1,2-ethanediamine (2:1) (hydrabamine penicillin G); $C_{16}H_{18}N_2O_4S \cdot 1/2 C_{42}H_{64}N_2$ ; [3344-16-9] (2) Benzene methanol (benzyl alcohol); $C_7H_8O$ ; [100-51-6]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of hydrabamine penicillin G in benzyl alcohol at <math>28 \pm 4^\circ\text{C}</math> was reported as greater than:</p> <p style="text-align: center;"><math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>3.2 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent was added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ\text{C}$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg. cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b>  Hydrabamine penicillin G was a pooled commercial product of high purity (95 to 100%).  Benzyl alcohol was of A.C.S. or U.S.P. grade.
	<b>ESTIMATED ERROR:</b>  Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).
	<b>REFERENCES:</b>

## COMPONENTS:

(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)-amino]-, complexed with *n,n'*-bis(phenylmethyl)-1,2-ethanediamine (2:1) (benzathine penicillin G);  $C_{32}H_{36}N_4O_8S_2 \cdot C_{16}H_{20}N_2$ ; [1538-09-6]

(2) Water;  $H_2O$ ; [7732-18-5]

## EVALUATOR:

Eric Tomlinson.  
Department of Pharmacy,  
University of Amsterdam,  
The Netherlands.

December 1983.

## CRITICAL EVALUATION:

Three groups have reported on the aqueous solubility of benzathine penicillin G (1-3).

The influence of pH (1.11 to 9.58) and temperature (297 K and 310 K) on the aqueous solubility have been studied by Brunner and Margreiter (1). The amount of penicillin dissolved in the solvent was determined by drying to constant weight. A precision of  $\pm 2\%$  is estimated for all the solubility values reported by these workers, (evaluator). It is not possible to estimate the precision in the reported temperature or pH values, though for the latter it is probably  $\pm 0.02$  pH units. The solubilities of benzathine penicillin G at 297 K and 310 K are reported as  $1.5 \times 10^{-4}$  mol dm $^{-3}$  and  $2.2 \times 10^{-4}$  mol dm $^{-3}$ , respectively. (Values converted to SI units by compiler). The Table gives the aqueous solubility of benzathine penicillin G in water at various pH's and at 297 K and at 310 K (1). From this it is possible to see that the solubility increases sharply in strongly acid solutions, but only slightly in alkaline solutions. Brunner and Margreiter have made a detailed theoretical study concerning the calculation of the solubility of this solute using appropriate acid and base dissociation constants (2). They found good agreement between results obtained experimentally and those obtained by calculation except at 297 K at pH's 1.11 and 1.61, and at 310 K at pH's 1.20 and 2.32, (which could be indicative of degradation effects). Accordingly, all the values given in the Table are designated as being **tentative**, except for those determined at these latter pH values - which are **rejected**. In addition, although benzathine penicillin G was found by the authors to be more stable than benzathine penicillin V, the solubility values above a pH of 8.50 are **doubtful** because of possible instability problems.

Solubility ( $10^4$ mol dm $^{-3}$ ) <sup>a</sup>			
pH <sup>b</sup>	at 297 K	pH <sup>b</sup>	at 310 K
1.11	81.9	1.20	136
1.61	14.9	2.32	9.35
2.30	3.68	2.72	4.01
3.03	1.70	3.05	3.30
7.66	5.00	7.35	12.5
8.41	8.74	8.00	14.1
8.95	14.8	8.50	20.8
9.58	32.7	8.85	35.7

<sup>a</sup> Calculated by compiler; <sup>b</sup> pH altered using either HCl or NaOH).

Weiss et al (3) reported the solubility in water of benzathine penicillin G at 301 $^{\pm}$  K as  $3.46 \times 10^{-4}$  mol dm $^{-3}$  (units - compiler), which is considerably different to that reported by Brunner and Margreiter at 297 K (1). A precision of  $\pm 5\%$  may be estimated for this solubility value (evaluator), though the value must be considered as **highly tentative**.

## REFERENCES

- (1) Brunner, R.; Margreiter, H. *Montash.* 1955, 86, 958.
- (2) Brunner, R.; Margreiter, H. *Montash.* 1955, 86, 767.
- (3) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* 1957, 7, 347.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, compd with N,N'-bis(phenylmethyl)-1,2-ethanediamine (2:1) benzathine penicillin G; $C_{32}H_{36}N_4O_8S_2 \cdot C_{16}H_{20}N_2$ ; [1538-09-6] (2) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Brunner, R.; Margreiter, H. <i>Montash.</i> <u>1955</u> , <b>86</b> , 958-85.												
<b>VARIABLES:</b> Temperature	<b>PREPARED BY:</b> A. Regosz												
<b>EXPERIMENTAL VALUES:</b>  <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th colspan="3" style="text-align: center;">Solubility</th> </tr> <tr> <th style="text-align: center;"><math>t/^\circ C</math></th> <th style="text-align: center;"><math>g\ dm^{-3}</math></th> <th style="text-align: center;"><math>10^4\ mol\ dm^{-3}^a</math></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">24</td> <td style="text-align: center;">0.14</td> <td style="text-align: center;">1.54</td> </tr> <tr> <td style="text-align: center;">37</td> <td style="text-align: center;">0.20</td> <td style="text-align: center;">2.20</td> </tr> </tbody> </table> <p style="text-align: center;"><sup>a</sup>Calculated by compiler, (using the molecular weight of anhydrous benzathine penicillin G calculated by the authors).</p>		Solubility			$t/^\circ C$	$g\ dm^{-3}$	$10^4\ mol\ dm^{-3}^a$	24	0.14	1.54	37	0.20	2.20
Solubility													
$t/^\circ C$	$g\ dm^{-3}$	$10^4\ mol\ dm^{-3}^a$											
24	0.14	1.54											
37	0.20	2.20											
<b>AUXILIARY INFORMATION</b>													
<b>METHOD/APPARATUS/PROCEDURE:</b>  20 cm <sup>3</sup> of water were added to an accurately weighed sample of antibiotic in a 50 cm <sup>3</sup> flask, and the suspension was shaken for about 1 hour at either 24°C or 37°C. The suspension was then filtered and the residue transferred quantitatively to a tared glass crucible. The sample was then dried to a constant weight under vacuum. The pH values of the clear filtrates were measured as 5.28 (at 24°C) and 5.21 (at 37°C).	<b>SOURCE AND PURITY OF MATERIALS:</b>  Benzathine penicillin G contained 6.74% by weight of crystalline water. The water content was determined by Karl-Fischer titration. The source of benzathine penicillin G was not given, nor was the purity of the water.  <b>ESTIMATED ERROR:</b>  None specified.  <b>REFERENCES:</b>												

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3,-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, compd with N,N'-bis(phenylmethyl)-1,2-ethanediamine (2:1) benzathine penicillin G; $C_{32}H_{36}N_4O_8S_2C_{16}H_{20}N_2$ ; [1538-09-6] (2) Hydrochloric acid; HCl; [7647-01-0] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Brunner, R.; Margreiter, H. <i>Montash.</i> <u>1955</u> , <b>86</b> , 958-85.																																				
<b>VARIABLES:</b> pH at 24°C and 37°C	<b>PREPARED BY:</b> A. Regosz																																				
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<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, compd with N,N'-bis(phenylmethyl)-1,2-ethanediamine (2:1) benzathine penicillin G;  <math>C_{32}H_{36}N_4O_8S_2 \cdot C_{16}H_{20}N_2</math>; [1538-09-6]</p> <p>(2) Sodium hydroxide; NaOH; [1310-73-2]</p> <p>(3) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Brunner, R.; Margreiter, H. <i>Montash.</i> <u>1955</u>, <b>86</b>, 958-85.</p>																																		
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<p>METHOD / APPARATUS / PROCEDURE:</p> <p>20 cm<sup>3</sup> of sodium hydroxide solutions of various pH values were added to an accurately weighed sample of antibiotic in a 50 cm<sup>3</sup> flask, and the suspension was shaken for about 1 hour at either 24°C or 37°C. The suspension was then filtered and the residue transferred quantitatively to a tared glass crucible. The sample was then dried to a constant weight under vacuum. The pH values of the clear filtrates were measured as 5.28 (at 24°C) and 5.21 (at 37°C).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Benzathine penicillin G contained 6.74% by weight of crystalline water. The water content was determined by Karl-Fischer titration. The source of benzathine penicillin G was not given, nor were the purities of water and sodium hydroxide.</p> <p>ESTIMATED ERROR:</p> <p>None specified.</p> <p>REFERENCES:</p> <p>1. Brunner, R. <i>Montash.</i> <u>1955</u>, <b>86</b>, 767-95.</p>																																		



## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, complexed with N,N'-bis(phenylmethyl)-1,2-ethanediamine (2:1) (benzathine penicillin G);  $C_{32}H_{36}N_4O_8S_2 \cdot C_{16}H_{20}N_2$ ; [1538-09-6]
- (2) All non aqueous solvents

## EVALUATOR:

Eric Tomlinson.  
Department of Pharmacy,  
University of Amsterdam,  
The Netherlands.  
December 1983.

## CRITICAL EVALUATION:

The solubilities of benzathine penicillin G in 23 different non aqueous solvents at  $301 \pm 4$  K have been reported by Weiss et al (1). These workers used a pooled commercial product sample of high purity (95 to 100%). The amount of penicillin dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than  $20 \text{ mg cm}^{-3}$ . All values reported were uncorrected for solvent blank, which was generally less than 0.05 mg total. All data according to Weiss et al have been recalculated to SI units (compiler), and are given in the Table.

Solvent	Solubility <sub>23</sub> (at $301 \pm 4$ K) ( $\text{mol dm}^{-3}$ )	
methanol	$1.9 \times 10^{-2}$	
ethanol	$1.7 \times 10^{-2}$	
isopropanol	$4.0 \times 10^{-3}$	
isoamyl alcohol	$6.6 \times 10^{-4}$	
cyclohexane	$3.5 \times 10^{-4}$	
benzene	$5.0 \times 10^{-4}$	
toluene	$7.9 \times 10^{-3}$	
ligroin	$1.1 \times 10^{-3}$	
isooctane	$9.9 \times 10^{-4}$	
carbon tetrachloride	$6.3 \times 10^{-3}$	
ethyl acetate	$1.3 \times 10^{-4}$	( <sup>a</sup> solubility greater than $2.2 \times 10^{-2} \text{ mol dm}^{-3}$ )
isoamyl acetate	$6.1 \times 10^{-4}$	
acetone	$3.3 \times 10^{-3}$	
methyl ethyl ketone	$3.5 \times 10^{-3}$	
diethylether	$4.4 \times 10^{-4}$	
ethylene chloride	$9.9 \times 10^{-4}$	
1,4-dioxane	$2.6 \times 10^{-3}$	
chloroform	$2.3 \times 10^{-3}$	
carbon disulfide	$5.5 \times 10^{-4}$	
pyridine	a	
formamide	a	
ethylene glycol	a	
benzyl alcohol	$1.4 \times 10^{-2}$	

(All solvents are of U.S.P. or A.C.S. grade).

All these values have an estimated precision of  $\pm 5\%$  (evaluator). However they are unconfirmed findings and must be designated as being **tentative**, except for where the solubility is reported as being greater than  $2.2 \times 10^{-2} \text{ mol dm}^{-3}$ , (which are regarded as being **doubtful**).

## REFERENCE

- (1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* 1957, 7, 374.



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, compd with N,N'-bis(phenylmethyl)-1,2-ethanediamine (2:1) benzathine penicillin G; $C_{32}H_{36}N_4O_8S_2 \cdot C_{16}H_{20}N_2$ ; [1538-09-6] (2) Ethanol; $C_2H_6O$ ; [64-17-5]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright W.W. <b>Antibiotics and Chemotherapy</b> <u>1957</u> , 7, 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of benzathine penicillin G in ethanol at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>15.4 \text{ mg cm}^{-3}</math>. (<math>1.7 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent was added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Benzathine penicillin G was a pooled commercial product of high purity (95 to 100%).           Ethanol was of A.C.S. or U.S.P. grade.</p> <hr/> <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).
<b>REFERENCES:</b>	





<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, compd with N,N'-bis(phenylmethyl)-1,2-ethanediamine (2:1) benzathine penicillin G; $C_{32}H_{36}N_4O_8S_2 \cdot C_{16}H_{20}N_2$ ; [1538-09-6] (2) Cyclohexane; $C_6H_{12}$ ; [110-82-7]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of benzathine penicillin G in cyclohexane at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.315 \text{ mg cm}^{-3}</math>. (<math>3.46 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD / APPARATUS / PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent was added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Benzathine penicillin G was a pooled commercial product of high purity (95 to 100%).          Cyclohexane was of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b>























<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, compd with N,N'-bis(phenylmethyl)-1,2-ethanediamine (2:1) benzathine penicillin G; $C_{32}H_{36}N_4O_8S_2 \cdot C_{16}H_{20}N_2$ ; [1538-09-6] (2) 1,4-Dioxane; $C_4H_8O_2$ ; [123-91-1]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright W.W. <b>Antibiotics and Chemotherapy</b> <u>1957</u> , <b>7</b> , 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of benzathine penicillin G in 1,4 dioxane at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>2.4 \text{ mg cm}^{-3}</math>. (<math>2.6 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent was added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $28 \pm 4^\circ\text{C}$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ\text{C}$ . The residue was further dried for 3 hr at $60^\circ\text{C}$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b>  Benzathine penicillin G was a pooled commercial product of high purity (95 to 100%).  1,4-Dioxane was of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).  <b>REFERENCES:</b>













## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid 3,3-dimethyl-7-oxo-6-[(4-methylphenoxyacetyl)amino]-, complexed with N,N'-bis(phenylmethyl)-1,2-ethanediamine (2:1) benzathine penicillin P;  $C_{34}H_{40}N_4O_{10}S_2 \cdot C_{16}H_{20}N_2$ ; [76082-03-6]  
 (2) Water;  $H_2O$ ; [7732-18-5]

## EVALUATOR:

Eric Tomlinson.  
 Department of Pharmacy,  
 University of Amsterdam,  
 The Netherlands.  
 December 1983

## CRITICAL EVALUATION:

The influence of pH (1.90 to 8.70) and temperature (297 K and 310 K) on the aqueous solubility of benzathine penicillin P have been studied by Brunner and Margreiter (1). The amount of penicillin dissolved in the solvent was determined by drying to constant weight. A precision  $\pm 2\%$  is estimated for all the solubility values reported, (evaluator). It is not possible to estimate the precision in the reported temperature or pH values, though for the latter it is probably  $\pm 0.02$  pH units.

The solubilities of benzathine penicillin P at 297 K and 310 K are reported as  $2.37 \times 10^{-4}$  mol dm<sup>-3</sup> and  $3.09 \times 10^{-4}$  mol dm<sup>-3</sup>, respectively. (Values converted to SI units by compiler). The Table gives the aqueous solubility of benzathine penicillin P at various pH's and at 297 K. From this it is possible to see that the solubility increases sharply in strongly acid solutions, but only slightly in alkaline solutions. Brunner and Margreiter have made a detailed theoretical study concerning the calculation of the solubility of this solute using appropriate acid and base dissociation constants (2). At pH's 8.07 and 8.42 there was good agreement between results obtained experimentally and those obtained by calculation. However, at the extreme pH's there was little agreement between the two, which could be indicative of degradation effects. All the values given in this evaluation are designated as being tentative, except that at pH 1.90, which is considered to be doubtful.

Solubility ( $10^4$ mol dm <sup>-3</sup> ) <sup>a</sup>	
pH <sup>b</sup>	at 297 K
1.90	245
2.21	96.3
2.74	16.6
3.00	4.75
6.68	3.97
8.07	10.8
8.42	15.7
8.70	38.3

(<sup>a</sup> Calculated by compiler; <sup>b</sup> pH altered using either HCl or NaOH).

## REFERENCES

- (1) Brunner, R.; Margreiter, H. *Montash.* 1955, **86**, 958.  
 (2) Brunner, R.; Margreiter, H. *Montash.* 1955, **86**, 767.

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(4-methylphenoxyacetyl)amino]-, compd with N,N'-bis(phenylmethyl)-1,2-ethanediamine (2:1) (benzathine penicillin B; <math>C_{34}H_{40}N_4O_{10}S_2 \cdot C_{16}H_{20}N_2</math>; [76082-03-6])</p> <p>(2) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Brunner, R.; Margreiter, H. <i>Monatsh.</i> <u>1955</u>, <b>86</b>, 958-65.</p>									
<p>VARIABLES:</p> <p>Temperature</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>									
<p>EXPERIMENTAL VALUES:</p> <p style="text-align: center;">Solubility</p> <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th style="text-align: center;"><math>t/^\circ C</math></th> <th style="text-align: center;"><math>mg\ cm^{-3}</math></th> <th style="text-align: center;"><math>10^4\ mol\ dm^{-3}{}^a</math></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">24</td> <td style="text-align: center;">0.23</td> <td style="text-align: center;">2.37</td> </tr> <tr> <td style="text-align: center;">37</td> <td style="text-align: center;">0.30</td> <td style="text-align: center;">3.09</td> </tr> </tbody> </table> <p style="text-align: center;"><sup>a</sup> Compiler</p>		$t/^\circ C$	$mg\ cm^{-3}$	$10^4\ mol\ dm^{-3}{}^a$	24	0.23	2.37	37	0.30	3.09
$t/^\circ C$	$mg\ cm^{-3}$	$10^4\ mol\ dm^{-3}{}^a$								
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37	0.30	3.09								
<p>AUXILIARY INFORMATION</p>										
<p>METHOD APPARATUS/PROCEDURE:</p> <p>To an accurately weighed sample of the antibiotic in a 50 cm<sup>3</sup> flask 20 cm<sup>3</sup> of water was added and the suspension shaken for about 1 hr at 24°C or 37°C. The suspension was then filtered and the residue quantitatively transferred into a tared glass crucible and dried in vacuum to const weight. The pH value of the clear filtrate was 5.20 measured at 24°C only.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Benzathine penicillin P contain 4.36% of water by weight; its source and purity were not specified. The water content was determined by Karl Fischer titration.</p> <p>The purity of the water was not specified.</p> <p>ESTIMATED ERROR:</p> <p>Nothing specified.</p> <p>REFERENCES:</p>									

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[[4-methylphenoxyacetyl]amino]-, compd with N,N'-bis(phenylmethyl)-1,2-ethanediamine (2:1) (benzathine penicillin P); <math>C_{34}H_{40}N_4O_{10}S_2 \cdot C_{16}H_{20}N_2</math>; [76082-03-6]</p> <p>(2) Hydrochloric acid; HCl; [7647-01-0]</p> <p>(3) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Brunner, R.; Margreiter, H. <i>Monatsh.</i> <u>1955</u>, <b>86</b>, 958-65.</p>															
<p>VARIABLES:</p> <p>pH at 24°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>															
<p>EXPERIMENTAL VALUES:</p> <p style="text-align: center;">Solubility</p> <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th style="text-align: center;">pH</th> <th style="text-align: center;">mg cm<sup>-3</sup></th> <th style="text-align: center;">10<sup>4</sup> mol dm<sup>-3</sup><sup>a</sup></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">3.00</td> <td style="text-align: center;">0.46</td> <td style="text-align: center;">4.75</td> </tr> <tr> <td style="text-align: center;">2.74</td> <td style="text-align: center;">1.61</td> <td style="text-align: center;">16.6</td> </tr> <tr> <td style="text-align: center;">2.21</td> <td style="text-align: center;">9.34</td> <td style="text-align: center;">96.3</td> </tr> <tr> <td style="text-align: center;">1.90</td> <td style="text-align: center;">23.8</td> <td style="text-align: center;">245</td> </tr> </tbody> </table> <p style="margin-left: 20px;"><sup>a</sup> Compiler</p>		pH	mg cm <sup>-3</sup>	10 <sup>4</sup> mol dm <sup>-3</sup> <sup>a</sup>	3.00	0.46	4.75	2.74	1.61	16.6	2.21	9.34	96.3	1.90	23.8	245
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<p>AUXILIARY INFORMATION</p>																
<p>METHOD APPARATUS/PROCEDURE:</p> <p>To an accurately weighed sample of the antibiotic in a 50 cm<sup>3</sup> flask 20 cm<sup>3</sup> HCl soln of the required pH were added and the suspension shaken for about 1 hr at 24°C. The suspension was then filtered and the pH of the clear filtrates accurately measured. The residues were quantitatively transferred into tared glass crucible and dried in vacuum to const weight. The solubilities were compared by the authors with values calculated in (1).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Benzathine penicillin P contain 4.36% of water by weight; its source and purity were not specified. The water content was determined by Karl Fischer titration.</p> <p>The purities of hydrochloric acid and water were not specified.</p> <p>ESTIMATED ERROR:</p> <p>Nothing specified.</p> <p>REFERENCES:</p> <p>(1) Brunner, R.; Margreiter, H. <i>Montash.</i> <u>1955</u>, <b>86</b>, 767.</p>															

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(4-methylphenoxyacetyl)amino]-, compd with N,N'-bis(phenylmethyl)-1,2-ethanediamine (2:1) (benzathine penicillin P); <math>C_{34}H_{40}N_4O_{10}S_2 \cdot C_{16}H_{20}N_2</math>; [76082-03-6]</p> <p>(2) Sodium hydroxide; NaOH; [1310-73-2]</p> <p>(3) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Brunner, R.; Margreiter, H. <i>Monatsh.</i> <u>1955</u>, <b>86</b>, 958-65.</p>															
<p>VARIABLES:</p> <p>pH at 24°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>															
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pH	$mg\ cm^{-3}$	$10^4\ mol\ dm^{-3}{}^a$														
6.68	0.39	3.97														
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<p>AUXILIARY INFORMATION</p>																
<p>METHOD APPARATUS/PROCEDURE:</p> <p>To an accurately weighed sample of the antibiotic in a 50 cm<sup>3</sup> flask 20 cm<sup>3</sup> NaOH soln of the required pH were added and the suspension shaken for about 1 hr at 24°C. The suspension was then filtered and the pH of the clear filtrates accurately measured. The residues were quantitatively transferred into tared glass crucible and dried in vacuum to const weight. The solubilities were compared by the authors with values calculated in (1).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Benzathine penicillin P contain 4.36% of water by weight; its source and purity were not specified. The water content was determined by Karl Fischer titration.</p> <p>The purities of sodium hydroxide and water were not specified.</p> <p>ESTIMATED ERROR:</p> <p>Nothing specified.</p> <p>REFERENCES:</p> <p>(1) Brunner, R.; Margreiter, H. <i>Montash.</i> <u>1955</u>, <b>86</b>, 767.</p>															

<p>COMPONENTS:</p> <p>(1) 4- Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[2-(allylthio)-acetamido]-, complexed with 2-(diethyl-amino)ethyl-4-amino-2-chlorobenzoate (1:1) (chloroprocaine penicillin O);  <math>C_{13}H_{18}N_2O_4S_2 \cdot C_{13}H_{19}ClN_2O_2</math>; [575-52-0]</p> <p>(2) All solvents</p>	<p>EVALUATOR:</p> <p>Eric Tomlinson,          Department of Pharmacy,          University of Amsterdam,          The Netherlands.          December 1983.</p>
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## CRITICAL EVALUATION:

The solubilities of chloroprocaine penicillin O in 24 different solvents at  $301 \pm 4$  K have been reported by Weiss et al (1). These workers used a pooled commercial product sample of high purity (95 to 100%). The amount of penicillin dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than  $20 \text{ mg cm}^{-3}$ . All values reported were uncorrected for solvent blank, which was generally less than 0.05 mg total. All data according to Weiss et al have been recalculated to SI units (compiler), and are given in the Table.

Solvent	Solubility <sub>2,3</sub> (at $301 \pm 4$ K) ( $\text{mol dm}^{-3}$ )	
water	$1.5 \times 10^{-2}$	
methanol	a	
ethanol	a	
isopropanol	a	
isoamyl alcohol	$1.0 \times 10^{-2}$	
cyclohexane	$4.8 \times 10^{-4}$	
benzene	$7.7 \times 10^{-4}$	
toluene	$8.7 \times 10^{-4}$	
ligroin	$1.1 \times 10^{-3}$	
isooctane	$2.1 \times 10^{-3}$	
carbon tetrachloride	$1.0 \times 10^{-3}$	
ethyl acetate	$1.9 \times 10^{-3}$	(a solubility greater than $3.3 \times 10^{-2} \text{ mol dm}^{-3}$ )
isoamyl acetate	$4.8 \times 10^{-3}$	
acetone	a	
methyl ethyl ketone	a	
diethylether	$2.4 \times 10^{-3}$	
ethylene chloride	$1.1 \times 10^{-2}$	
1,4-dioxane	a	
chloroform	a	
carbon disulfide	$7.5 \times 10^{-4}$	
pyridine	a	
formamide	a	
ethylene glycol	a	
benzyl alcohol	a	

(All solvents are of U.S.P. or A.C.S. grade).

All these values have an estimated precision of  $\pm 5\%$  (evaluator). However they are unconfirmed findings and must be designated as being **tentative**, except for where the solubility is reported as being greater than  $3.3 \times 10^{-2} \text{ mol dm}^{-3}$ , (which are regarded as being **doubtful**).

## REFERENCE

(1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* 1957, 7, 374.









<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[2-(allylthio)acetamido]-, compd with 2-(diethylamino)ethyl-4-amino-2-chlorobenzoate (1:1)(chloroprocaine penicillin O); $C_{13}H_{18}N_2O_4S_2 \cdot C_{13}H_{19}ClN_2O_2$ ; [575-52-0] (2) 1-Butanol, 3-methyl- (isoamyl alcohol); $C_5H_{12}O$ ; [123-51-3]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <b>Antibiotics and Chemotherapy</b> 1957, 7, 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of chloroprocaine penicillin O in isoamyl alcohol at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>6.05 \text{ mg cm}^{-3}</math>. (<math>1.01 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Chloroprocaine penicillin O was a pooled commercial product of high purity (95 to 100%).</p> <p>Isoamyl alcohol was of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[2-(allylthio)acetamido], compd with 2-(diethylamino)ethyl-4-amino-2-chlorobenzoate (1:1) (chloroprocaine penicillin O); $C_{13}H_{18}N_2O_4S_2 \cdot C_{13}H_{19}ClN_2O_2$ ; [575-52-0] (2) Benzene; $C_6H_6$ ; [71-43-2]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of chloroprocaine penicillin O in benzene at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.46 \text{ mg cm}^{-3}</math>. (<math>7.73 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a 15 $\text{cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $28 \pm 4^\circ\text{C}$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 $\text{cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ\text{C}$ . The residue was further dried for 3 hr at $60^\circ\text{C}$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b>  Chloroprocaine penicillin O was a pooled commercial product of high purity (95 to 100%).  Benzene was of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).  <b>REFERENCES:</b>





<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[2-(allylthio)acetamido]-, compd with 2-(diethylamino)ethyl-4-amino-2-chlorobenzoate (1:1) (chloroprocaine penicillin O); $C_{13}H_{18}N_2O_4S_2 \cdot C_{13}H_{19}ClN_2O_2$ ; [575-52-0] (2) Pentane, 2,2,4-trimethyl- (isooctane); $C_8H_{18}$ ; [540-84-1]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of chloroprocaine penicillin O in isooctane at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.12 \text{ mg cm}^{-3}</math>. (<math>2.08 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Chloroprocaine penicillin O was a pooled commercial product of high purity (95 to 100%).           Isooctane was of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> Solubility: None specified. Temperature precision: $\pm 4^\circ\text{C}$ (authors).
	<b>REFERENCES:</b>













<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[2-(allylthio)acetamido]-, compd with 2-(diethylamino)ethyl-4-amino-2-chlorobenzoate (1:1) (chlorprocaine penicillin O); $C_{13}H_{18}N_2O_4S_2 \cdot C_{13}H_{19}ClN_2O_2$ ; [575-52-0] (2) Ethane, dichloro- (ethylene chloride); $C_2H_4Cl_2$ ; [1300-21-6]	<b>ORIGINAL MEASUREMENTS:</b> Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 347-7.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of chlorprocaine penicillin O in ethylene chloride at <math>28 \pm 4^\circ C</math> was reported as: <math>6.40 \text{ mg cm}^{-3}</math>. (<math>1.10 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Chlorprocaine penicillin O was a pooled commercial product of high purity (95 to 100%).           Ethylene chloride was of A.C.S. or U.S.P. grade.</p> <hr/> <b>ESTIMATED ERROR:</b>  <p>Solubility: None specified.          Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <hr/> <b>REFERENCES:</b>















## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[1-aminocyclohexyl]carbonyl]amino]-3,3-dimethyl-7-oxo (ciclacillin anhydrate);  $C_{15}H_{23}N_3O_4S$ ; [3485-14-1]
- (2) Aqueous solution

## EVALUATOR:

Eric Tomlinson.  
Department of Pharmacy,  
University of Amsterdam,  
The Netherlands.  
December 1983.

## CRITICAL EVALUATION:

The solubility of ciclacillin anhydrate in aqueous solution has been reported by three groups (1-3). Tsuji et al (1) have studied the pH - solubility behavior of ciclacillin anhydrate at constant ionic strength ( $\mu = 0.5$ ) and temperature (310 K) using HCl or KOH to regulate the pH. Their results were presented graphically, and exhibited a U-shaped curve, with a minimum solubility being seen between about pH 3.5 and pH 5.5. The original data have been obtained directly from the authors (4), and are given in the appropriate compilation sheet. The precision in solubility determination can be estimated as  $\pm 5\%$  (evaluator), and the precision in the temperature was probably  $\pm 1$  K (evaluator). The authors fitted the experimental data using:

$$C_T = C_0 [(a_{H^+}/K_1) + 1 + (K_2/a_{H^+})]$$

where  $C_T$  is the total solubility,  $C_0$  the intrinsic solubility of amphoteric ciclacillin,  $a_{H^+}$  is the hydrogen ion activity, and  $K_1$  and  $K_2$  are the dissociation constants for 2-carboxylic acid and the conjugated acid of the  $\alpha$ -amino group, respectively. The authors have stated (4) that the intrinsic solubility of ciclacillin anhydrate is calculated using this relationship to be  $8.9 \times 10^{-2} \text{ mol dm}^{-3}$ , which accords with their experimentally obtained values at pH's 4.61 and 5.12 of  $8.9 \times 10^{-2} \text{ mol dm}^{-3}$  and  $10 \times 10^{-2} \text{ mol dm}^{-3}$ , respectively. Of all the amphoteric penicillins studied by these workers (see later compilations), ciclacillin anhydrate was found to have the highest aqueous solubility. Being an ampholyte it showed increased solubility both in acid and alkaline solutions (i.e. below pH 2.50 and above pH 7.90). All the numerical values provided by Tsuji et al are designated as **tentative**.

Poole and Bahal (2) have determined the apparent equilibrium solubilities of ciclacillin anhydrate and dihydrate (see following compilation) in water as a function of temperature. Their sample was a pure sample characterized by IR and differential thermal analysis, their assay procedure was iodometric titration. The precision in temperature is estimated to be  $\pm 1$  K (compiler), and a precision in solubility determination of  $\pm 5\%$  is estimated (evaluator). These authors presented their data in graphical form, which showed a good linear relationship between log solubility and reciprocal absolute temperature between 280 K and 313 K. Non linear behavior above these temperatures is probably attributable to degradation of the penicillin (evaluator). The value for the heat of solution over the 280 K to 313 K interval was calculated to be  $-19.7 \text{ kJ mol}^{-1}$ . This behavior is very different to that observed with the dihydrate (see following compilation). The data have been estimated from the original figure, and are given in the following Table. Because of this, the values given are estimated to have a precision of  $\pm 10\%$  (evaluator), and must be regarded as **tentative**.

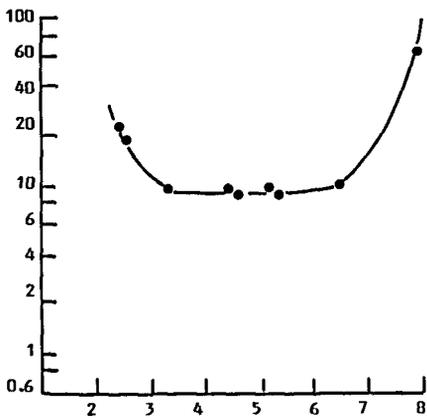
Temperature <sup>a</sup> K	Solubility <sup>b</sup> ( $\text{mol dm}^{-3}$ ) <sup>c</sup>
280	$17 \times 10^{-2}$
293	$11 \times 10^{-2}$
298	$9.4 \times 10^{-2}$
303	$7.8 \times 10^{-2}$

(<sup>a</sup> given by authors; <sup>b</sup> estimated by evaluator from original figure; <sup>c</sup> units - evaluator).

Finally, Braun and Moll (3) have published the solubility of ciclacillin anhydrate in synthetic and natural gastric juice at 310 K. The solubility in these was found to be  $1.3 \times 10^{-2} \text{ mol dm}^{-3}$  and  $1.4 \times 10^{-2} \text{ mol dm}^{-3}$ , respectively. A precision in solubility determination of  $\pm 5\%$  is estimated (evaluator). The temperature precision during this study was probably  $\pm 1$  K. However, the fact that the source and purity of the ciclacillin anhydrate used were not given means that these data must be **rejected**.

## REFERENCES

- (1) Tsuji, A.; Nakashima, E.; Hamano, S.; Yamana, T. *J. Pharm. Sci.* **1978**, *67*, 1059.
- (2) Poole, J.W.; Bahal, C.K. *J. Pharm. Sci.* **1970**, *59*, 1265.
- (3) Braun, A.; Moll, F. *Acta Pharm. Technol.* **1980**, *26*, 258.
- (4) Tsuji, A. Personal Communication.

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[(1-aminocyclohexyl)carbonyl]amino]-3,3-dimethyl-7-oxo, (ciclacillin anhydrate); <math>C_{15}H_{23}N_3O_4S</math>; [3485-14-1]</p> <p>(2) Hydrochloric acid; HCl; [7647-01-0]</p> <p>(3) Potassium hydroxide; KOH; [1310-58-3]</p> <p>(4) Potassium chloride; KCl; [7447-40-7]</p> <p>(5) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS: Tsuji, A.; Nakashima, E.; Hamano, S.; Yamana, T. <i>J. Pharm. Sci.</i> 1979, 67, 1059-66.</p>																																			
<p>VARIABLES:</p> <p>pH at 37°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>																																			
<p>EXPERIMENTAL VALUES:</p> <table border="1" data-bbox="207 493 707 844"> <thead> <tr> <th rowspan="2">pH<sup>a</sup></th> <th colspan="2">Solubility</th> </tr> <tr> <th><math>10^2 \text{ mol dm}^{-3a}</math></th> <th><math>\text{mg cm}^{-3b}</math></th> </tr> </thead> <tbody> <tr><td>2.40</td><td>23.00</td><td>78.52</td></tr> <tr><td>2.50</td><td>20.50</td><td>69.99</td></tr> <tr><td>3.28</td><td>9.82</td><td>33.52</td></tr> <tr><td>4.46</td><td>9.88</td><td>33.73</td></tr> <tr><td>4.61</td><td>8.85</td><td>30.21</td></tr> <tr><td></td><td>8.90 - <math>C_o</math></td><td>30.38</td></tr> <tr><td>5.12</td><td>9.99</td><td>34.11</td></tr> <tr><td>5.32</td><td>8.92</td><td>30.45</td></tr> <tr><td>6.38</td><td>10.20</td><td>34.82</td></tr> <tr><td>7.90</td><td>64.00</td><td>218.50</td></tr> </tbody> </table> <div style="display: flex; justify-content: space-between; align-items: flex-start; margin-top: 20px;"> <div data-bbox="207 870 725 950" style="width: 45%;"> <p>In the figure, the points are experimental values<sup>a</sup> and the line was calculated from equation [1].</p> <math display="block">C_T = C_o \left( \frac{a_{H^+}}{K_1} + 1 + \frac{K_2}{a_{H^+}} \right) \quad [1]</math> <p>where <math>C_T</math> is the total solubility, <math>C_o</math> is the intrinsic solubility of amphoteric ciclacillin with the electrically neutral zwitterion, <math>a_{H^+}</math> is the hydrogenion activity of the solution, and <math>K_1</math> and <math>K_2</math> are dissociation constants for 2-carboxylic acid and the conjugated acid of the <math>\alpha</math>-amino group, respectively.</p> <p><sup>a</sup> Numerical data obtained from the author (A. Tsuji).</p> <p><sup>b</sup> Calculated by compiler. The <math>C_o</math> value (intrinsic solubility) estimated from the solubility at the isoelectric point is defined by Eqn [1].</p> </div> <div data-bbox="763 473 1281 990" style="width: 45%;"> <p>Solubility [<math>10^2 \text{ mol dm}^{-3}</math>]</p>  <p>pH at constant ionic strength [<math>\mu = 0.5</math>]</p> </div> </div>		pH <sup>a</sup>	Solubility		$10^2 \text{ mol dm}^{-3a}$	$\text{mg cm}^{-3b}$	2.40	23.00	78.52	2.50	20.50	69.99	3.28	9.82	33.52	4.46	9.88	33.73	4.61	8.85	30.21		8.90 - $C_o$	30.38	5.12	9.99	34.11	5.32	8.92	30.45	6.38	10.20	34.82	7.90	64.00	218.50
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<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of ciclacillin anhydrate was added to a glass-stoppered flask, followed by addition of <math>0.5 \text{ mol dm}^{-3}</math> KCl aqueous solution to a constant ionic strength (<math>\mu = 0.5</math>). The suspension was then adjusted to the appropriate pH with standard HCl or KOH solution. The flask was placed in a constant temperature bath at 37°C and mechanically shaken for 2 hr. A sample was taken through a 0.45 micron Sartorius membrane filter, the pH was measured, and the sample was assayed after appropriate dilution, if necessary with distilled water. The amount of ciclacillin was determined by iodometric titration.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Ciclacillin anhydrate was supplied by Takeda Chemical Industries, Osaka, Japan, and had a potency of <math>999 \mu\text{g mg}^{-1}</math></p> <p>All other chemicals were reagent grade and were used without further purification. Distilled water was used.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: probably <math>\pm 1^\circ\text{C}</math> (compiler)</p> <p>REFERENCES:</p>																																			

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<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of ciclacillin anhydrate (4 g), was added to 50 <math>\text{cm}^3</math> of distilled water previously equilibrated at the desired temperature. The bottles were rotated at a constant speed in a water-bath maintained at the appropriate temperature. Samples withdrawn at definite intervals, filtered through a Milipore filter and diluted immediately to avoid any precipitation. The amount of the ciclacillin was determined by iodometric titration.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Anhydrous ciclacillin was from Wyeth Laboratories (Batch C-10777, m.p. 181-182°C).</p> <p>The anhydrous form was conclusively characterized by IR spectra, differential thermal analysis, and Karl Fischer moisture determination.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: probably <math>\pm 1^\circ\text{C}</math> (compiler)</p> <p>REFERENCES:</p>														

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<p>EXPERIMENTAL VALUES:</p> <p>The authors determined the maximal solubility of ciclacillin in synthetic gastric juice<sup>a</sup> (without pepsin) and compared the results with those obtained for solubility in human natural gastric juice.</p> <p style="text-align: center;">Solubility</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="2" style="text-align: center;">Synthetic gastric juice<sup>a</sup> (without pepsin)</th> <th colspan="2" style="text-align: center;">Human natural gastric juice</th> </tr> <tr> <th style="text-align: center;"><math>10^2 \text{ mg cm}^{-3}</math></th> <th style="text-align: center;"><math>10^2 \text{ mol dm}^{-3b}</math></th> <th style="text-align: center;"><math>10^2 \text{ mg cm}^{-3}</math></th> <th style="text-align: center;"><math>10^2 \text{ mol dm}^{-3b}</math></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">465</td> <td style="text-align: center;">1.36</td> <td style="text-align: center;">447</td> <td style="text-align: center;">1.31</td> </tr> </tbody> </table> <p><sup>a</sup> According to USP XIX composition of the synthetic gastric fluid, simulated is: HCl(35%) - 7.0 cm<sup>3</sup>, NaCl - 2.0 g, pepsin - 3.2 g, distilled water to 1000 cm<sup>3</sup>.</p> <p><sup>b</sup> Calculated by compiler.</p>		Synthetic gastric juice <sup>a</sup> (without pepsin)		Human natural gastric juice		$10^2 \text{ mg cm}^{-3}$	$10^2 \text{ mol dm}^{-3b}$	$10^2 \text{ mg cm}^{-3}$	$10^2 \text{ mol dm}^{-3b}$	465	1.36	447	1.31
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<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of antibiotic was added to a 250 cm<sup>3</sup> flask, followed by addition of 100 cm<sup>3</sup> of synthetic or natural gastric juice. The fluid was stirred at a speed of 55 r.p.m. at a temperature 37°C for about 1 hr. The fluid was then buffered to pH 4.6 using <math>Na_3PO_4</math> solution and filtered through a Sartorius SM 11307 filter. The amount of antibiotic in the filtrate was determined spectrophotometrically at 320 nm (1).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Source and purity of the ciclacillin as well as chemicals used were not specified.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: probably <math>\pm 1^\circ\text{C}</math> (compiler)</p> <p>REFERENCES:</p> <p>(1) Smith, H.W.G.; De Grey, G.E.; Patel, V.J. <i>Analyst</i> <b>1967</b>, <b>92</b>, 247.</p>												

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[(2-aminocyclohexyl)carbonyl]amino]-3,3-dimethyl-7-oxo, dihydrate (ciclacillin dihydrate; $C_{15}H_{23}N_3O_4S \cdot 2H_2O$ ) (2) Water; $H_2O$ ; [7732-18-5]	<b>EVALUATOR:</b> Eric Tomlinson. Department of Pharmacy, University of Amsterdam, The Netherlands. December 1983.
<b>CRITICAL EVALUATION:</b> <p>Poole and Bahal (1) have determined the apparent equilibrium solubilities of ciclacillin anhydrate and dihydrate (see previous compilation) in water as a function of temperature. Their sample of ciclacillin dihydrate was a pure sample prepared from anhydrous ciclacillin and conclusively characterized by IR and differential thermal analysis. Their assay procedure was iodometric titration. The precision in temperature was probably <math>\pm 1</math> K (evaluator), and a precision in solubility determination of <math>\pm 5</math> % is estimated (evaluator). These authors presented their data in graphical form, which showed a constant relationship between log solubility and reciprocal absolute temperature between 283 K and 313 K. Non regular behavior above these temperatures is probably attributable to degradation of the penicillin (evaluator). The value for the heat of solution over the 280 K to 313 K interval was calculated to be <math>0.0 \text{ kJ mol}^{-1}</math> (units - evaluator). This behavior is very different to that observed with the dihydrate (see previous compilation). A solubility over the temperature interval 283 K to 310 K of <math>4.2 \times 10^{-2} \text{ mol dm}^{-3}</math> may be estimated from the original figure, (evaluator), which is much lower than that given for ciclacillin anhydrate. This value is estimated to have a precision of <math>\pm 10</math> % (evaluator), and must be regarded as <b>tentative</b>.</p> <b>REFERENCE</b> <p>(1) Poole, J.W.; Bahal, C.K. <i>J. Pharm. Sci.</i> <u>1970</u>, <b>59</b>, 1265.</p>	

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<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of ciclacillin dihydrate (4 g), was added to 50 cm<sup>3</sup> of distilled water previously equilibrated at the desired temperature. The bottles were rotated at a constant speed in a water-bath maintained at the appropriate temperature. Samples withdrawn at definite intervals, filtered through a Milipore filter and diluted immediately to avoid any precipitation. The amount of the ciclacillin was determined by iodometric titration.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>The dihydrate form of ciclacillin was prepared from anhydrous ciclacillin (Wyeth Laboratories batch C-10777, m.p. 181-182°C), by preparing a saturated solution of the penicillin in 1.0 N HCl solution and precipitating the hydrated form at pH 7.</p> <p>The dihydrate form was conclusively characterized by IR spectra, differential thermal analysis, and Karl Fischer moisture determination.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: probably <math>\pm 1^\circ\text{C}</math> (compiler)</p>														
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<p>CRITICAL EVALUATION</p> <p>Braun and Moll (1) have published the solubility of azidocillin in synthetic and natural gastric juice at 310 K. The solubility in these was found to be <math>7.9 \times 10^{-3} \text{ mol dm}^{-3}</math> and <math>6.6 \times 10^{-3} \text{ mol dm}^{-3}</math>, respectively. A precision in solubility determination of <math>\pm 5\%</math> is estimated (evaluator). The temperature precision during this study was probably <math>\pm 1 \text{ K}</math>. The amount of penicillin in the sample was determined spectroscopically. However, the fact that the source and purity of the azidocillin used were not given means that these data must be rejected.</p> <p>REFERENCE</p> <p>(1) Braun, A.; Moll, F. <i>Acta Pharm. Technol.</i> <u>1980</u>, 26, 258.</p>	

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[2-azido-2-phenyl-acetamido]-3,3-dimethyl-7-oxo (azidocillin); C <sub>16</sub> H <sub>17</sub> N <sub>5</sub> O <sub>4</sub> S; [17243-38-8] (2) Hydrochloric acid; HCl; [7647-01-0] (3) Phosphoric acid, trisodium salt; Na <sub>3</sub> PO <sub>4</sub> ; [7601-54-9] (4) Sodium chloride; NaCl; [7647-14-5] (5) Water; H <sub>2</sub> O; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Braun, A.; Moll, F. <i>Acta Pharm. Technol.</i> <u>1980</u> , <b>26</b> , 258-60.												
<b>VARIABLES:</b> One temperature: 37°C	<b>PREPARED BY:</b> A. Regosz												
<b>EXPERIMENTAL VALUES:</b>  The authors determined maximal solubility of azidocillin in synthetic gastric juice <sup>a</sup> (without pepsin) and compared the results with those obtained for solubility in human natural gastric juice.  <div style="text-align: center;">Solubility</div> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="2" style="text-align: center;">Synthetic gastric juice<sup>a</sup> (without pepsin)</th> <th colspan="2" style="text-align: center;">Human natural gastric juice</th> </tr> <tr> <th style="text-align: center;">10<sup>2</sup> mg cm<sup>-3</sup></th> <th style="text-align: center;">10<sup>2</sup> mol dm<sup>-3</sup><sup>b</sup></th> <th style="text-align: center;">10<sup>2</sup> mg cm<sup>-3</sup></th> <th style="text-align: center;">10<sup>2</sup> mol dm<sup>-3</sup><sup>b</sup></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">250</td> <td style="text-align: center;">0.66</td> <td style="text-align: center;">298</td> <td style="text-align: center;">0.79</td> </tr> </tbody> </table> <p><sup>a</sup> According to USP XIX composition of simulated synthetic gastric fluid is: HCl (35%) - 7.0 cm<sup>3</sup>; NaCl - 2.0 g; pepsin - 3.2 g; distilled water to 1000 cm<sup>3</sup>.  <sup>b</sup> Calculated by compiler.</p>		Synthetic gastric juice <sup>a</sup> (without pepsin)		Human natural gastric juice		10 <sup>2</sup> mg cm <sup>-3</sup>	10 <sup>2</sup> mol dm <sup>-3</sup> <sup>b</sup>	10 <sup>2</sup> mg cm <sup>-3</sup>	10 <sup>2</sup> mol dm <sup>-3</sup> <sup>b</sup>	250	0.66	298	0.79
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## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (ampicillin sodium);  $C_{16}H_{18}N_3O_4SNa$ ; [69-52-3]
- (2) All solvents

## EVALUATOR:

Eric Tomlinson.  
Department of Pharmacy,  
University of Amsterdam,  
The Netherlands.

December 1983.

## CRITICAL EVALUATION:

Marsh and Weiss have determined the solubilities of ampicillin sodium in 26 different solvents at  $294 \pm 1$  K. These workers studied two different samples of the antibiotic from the same reputable manufacturer (Bristol Laboratories). Sample A exhibited definite birefringence when viewed under the microscope, whereas sample B was practically amorphous and showed very few crystalline particles. The amount of penicillin dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than  $20 \text{ mg cm}^{-3}$ . All values reported were uncorrected for solvent blank, which was generally less than 0.05 mg total. All data according Marsh and Weiss have been recalculated to SI units (compiler), and are given in the Table.

Solvent	Solubility (at $294 \pm 1$ K), ( $\text{mol dm}^{-3}$ ) <sup>a</sup>	
	Sample A	Sample B
water	b	b
0.1 N HCl	b	b
0.1 N NaOH	b	b
methanol	b	b
ethanol	b	$5.33 \times 10^{-2}$
isopropanol	$3.04 \times 10^{-3}$	$1.73 \times 10^{-2}$
isoamyl alcohol	$5.12 \times 10^{-3}$	$5.20 \times 10^{-2}$
cyclohexane	$2.02 \times 10^{-4}$	0
benzene	$5.4 \times 10^{-5}$	0
ligroin	$6.7 \times 10^{-5}$	0
isooctane	$5.9 \times 10^{-5}$	0
carbon tetrachloride	$8.6 \times 10^{-5}$	0
ethyl acetate	$9.4 \times 10^{-4}$	$1.5 \times 10^{-4}$
isoamyl acetate	$2.83 \times 10^{-4}$	$1.29 \times 10^{-4}$
acetone	$1.40 \times 10^{-4}$	b
methyl ethyl ketone	$4.79 \times 10^{-4}$	b
diethylether	$5.9 \times 10^{-5}$	0
ethylene chloride	$1.62 \times 10^{-4}$	$8.6 \times 10^{-5}$
1,4-dioxane	$3.70 \times 10^{-3}$	$4.97 \times 10^{-3}$
chloroform	$3.18 \times 10^{-4}$	$4.17 \times 10^{-4}$
carbon disulfide	$2.7 \times 10^{-5}$	0
pyridine	$8.77 \times 10^{-3}$	b
formamide	b	b
ethylene glycol	b	b
propylene glycol	b	b
dimethyl sulfoxide	b	b

(<sup>a</sup> All solvents are probably of U.S.P. or A.C.S. grade as previous (2); <sup>b</sup> solubility greater than  $5.40 \times 10^{-2} \text{ mol dm}^{-3}$ ).

All these values have an estimated precision of  $\pm 5\%$  (evaluator). Sample A and sample B may be designated as crystalline and amorphous forms of ampicillin sodium. However, because of this, and the unstated purity of the samples, and since the values in the Table are unconfirmed, the reported solubilities are designated as being highly **tentative**, except for (i) where the solubility is reported as being greater than  $5.40 \times 10^{-2} \text{ mol dm}^{-3}$ , (which are regarded as being **doubtful**), and (ii) where the solubility is given as 0, (these being **rejected** since the analytical method used is too insensitive for this value to have any significance).

## REFERENCES

- (1) Marsh, J.R.; Weiss, P.J. *J. Ass. Offic. Anal. Chem.* **1967**, *50* 457.  
(2) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* **1957**, *7*, 374.

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (ampicillin sodium); <math>C_{16}H_{18}N_3O_4SNa</math>; [69-52-3]</p> <p>(2) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1967</b>, <i>50</i>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin sodium in water at <math>21 \pm 1^\circ C</math> was reported for two samples of antibiotic as being:</p> <p>(1) greater than <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.40 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler)</p> <p>(2) greater than <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.40 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler)</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>The ampicillin salts were provided by Bristol Laboratories; their purity was not specified. The first sample exhibited definite birefringence when viewed under the microscope, while the second sample was practically amorphous, showing very few crystalline particles.</p> <p>Water was probably of U.S.P. or A.C.S. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <b>1957</b>, <i>7</i>, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (ampicillin sodium); $C_{16}H_{18}N_3O_4SNa$ ; [69-52-3] (2) Hydrochloric acid; HCl; [7647-01-0] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> 1967, 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of ampicillin sodium in 0.1 N HCl at <math>21 \pm 1^\circ C</math> was reported for two samples of antibiotic as being:</p> <p>(1) greater than <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.40 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler)          (2) greater than <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.40 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of 0.1 N HCl were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $21 \pm 1^\circ C$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b>  The ampicillin salts were provided by Bristol Laboratories; their purity was not specified. The first sample exhibited definite birefringence when viewed under the microscope, while the second sample was practically amorphous, showing very few crystalline particles.  Purities of hydrochloric acid and water were not specified.  <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (ampicillin sodium); $C_{16}H_{18}N_3O_4SNa$ ; [69-52-3] (2) Methanol; $CH_4O$ ; [67-56-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of ampicillin sodium in methanol at $21 \pm 1^\circ C$ was reported for two samples of antibiotic as being: (1) greater than $20 \text{ mg cm}^{-3}$ . (Greater than $5.40 \times 10^{-2} \text{ mol dm}^{-3}$ solution - compiler) (2) greater than $20 \text{ mg cm}^{-3}$ . (Greater than $5.40 \times 10^{-2} \text{ mol dm}^{-3}$ solution - compiler)	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $21 \pm 1^\circ C$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b>  The ampicillin salts were provided by Bristol Laboratories; their purity was not specified. The first sample exhibited definite birefringence when viewed under the microscope, while the second sample was practically amorphous, showing very few crystalline particles.  Methanol was probably of U.S.P. or A.C.S. grade.  <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (ampicillin sodium); <math>C_{16}H_{18}N_3O_4SNa</math>; [69-52-3]</p> <p>(2) Ethanol; <math>C_2H_6O</math>; [64-17-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. 1967, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin sodium in ethanol at <math>21 \pm 1^\circ C</math> was reported for two samples of antibiotic as being:</p> <p>(1) greater than <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.40 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler)</p> <p>(2) <math>19.78 \text{ mg cm}^{-3}</math>. (<math>5.33 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler)</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>The ampicillin salts were provided by Bristol Laboratories; their purity was not specified. The first sample exhibited definite birefringence when viewed under the microscope, while the second sample was practically amorphous, showing very few crystalline particles.</p> <p>Ethanol was probably of U.S.P. or A.C.S. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p>
	<p>REFERENCES.</p>



<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (ampicillin sodium); <math>C_{16}H_{18}N_3O_4SNa</math>; [69-52-3]</p> <p>(2) 1-Butanol,3-methyl- (isoamyl alcohol); <math>C_5H_{12}O</math>; [123-51-3]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin sodium in isoamyl alcohol at <math>21 \pm 1^\circ C</math> was reported for two samples of antibiotic as being:</p> <p>(1) <math>1.90 \text{ mg cm}^{-3}</math>. (<math>5.12 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler)</p> <p>(2) <math>19.30 \text{ mg cm}^{-3}</math>. (<math>5.20 \times 10^{-2} \text{ mol dm}^{-2}</math> solution - compiler)</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>The ampicillin salts were provided by Bristol Laboratories; their purity was not specified. The first sample exhibited definite birefringence when viewed under the microscope, while the second sample was practically amorphous, showing very few crystalline particles.</p> <p>Isoamyl alcohol was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES.</p>



<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (ampicillin sodium); <math>C_{16}H_{18}N_3O_4SNa</math>; [69-52-3]</p> <p>(2) Benzene; <math>C_6H_6</math>; [71-43-2]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> 1967, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin sodium in benzene at <math>21 \pm 1^\circ C</math> was reported for two samples of antibiotic as being:</p> <p>(1) <math>0.02 \text{ mg cm}^{-3}</math>. (<math>5.39 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler)</p> <p>(2) <math>0.0 \text{ mg cm}^{-3}</math>. (<math>0.0 \text{ mol dm}^{-3}</math> solution - compiler)</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>The ampicillin salts were provided by Bristol Laboratories; their purity was not specified. The first sample exhibited definite birefringence when viewed under the microscope, while the second sample was practically amorphous, showing very few crystalline particles.</p> <p>Benzene was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (ampicillin sodium); <math>C_{16}H_{18}N_3O_4SNa</math>; [69-52-3]</p> <p>(2) Petroleum ether (ligroin)</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin sodium in ligroin at <math>21 \pm 1^\circ C</math> was reported for two samples of antibiotic as being:</p> <p>(1) <math>0.03 \text{ mg cm}^{-3}</math>. (<math>6.73 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p> <p>(2) <math>0.0 \text{ mg cm}^{-3}</math>. (<math>0.0 \text{ mol dm}^{-3}</math> solution - compiler)</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>The ampicillin salts were provided by Bristol Laboratories; their purity was not specified. The first sample exhibited definite birefringence when viewed under the microscope, while the second sample was practically amorphous, showing very few crystalline particles.</p> <p>Ligroin was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p>
	<p>REFERENCES:</p>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (ampicillin sodium); $C_{16}H_{18}N_3O_4SNa$ ; [69-52-3] (2) Methane,tetrachloro- (carbon tetrachloride); $CCl_4$ ; [56-23-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. 1967, 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of ampicillin sodium in carbon tetrachloride at $21 \pm 1^\circ C$ was reported for two samples of antibiotic as being: (1) $0.03 \text{ mg cm}^{-3}$ . ( $8.62 \times 10^{-5} \text{ mol dm}^{-3}$ solution - compiler) (2) $0.0 \text{ mg cm}^{-3}$ . ( $0.0 \text{ mol dm}^{-3}$ solution - compiler)	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $21 \pm 1^\circ C$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ C$ . The residue was further dried for 3 hr at $60^\circ C$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b>  The ampicillin salts were provided by Bristol Laboratories; their purity was not specified. The first sample exhibited definite birefringence when viewed under the microscope, while the second sample was practically amorphous, showing very few crystalline particles.  Carbon tetrachloride was probably of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (ampicillin sodium); <math>C_{16}H_{18}N_3O_4SNa</math>; [69-52-3]</p> <p>(2) Acetic acid, ethyl ester (ethyl acetate); <math>C_4H_8O_2</math>; [141-78-6]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. 1967, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin sodium in ethyl acetate at <math>21 \pm 1^\circ C</math> was reported for two samples of antibiotic as being:</p> <p>(1) <math>0.04 \text{ mg cm}^{-3}</math>. (<math>9.42 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler)</p> <p>(2) <math>0.06 \text{ mg cm}^{-3}</math>. (<math>1.56 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler)</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>The ampicillin salts were provided by Bristol Laboratories; their purity was not specified. The first sample exhibited definite birefringence when viewed under the microscope, while the second sample was practically amorphous, showing very few crystalline particles.</p> <p>Ethyl acetate was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (ampicillin sodium); $C_{16}H_{18}N_3O_4SNa$ ; [69-52-3] (2) 1-Butanol,3-methyl acetate (isoamyl acetate); $C_7H_{14}O_2$ ; [123-92-2]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of ampicillin sodium in isoamyl acetate at $21 \pm 1^\circ\text{C}$ was reported for two samples of antibiotic as being: (1) $0.11 \text{ mg cm}^{-3}$ . ( $2.83 \times 10^{-4} \text{ mol dm}^{-3}$ solution - compiler) (2) $0.05 \text{ mg cm}^{-3}$ . ( $1.29 \times 10^{-4} \text{ mol dm}^{-3}$ solution - compiler)	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $21 \pm 1^\circ\text{C}$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ\text{C}$ . The residue was further dried for 3 hr at $60^\circ\text{C}$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b>  The ampicillin salts were provided by Bristol Laboratories; their purity was not specified. The first sample exhibited definite birefringence when viewed under the microscope, while the second sample was practically amorphous, showing very few crystalline particles.  Isoamyl acetate was probably of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b>  Solubility precision: none specified Temperature precision: $\pm 1^\circ\text{C}$ (authors).  <b>REFERENCES:</b>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (ampicillin sodium); $C_{16}H_{18}N_3O_4SNa$ ; [69-52-3] (2) 2-Butanone (methyl ethyl ketone); $C_4H_8O$ ; [78-93-3]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> 1967, 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of ampicillin sodium in methyl ethyl ketone at <math>21 \pm 1^\circ C</math> was reported for two samples of antibiotic as being:</p> <p>(1) <math>0.18 \text{ mg cm}^{-3}</math>. (<math>4.79 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler)          (2) greater than <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.40 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler)</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>The ampicillin salts were provided by Bristol Laboratories; their purity was not specified. The first sample exhibited definite birefringence when viewed under the microscope, while the second sample was practically amorphous, showing very few crystalline particles.</p> <p>Methyl ethyl ketone was probably of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b>



<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (ampicillin sodium); <math>C_{16}H_{18}N_3O_4SNa</math>; [69-52-3]</p> <p>(2) Ethane,dichloro- (ethylene chloride); <math>C_2H_4Cl_2</math>; [1300-21-6]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> 1967, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin sodium in ethylene chloride at <math>21 \pm 1^\circ C</math> was reported for two samples of antibiotic as being:</p> <p>(1) <math>0.06 \text{ mg cm}^{-3}</math>. (<math>1.62 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler)</p> <p>(2) <math>0.03 \text{ mg cm}^{-3}</math>. (<math>8.62 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler)</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was <math>0.5 \text{ mg}</math> or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>The ampicillin salts were provided by Bristol Laboratories; their purity was not specified. The first sample exhibited definite birefringence when viewed under the microscope, while the second sample was practically amorphous, showing very few crystalline particles.</p> <p>Ethylene chloride was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p>
	<p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (ampicillin sodium); <math>C_{16}H_{18}N_3O_4SNa</math>; [69-52-3]</p> <p>(2) 1,4-Dioxane; <math>C_4H_8O_2</math>; [123-91-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1967</b>, <i>50</i>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin sodium in 1,4-Dioxane at <math>21 \pm 1^\circ C</math> was reported for two samples of antibiotic as being:</p> <p>(1) <math>1.38 \text{ mg cm}^{-3}</math>. (<math>3.70 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler)</p> <p>(2) <math>1.85 \text{ mg cm}^{-3}</math>. (<math>4.97 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler)</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was <math>0.5 \text{ mg}</math> or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>The ampicillin salts were provided by Bristol Laboratories; their purity was not specified. The first sample exhibited definite birefringence when viewed under the microscope, while the second sample was practically amorphous, showing very few crystalline particles.</p> <p>1,4-Dioxane was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (ampicillin sodium); <math>C_{16}H_{18}N_3O_4SNa</math>; [69-52-3]</p> <p>(2) Methane, trichloro- (chloroform); <math>CHCl_3</math>; [67-66-3]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin sodium in chloroform at <math>21 \pm 1^\circ C</math> was reported for two samples of antibiotic as being:</p> <p>(1) <math>0.12 \text{ mg cm}^{-3}</math>. (<math>3.18 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler)</p> <p>(2) <math>0.16 \text{ mg cm}^{-3}</math>. (<math>4.17 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler)</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>The ampicillin salts were provided by Bristol Laboratories; their purity was not specified. The first sample exhibited definite birefringence when viewed under the microscope, while the second sample was practically amorphous, showing very few crystalline particles.</p> <p>Chloroform was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (ampicillin sodium); <math>C_{16}H_{18}N_3O_4SNa</math>; [69-52-3]</p> <p>(2) Carbon disulfide; <math>CS_2</math>; [75-15-0]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. 1967, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin sodium in carbon disulfide at <math>21 \pm 1^\circ C</math> was reported for two samples of antibiotic as being:</p> <p>(1) <math>0.010 \text{ mg cm}^{-3}</math>. (<math>2.69 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler)</p> <p>(2) <math>0.0 \text{ mg cm}^{-3}</math>. (<math>0.0 \text{ mol dm}^{-3}</math> solution - compiler)</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was <math>0.5 \text{ mg}</math> or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>The ampicillin salts were provided by Bristol Laboratories; their purity was not specified. The first sample exhibited definite birefringence when viewed under the microscope, while the second sample was practically amorphous, showing very few crystalline particles.</p> <p>Carbon disulfide was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p>
	<p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (ampicillin sodium); <math>C_{16}H_{18}N_3O_4SNa</math>; [69-52-3]</p> <p>(2) Pyridine; <math>C_5H_5N</math>; [110-86-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <u>50</u>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin sodium in pyridine at <math>21 \pm 1^\circ\text{C}</math> was reported for two samples of antibiotic as being:</p> <p>(1) 3.26 mg <math>\text{cm}^{-3}</math>. (<math>8.77 \times 10^{-3}</math> mol <math>\text{dm}^{-3}</math> solution - compiler)</p> <p>(2) greater than 20 mg <math>\text{cm}^{-3}</math>. (Greater than <math>5.40 \times 10^{-2}</math> mol <math>\text{dm}^{-3}</math> solution - compiler)</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1</math> mg) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1</math> mg). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01</math> mg) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01</math> mg) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>The ampicillin salts were provided by Bristol Laboratories; their purity was not specified. The first sample exhibited definite birefringence when viewed under the microscope, while the second sample was practically amorphous, showing very few crystalline particles.</p> <p>Pyridine was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (ampicillin sodium); $C_{16}H_{18}N_3O_4SNa$ ; [69-52-3] (2) Formamide; $CH_3NO$ ; [75-12-7]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of ampicillin sodium in formamide at <math>21 \pm 1^\circ C</math> was reported for two samples of antibiotic as being:</p> <p>(1) greater than <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.40 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler)</p> <p>(2) greater than <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.40 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler)</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $21 \pm 1^\circ C$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b>  The ampicillin salts were provided by Bristol Laboratories; their purity was not specified. The first sample exhibited definite birefringence when viewed under the microscope, while the second sample was practically amorphous, showing very few crystalline particles.  Formamide was probably of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES.</b>



<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (ampicillin sodium); <math>C_{16}H_{18}N_3O_4SNa</math>; [69-52-3]</p> <p>(2) 1,2-Propanediol (propylene glycol); <math>C_3H_8O_2</math>; [57-55-6]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1967</b>, <i>50</i>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin sodium in propylene glycol at <math>21 \pm 1^\circ C</math> was reported for two samples of antibiotic as being:</p> <p>(1) greater than <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.40 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler)</p> <p>(2) greater than <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.40 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler)</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>The ampicillin salts were provided by Bristol Laboratories; their purity was not specified. The first sample exhibited definite birefringence when viewed under the microscope, while the second sample was practically amorphous, showing very few crystalline particles.</p> <p>Propylene glycol was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (ampicillin sodium); <math>C_{16}H_{18}N_3O_4SNa</math>; [69-52-3]</p> <p>(2) Methane, sulfinylbis- (dimethyl sulfoxide); <math>C_2H_6OS</math>; [67-68-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u>, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin sodium in dimethyl sulfoxide at <math>21 \pm 1^\circ C</math> was reported for two samples of antibiotic as being:</p> <p>(1) greater than <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.40 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler)</p> <p>(2) greater than <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.40 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler)</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>The ampicillin salts were provided by Bristol Laboratories; their purity was not specified. The first sample exhibited definite birefringence when viewed under the microscope, while the second sample was practically amorphous, showing very few crystalline particles.</p> <p>Dimethyl sulfoxide was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo (ampicillin, ampicillin anhydrate); <math>C_{16}H_{19}N_3O_4S</math>; [69-53-4]</p> <p>(2) Aqueous solvents</p>	<p>EVALUATOR:</p> <p>Eric Tomlinson. Department of Pharmacy, University of Amsterdam, The Netherlands.</p> <p>December 1983.</p>
<p>CRITICAL EVALUATION:</p> <p>The solubilities of ampicillin anhydrate in various aqueous and aqueous/organic mixtures have been reported by six groups (1-6). Austin et al first reported the solubility in water at 303 K and 360 K to be <math>3.1 \times 10^{-2} \text{ mol dm}^{-3}</math> and <math>3.7 \times 10^{-2} \text{ mol dm}^{-3}</math> (units - evaluator), respectively. Neither a method nor the purity or source of the antibiotic were specified. Later, Marsh and Weiss (2) reported the solubility in water at <math>294 \pm 1 \text{ K}</math> to be <math>2.90 \times 10^{-2} \text{ mol dm}^{-3}</math> (units - evaluator). Again, no purity of sample was given, although the source was a reputable pharmaceutical company (Ayerst Laboratories). Poole et al (3) gave the solubility in water as <math>2.90 \times 10^{-2} \text{ mol dm}^{-3}</math> (units - evaluator), again, only the commercial source of the sample was given. Hill et al (4) have reported the solubility of ampicillin anhydrate in water at <math>310.2 \pm 0.5 \text{ K}</math> to be <math>2.94 \times 10^{-2} \text{ mol dm}^{-3}</math>. The ampicillin content was assayed for using an acid degradation method. The precision in the solubility determination may be estimated as <math>\pm 5\%</math> (evaluator). Because of the nature of preparation of the sample of antibiotic, and the reasonable temperature control, this value only is designated as <b>recommended</b>.</p> <p>Following their earlier studies (3) Hou and Poole (5) described the influence of ionic strength (KCl) on the solubility of ampicillin anhydrate in water at 298 K, (estimated temperature precision <math>\pm 1 \text{ K}</math>). They report a value at <math>\mu = 0.2</math> of <math>3.97 \times 10^{-2} \text{ mol dm}^{-3}</math> in water of pH 6.75. At ionic strengths above and below this (upto <math>\mu = 0.8</math>) the solubility decreased to a minimum of about <math>3 \times 10^{-2} \text{ mol dm}^{-3}</math>. However the graphically given data are not considered further.</p> <p>The influence of pH on the solubility of ampicillin anhydrate has been studied by a number of groups. Tsuji et al (6) examined the pH - solubility behavior at constant ionic strength (<math>\mu = 0.5 - \text{KCl}</math>) and temperature (310 K) using HCl or KOH to regulate the pH. Their results were presented graphically, and exhibited a U-shaped curve, with a minimum solubility between about pH 4.5 and pH 5.5. The original data have been obtained directly from the authors (7), and are given in the appropriate compilation sheet. The precision in solubility determination and the temperature can be estimated as <math>\pm 5\%</math> and <math>\pm 1 \text{ K}</math>, respectively (evaluator). The authors fitted the experimental data using:</p> $C_T C_o [(a_{H^+}/K_1) + 1 + (K_2/a_{H^+})]$ <p>where <math>C_T</math> is the total solubility, <math>C_o</math> the intrinsic solubility of the amphoteric ampicillin, <math>a_{H^+}</math> the hydrogen ion activity, and <math>K_1</math> and <math>K_2</math> the dissociation constants for 2-carboxylic acid and the conjugated acid of the alpha-amino group, respectively. The authors have stated (7) that the intrinsic solubility of ampicillin anhydrate calculated in this manner is <math>3.97 \times 10^{-2} \text{ mol dm}^{-3}</math>, which accords with their experimentally obtained values at pH's 5.20 and 5.60 of <math>3.93 \times 10^{-2} \text{ mol dm}^{-3}</math> and <math>3.96 \times 10^{-2} \text{ mol dm}^{-3}</math>, respectively. (The isoelectric point of this penicillin is at pH 4.91). Being an ampholyte, ampicillin anhydrate showed increased solubility both in acid (below pH 3.0) and in alkali (above pH 7.0). Hou and Poole (5) have graphically described a similar U-shaped relationship between pH and solubility in water of ampicillin anhydrate at 298 K (<math>\mu = 0.5</math>). The values appear to be in reasonable agreement with those of Tsuji et al, particularly over the pH interval 3.0 to 7.0. Hou and Poole have also determined the pH-apparent rate profile of ampicillin at 308 K in buffers of total ionic strength 0.5. They find that although the half life at pH 4.85 is about 200 hours, this falls to about 30 hours at pH's 3.0 and 7.0, and to about 10 hours at pH 1.5. This means that solubility values determined below pH 2.0 and above pH 8, must be regarded as <b>doubtful</b>. This applies to the data of Tsuji et al, although at other pH's their values may be given a <b>tentative</b> designation. A similar consideration applies to the values reported by Marsh and Weiss (2) for the solubility in 0.1 N HCl and 0.1 N NaOH at <math>294 \pm 1 \text{ K}</math> of greater than <math>5.7 \times 10^{-2} \text{ mol dm}^{-3}</math>. However the value of <math>9.90 \times 10^{-2} \text{ mol dm}^{-3}</math> (units - evaluator) at <math>310.2 \pm 0.5 \text{ K}</math> in 0.053 N HCl (4), which has a precision of determination of <math>\pm 5\%</math> (evaluator) is regarded as being <b>tentative</b>. Tsuji et al have determined the effect of <math>0.05 \text{ mol dm}^{-3}</math> sodium dodecylsulfate and <math>0.04 \text{ mol dm}^{-3}</math> cholic acid at pH 4.91 (i.e. the isoelectric point) and at 310 K (estimated precision <math>\pm 1 \text{ K}</math>, evaluator) on the aqueous solubility of ampicillin anhydrate. These are <math>7.8 \times 10^{-2} \text{ mol dm}^{-3}</math> and <math>4.4 \times 10^{-2} \text{ mol dm}^{-3}</math>, respectively. These values are estimated to have a precision of <math>\pm 5\%</math> (evaluator), and are designated as <b>tentative</b>.</p> <p>REFERENCES</p> <p>(1) Austin, K.W.B.; Marshall, A.C.; Smith, H. <i>Nature</i> <b>1965</b>, <b>208</b>, 999.  (2) Marsh, J.R.; Weiss, P.J. <i>J.Ass. Offic. Anal. Chem.</i> <b>1967</b>, <b>50</b>, 457.  (3) Poole, J.W.; Owen, G.; Silverio, J.; Freyhof, J.N.; Rosenman, S.B. <i>Curr. Ther. Res. Clin. Exp.</i> <b>1968</b>, <b>10</b>, 292.  (4) Hill, S.A.; Jones, K.H.; Seager, H; Taskis, C.B. <i>J. Pharm. Pharmacol.</i> <b>1975</b>, <b>27</b>, 594.  (5) Hou, J.P.; Poole, J.W. <i>J. Pharm. Sci.</i> <b>1969</b>, <b>58</b>, 1510.  (6) Tsuji, A.; Nakashima, E.; Hamano, S.; Yamana, T. <i>J. Pharm. Sci.</i> <b>1978</b>, <b>67</b>, 1059.  (7) Tsuji, A. Personal communication.</p>	

## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo (ampicillin, ampicillin anhydrate);  $C_{16}H_{19}N_3O_4S$ ; [69-53-4]  
 (2) Water;  $H_2O$ ; [7732-18-5]

## EVALUATOR:

Eric Tomlinson.  
 Department of Pharmacy,  
 University of Amsterdam,  
 The Netherlands.

December 1983.

## CRITICAL EVALUATION: continued

Poole and Bahal (1) have studied the influence of temperature on the solubility of ampicillin anhydrate in water. Over the temperature interval 293 K to 323 K (temperature precision estimated as  $\pm 1$  K, evaluator) they report a constant heat of solution of  $-4.2 \text{ kJ mol}^{-1}$  (units, evaluator). They report their results graphically, from which the following Table may be constructed:

Temperature K	Solubility ( $\text{mol dm}^{-3}$ ) <sup>a</sup>
293	$2.9 \times 10^{-2}$
303	$3.4 \times 10^{-2}$
313	$3.9 \times 10^{-2}$
323	$4.2 \times 10^{-2}$

(<sup>a</sup> units, evaluator)

These workers used iodometric titration to assay the amount of penicillin in their sample. The values given in the table are estimated to have a precision of  $\pm 10\%$  (evaluator). However since the purity of the sample was not specified (although the source was given) these values must be regarded as highly tentative.

## REFERENCE

- (1) Poole, J.W.; Bahal, C.K. *J. Pharm. Sci.* **1968**, *57*, 1945.

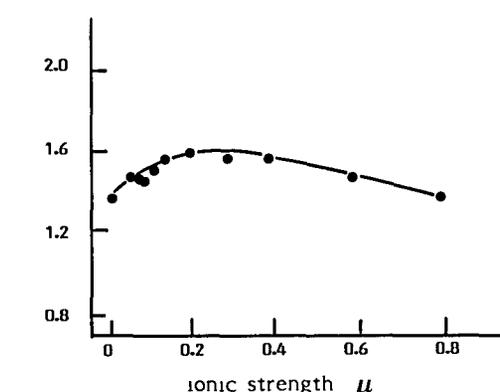
<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo- (ampicillin; ampicillin anhydrate); $C_{16}H_{19}N_3O_4S$ ; [69-53-4] (2) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Austin, K.W.B.; Marshall, A.C.; Smith, H. <b>Nature</b> <u>1965</u> , <b>208</b> , 999-1000.												
<b>VARIABLES:</b>  Temperature	<b>PREPARED BY:</b>  A. Regosz												
<b>EXPERIMENTAL VALUES:</b>  <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th colspan="3" style="text-align: center;">Solubility</th> </tr> <tr> <th style="text-align: center;"><math>t/^\circ C</math></th> <th style="text-align: center;">percent <sup>a</sup></th> <th style="text-align: center;"><math>10^2 \text{ mol dm}^{-3}</math> <sup>b</sup></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">30</td> <td style="text-align: center;">1.1</td> <td style="text-align: center;">3.1</td> </tr> <tr> <td style="text-align: center;">87</td> <td style="text-align: center;">1.3</td> <td style="text-align: center;">3.7</td> </tr> </tbody> </table> <p style="margin-left: 40px;"> <sup>a</sup> probably w/v (compiler).  <sup>b</sup> calculated by compiler         </p>		Solubility			$t/^\circ C$	percent <sup>a</sup>	$10^2 \text{ mol dm}^{-3}$ <sup>b</sup>	30	1.1	3.1	87	1.3	3.7
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30	1.1	3.1											
87	1.3	3.7											
<b>AUXILIARY INFORMATION</b>													
<b>METHOD APPARATUS/PROCEDURE:</b>  Nothing specified	<b>SOURCE AND PURITY OF MATERIALS:</b>  Ampicillin anhydrate was prepared by either drying the trihydrate form of ampicillin at 80-100°C, or by heating a suspension of hydrated ampicillin in either nitromethane or an other nitrocarbon.  The purities of the antibiotic and water were not specified.												
<b>ESTIMATED ERROR:</b>  Nothing specified													
<b>REFERENCES:</b>													

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo- (ampicillin; ampicillin anhydrate); $C_{16}H_{19}N_3O_4S$ ; [69-53-4] (2) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of ampicillin anhydrate in water at <math>21 \pm 1^\circ C</math> was reported as:  <math>10.00 \text{ mg cm}^{-3}</math>. (<math>2.90 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD / APPARATUS / PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ C</math>. The residue was further dried for 3 hours at <math>60^\circ C</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Ampicillin anhydrate was provided by Ayerst Labs, Inc., its purity was not specified.</p> <p>Water was probably of U.S.P. or A.C.S. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7-</p>

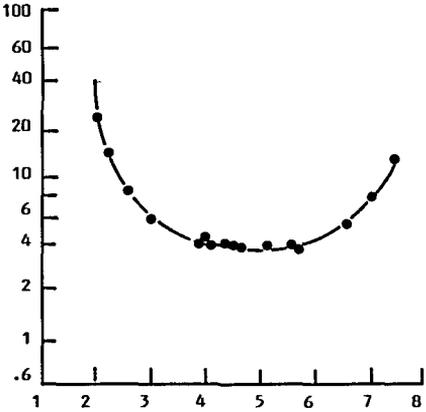
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<p>VARIABLES:</p> <p>One temperature: 37°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin anhydrate in water at <math>37 \pm 0.5^\circ C</math> was reported as:  <math>10.00 \text{ mg cm}^{-3}</math>. (<math>2.90 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of the antibiotic was placed in distilled water maintained at <math>37^\circ C \pm 0.5^\circ C</math>, and agitated at a constant rate by means of an electronically controlled stirrer. Samples were drawn through a 0.45 micron Millipore filter, diluted with water, and the solute content was determined spectrophotometrically.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Ampicillin anhydrate was supplied by Wyeth Lab. Inc., Radnor, Pennsylvania.</p> <p>Water was distilled.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: not specified  Temperature precision: <math>\pm 0.5^\circ C</math> (authors).</p> <p>REFERENCES:</p>



<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo- (ampicillin; ampicillin anhydrate); <math>C_{16}H_{19}N_3O_4S</math>; [69-53-4]</p> <p>(2) Potassium chloride; KCl; [7447-40-7]</p> <p>(3) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Hou, J.P.; Poole, J.W. <i>J. Pharm. Sci.</i> <b>1969</b>, <b>58</b>, 1510-5.</p>
<p>VARIABLES:</p> <p>One temperature: 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin anhydrate in water at constant ionic strength (<math>\mu = 0.2</math>) was reported as:</p> <p style="text-align: center;"><math>13.90 \text{ mg cm}^{-3}</math>. (<math>3.97 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of the antibiotic in 50 cm<sup>3</sup> water were placed in a 120 cm<sup>3</sup> bottle and rotated mechanically in a constant temperature bath for about 2 hours at 25°C. The ionic strength was adjusted to 0.2 <math>\mu</math> with potassium chloride. Samples were taken from the supernatant and filtered through a Milipore filter, then diluted with water to give a final conc of about 1-4 mg cm<sup>-3</sup>. The content of ampicillin was determined by a modified iodometric procedure (1).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Ampicillin anhydrate was supplied by Wyeth Labs. Its purity was greater than 98%.</p> <p>Potassium chloride was reagent grade. Water was deionised, distilled and freshly boiled with a pH of 6.75 at 25°C.</p> <p>ESTIMATED ERROR:</p> <p>Nothing specified</p> <p>REFERENCES:</p> <p>(1) Weiss, P.J. <i>Antibiotics and Chemotherapy</i> <b>1959</b>, <b>9</b>, 660-6.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo- (ampicillin; ampicillin anhydrate); <math>C_{16}H_{19}N_3O_4S</math>; [69-53-4]</p> <p>(2) Potassium chloride; KCl; [7447-40-7]</p> <p>(3) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Hou, J.P.; Poole, J.W. <i>J. Pharm. Sci.</i> <b>1969</b>, <b>58</b>, 1510-5.</p>																												
<p>VARIABLES:</p> <p>Ionic strength at 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>																												
<p>EXPERIMENTAL VALUES:</p> <div style="text-align: center;">  <p>solubility of ampicillin in water [g 100cm<sup>-3</sup>]</p> <p>ionic strength <math>\mu</math></p> <table border="1" data-bbox="394 490 894 882"> <caption>Data points from the solubility graph</caption> <thead> <tr> <th>Ionic strength (<math>\mu</math>)</th> <th>Solubility (g 100cm<sup>-3</sup>)</th> </tr> </thead> <tbody> <tr><td>0.0</td><td>1.40</td></tr> <tr><td>0.02</td><td>1.45</td></tr> <tr><td>0.04</td><td>1.48</td></tr> <tr><td>0.06</td><td>1.50</td></tr> <tr><td>0.08</td><td>1.52</td></tr> <tr><td>0.10</td><td>1.54</td></tr> <tr><td>0.15</td><td>1.58</td></tr> <tr><td>0.20</td><td>1.60</td></tr> <tr><td>0.25</td><td>1.58</td></tr> <tr><td>0.30</td><td>1.55</td></tr> <tr><td>0.40</td><td>1.52</td></tr> <tr><td>0.60</td><td>1.45</td></tr> <tr><td>0.80</td><td>1.40</td></tr> </tbody> </table> </div>		Ionic strength ( $\mu$ )	Solubility (g 100cm <sup>-3</sup> )	0.0	1.40	0.02	1.45	0.04	1.48	0.06	1.50	0.08	1.52	0.10	1.54	0.15	1.58	0.20	1.60	0.25	1.58	0.30	1.55	0.40	1.52	0.60	1.45	0.80	1.40
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<b>VARIABLES:</b>  pH at 37°C	<b>PREPARED BY:</b>  A. Regosz																																																												
<b>EXPERIMENTAL VALUES:</b>  <div style="text-align: center;">Solubility</div> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: center;">pH<sup>a</sup></th> <th style="text-align: center;"><math>10^2 \text{ mol dm}^{-3a}</math></th> <th style="text-align: center;"><math>\text{mg cm}^{-3b}</math></th> <th style="text-align: center;">pH<sup>a</sup></th> <th style="text-align: center;"><math>10^2 \text{ mol dm}^{-3a}</math></th> <th style="text-align: center;"><math>\text{mg cm}^{-3b}</math></th> </tr> </thead> <tbody> <tr> <td>2.05</td> <td>22.60</td> <td>78.96</td> <td>4.66</td> <td>3.81</td> <td>13.31</td> </tr> <tr> <td>2.22</td> <td>14.00</td> <td>48.92</td> <td>5.20</td> <td>3.93</td> <td>13.73</td> </tr> <tr> <td>2.62</td> <td>8.14</td> <td>28.44</td> <td></td> <td>3.97 - C<sub>o</sub></td> <td>13.87</td> </tr> <tr> <td>2.99</td> <td>5.56</td> <td>19.43</td> <td>5.60</td> <td>3.96</td> <td>13.84</td> </tr> <tr> <td>3.90</td> <td>4.12</td> <td>14.39</td> <td>5.64</td> <td>3.89</td> <td>13.59</td> </tr> <tr> <td>4.04</td> <td>4.19</td> <td>14.64</td> <td>6.58</td> <td>5.47</td> <td>19.11</td> </tr> <tr> <td>4.09</td> <td>3.92</td> <td>13.70</td> <td>7.05</td> <td>7.98</td> <td>27.88</td> </tr> <tr> <td>4.45</td> <td>4.00</td> <td>13.98</td> <td>7.37</td> <td>13.50</td> <td>47.17</td> </tr> <tr> <td>4.59</td> <td>3.95</td> <td>13.80</td> <td></td> <td></td> <td></td> </tr> </tbody> </table> <p><sup>a</sup>Numerical data obtained from the author (A. Tsuji).  <sup>b</sup>Calculated by compiler            C<sub>o</sub> - the intrinsic solubility estimated from the solubility at the isoelectric point - is defined by equation [1].</p>		pH <sup>a</sup>	$10^2 \text{ mol dm}^{-3a}$	$\text{mg cm}^{-3b}$	pH <sup>a</sup>	$10^2 \text{ mol dm}^{-3a}$	$\text{mg cm}^{-3b}$	2.05	22.60	78.96	4.66	3.81	13.31	2.22	14.00	48.92	5.20	3.93	13.73	2.62	8.14	28.44		3.97 - C <sub>o</sub>	13.87	2.99	5.56	19.43	5.60	3.96	13.84	3.90	4.12	14.39	5.64	3.89	13.59	4.04	4.19	14.64	6.58	5.47	19.11	4.09	3.92	13.70	7.05	7.98	27.88	4.45	4.00	13.98	7.37	13.50	47.17	4.59	3.95	13.80			
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<b>METHOD APPARATUS/PROCEDURE:</b>  An excess of ampicillin anhydrate was added to a glass-stoppered flask, followed by addition of $0.5 \text{ mol dm}^{-3}$ KCl aqueous solution to a constant ionic strength ( $\mu = 0.5$ ). The suspension was then adjusted to the appropriate pH with standard hydrochloric acid or potassium hydroxide solution. The flask was placed in a constant temperature water bath at 37°C and mechanically shaken for 2 hours. A sample was taken through a 0.45 micron Sartorius membrane filter, the pH was measured, and the sample was assayed after appropriate dilution with water. The content of ampicillin was determined by iodometric titration and by spectrophotometric measurement at 260 nm.	<b>SOURCE AND PURITY OF MATERIALS:</b>  Ampicillin anhydrate was supplied by Takeda Chemical Industries, Osaka, Japan and had a potency of $1015 \mu\text{g}/\text{mg}^{-1}$ .  All other chemicals were reagent grade and were used without further purification. Water was distilled.																																																												
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<p>VARIABLES:</p> <p>pH at 37°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>COMMENTS AND/OR ADDITIONAL DATA:</p> <p style="text-align: right;">solubility [<math>10^2 \text{ mol dm}^{-3}</math>]</p> <p>In the figure, the points are the experimental results<sup>a</sup>. The line was calculated from equation [1].</p> $C_T = C_o \left( \frac{a_{H^+}}{K_1} + 1 + \frac{K_2}{a_{H^+}} \right) \quad [1]$ <p>where <math>C_T</math> is the total solubility, <math>C_o</math> is the intrinsic solubility of amphoteric ampicillin (i.e. of the electrically neutral zwitterion), <math>a_{H^+}</math> is the hydrogen-ion activity of the solution, and <math>K_1</math> and <math>K_2</math> are dissociation constants for 2-carboxylic acid and the conjugated acid of the <math>\alpha</math>-amino group, respectively.</p> <div style="text-align: right;">  <p>pH at a constant ionic strength of <math>0.5 \mu</math></p> </div>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p>	<p>SOURCE AND PURITY OF MATERIALS:</p>
	<p>ESTIMATED ERROR:</p>
	<p>REFERENCES:</p>

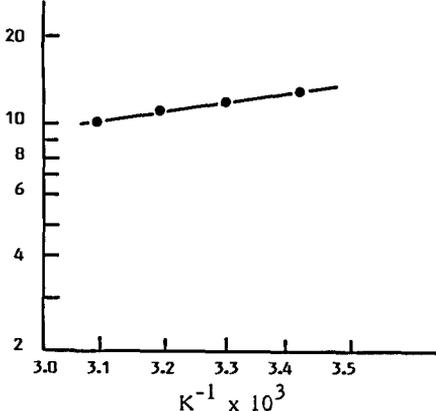


<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo- (ampicillin; ampicillin anhydrate); $C_{16}H_{19}N_3O_4S$ ; [69-53-4] (2) Hydrochloric acid; HCl; [7647-01-0] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of ampicillin anhydrate in 0.1 N hydrochloric acid at <math>21 \pm 1^\circ\text{C}</math> was reported as greater than:</p> <p style="text-align: center;"><math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.70 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of 0.1 N HCl were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $21 \pm 1^\circ\text{C}$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b>  Ampicillin anhydrate was provided by Ayerst Lab. Inc., its purity was not specified.  The purity of hydrochloric acid and water was not specified.
<b>ESTIMATED ERROR:</b>  Solubility precision: none specified Temperature precision: $\pm 1^\circ\text{C}$ (authors).	
<b>REFERENCES:</b>	

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo- (ampicillin; ampicillin anhydrate); <math>C_{16}H_{19}N_3O_4S</math>; [69-53-4]</p> <p>(2) Hydrochloric acid; HCl; [7647-01-0]</p> <p>(3) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Hill, S.A.; Jones, K.H.; Seager, H.; Taskis, C.B. <i>J. Pharm. Pharmacol.</i> <u>1975</u>, <b>27</b>, 594-8.</p>
<p>VARIABLES:</p> <p>One temperature: 37°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin anhydrate in 0.053 N hydrochloric acid at <math>37 \pm 0.5^\circ\text{C}</math> was reported as: <math>34.50 \text{ mg cm}^{-3}</math>. (<math>9.90 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of ampicillin anhydrate was stirred in 0.053 N HCl for about 3 hours at <math>37 \pm 0.5^\circ\text{C}</math>. A sample was taken from the supernatant and assayed for ampicillin content by the acid degradation method (1).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Ampicillin anhydrate was prepared by refluxing the trihydrate form in a mixture of 15% v/v water in isopropanol. The cooled suspension was filtered, and the precipitated anhydrate was washed in isopropanol and dried under vacuum at room temperature. The identity of the sample was investigated by X-ray diffraction and infrared spectroscopy.</p> <p>Distilled water was used. The source and purity of HCl were not described.</p> <p>ESTIMATED ERROR:</p> <p>Nothing specified</p> <p>REFERENCES:</p> <p>(1) Smith, J.W.G.; De Grey, G.E.; Patel, V.J. <i>Analyst</i> <u>1967</u>, <b>92</b>, 247-52.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo- (ampicillin; ampicillin anhydrate); <math>C_{16}H_{19}N_3O_4S</math>; [69-53-4]</p> <p>(2) Sulfuric acid monododecyl ester sodium salt (Sodium dodecyl sulfate); <math>C_{12}H_{25}O_4SNa</math>; [151-21-3]</p> <p>(3) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Tsuji, A.; Nakashima, E.; Hamano, S.; Yamana, T. <i>J. Pharm. Sci.</i> 1978, 67, 1059-66.</p>
<p>VARIABLES:</p> <p>One temperature: 37°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility<sup>a</sup> of ampicillin anhydrate in aqueous solution at 37°C containing 0.05 mol dm<sup>-3</sup> sodium dodecyl sulfate was reported as:</p> <p style="text-align: center;"><math>7.80 \times 10^{-2}</math> mol dm<sup>-3</sup>. (27.25 mg cm<sup>-3</sup> - compiler).</p> <p><sup>a</sup>Estimated from solubility at the isoelectric point.</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of ampicillin anhydrate and water containing 0.05 mol dm<sup>-3</sup> sodium dodecyl sulfate were placed in a glass-stoppered flask, and mechanically shaken for about 2 hours in a constant temperature water bath at 37°C. Samples were taken through a 0.45 micron membrane filter, and determined by iodometric titration.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Ampicillin anhydrate was supplied by Takeda Chemical Industries, Osaka, Japan, and had a potency of 1015 µg/mg<sup>-1</sup>.</p> <p>All other chemicals were reagent grade and were used without further purification. Water was distilled.</p> <p>ESTIMATED ERROR:</p> <p>Nothing specified</p> <p>REFERENCES:</p>



<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo- (ampicillin; ampicillin anhydrate); <math>C_{16}H_{19}N_3O_4S</math>; [69-53-4]</p> <p>(2) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Poole, J.W.; Bahal, C.K. <i>J. Pharm. Sci.</i> <u>1968</u>, <u>57</u>, 1945-8.</p>														
<p>VARIABLES:</p> <p>Temperature</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>														
<p>EXPERIMENTAL VALUES:</p> <p>The apparent equilibrium solubilities of ampicillin anhydrate in distilled water were determined over the temperature range 20 to 50°C. The value of the heat of solution was calculated from the slope of the van 't Hoff plot to be <math>-1.0 \text{ kcal mol}^{-1}</math>.</p> <div style="text-align: center;">  <table border="1" style="margin-left: auto; margin-right: auto;"> <caption>Data points from the Van't Hoff plot</caption> <thead> <tr> <th><math>K^{-1} \times 10^3</math></th> <th>Solubility [<math>\text{mg cm}^{-3}</math>]</th> </tr> </thead> <tbody> <tr> <td>3.0</td> <td>9.5</td> </tr> <tr> <td>3.1</td> <td>10.0</td> </tr> <tr> <td>3.2</td> <td>10.5</td> </tr> <tr> <td>3.3</td> <td>11.0</td> </tr> <tr> <td>3.4</td> <td>11.5</td> </tr> <tr> <td>3.5</td> <td>12.0</td> </tr> </tbody> </table> </div>		$K^{-1} \times 10^3$	Solubility [ $\text{mg cm}^{-3}$ ]	3.0	9.5	3.1	10.0	3.2	10.5	3.3	11.0	3.4	11.5	3.5	12.0
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<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of ampicillin anhydrate (2 g) was added to 100 <math>\text{cm}^3</math> of distilled water previously equilibrated at the desired temp. The bottles were rotated in a constant temperature water bath. Samples were withdrawn at intervals and filtered through a Millipore filter and diluted immediately to avoid any precipitation. The ampicillin content was determined by iodometric titration.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Ampicillin anhydrate was from Wyeth Laboratories, and had a melting point of 203-204°C. Its purity was not specified.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: <math>\pm 2\%</math> (compiler)  Temperature precision: <math>\pm 1\%</math> (compiler).</p> <p>REFERENCES:</p>														

## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo (ampicillin, ampicillin anhydrate);  $C_{16}H_{19}N_3O_4S$ ; [69-53-4]
- (2) All organic and organic/aqueous solvents

## EVALUATOR:

Eric Tomlinson.  
Department of Pharmacy,  
University of Amsterdam,  
The Netherlands.  
December 1983.

## CRITICAL EVALUATION:

Marsh and Weiss have determined the solubilities of ampicillin anhydrate in 23 different non aqueous solvents at  $294 \pm 1$  K. These workers studied a sample of the antibiotic provided by Ayerst Laboratories, its purity was not specified. The amount of penicillin dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than  $20 \text{ mg cm}^{-3}$ . All values reported were uncorrected for solvent blank, which was generally less than  $0.05 \text{ mg total}$ . All data according to Marsh and Weiss have been recalculated to SI units (compiler), and are given in the Table.

Solvent <sup>a</sup>	Solubility (at $294 \pm 1$ K), ( $\text{mol dm}^{-3}$ ) <sup>b</sup>
methanol	$8.49 \times 10^{-3}$
ethanol	$1.12 \times 10^{-4}$
isopropanol	$1.57 \times 10^{-4}$
isoamyl alcohol	$3.58 \times 10^{-4}$
cyclohexane	$1.37 \times 10^{-4}$
benzene	$5.7 \times 10^{-6}$
ligroin	$2.9 \times 10^{-5}$
isooctane	0
carbon tetrachloride	$2.3 \times 10^{-5}$
ethyl acetate	$7.2 \times 10^{-5}$
isoamyl acetate	$8.6 \times 10^{-5}$
acetone	$3.58 \times 10^{-4}$
methyl ethyl ketone	$1.49 \times 10^{-4}$
diethylether	$6.3 \times 10^{-5}$
ethylene chloride	$9.2 \times 10^{-5}$
1,4-dioxane	$1.70 \times 10^{-4}$
chloroform	$2.72 \times 10^{-4}$
carbon disulfide	$4.3 \times 10^{-3}$
pyridine	$6.01 \times 10^{-3}$
formamide	c
ethylene glycol	$5.27 \times 10^{-2}$
propylene glycol	$6.38 \times 10^{-3}$
dimethyl sulfoxide	c

(<sup>a</sup> All solvents are probably of U.S.P. or A.C.S. grade as previous (2); <sup>b</sup> units calculated by evaluator; <sup>c</sup> solubility greater than  $5.70 \times 10^{-2} \text{ mol dm}^{-3}$ ).

All these values have an estimated precision of  $\pm 5\%$  (evaluator). Because of the unstated purity of the sample, and since the values in the Table are unconfirmed, the reported solubilities are designated as being highly **tentative**, except for (u) where the solubility is reported as being greater than  $5.70 \times 10^{-2} \text{ mol dm}^{-3}$ , (which are regarded as being **doubtful**), and (u) where the solubilities given are less than  $4 \times 10^{-5} \text{ mol dm}^{-3}$ , (these being **rejected** since the analytical method used is too insensitive for this value to have any significance).

Hou and Poole have reported the effect of salt and organic solvent (20% v/v) on the aqueous solubility of ampicillin anhydrate at 298 K (2). They presented their results in graphical form (see compilation sheets), though they stated that the solubility in water was  $3.97 \times 10^{-2} \text{ mol dm}^{-3}$ , (see previous evaluation), but that due to the presence of the organic solvents (i.e. either methanol, ethanol, n-propanol, isopropanol, acetone, 1,4-dioxane, tetrahydrofuran or dimethyl sulfoxide), at low salt concentrations a relatively low solubility was found, but that this increased noticeably with an increase in salt concentration (particularly in the presence of 1,4-dioxane and tetrahydrofuran). The data are estimated to have been determined with a precision of  $\pm 5\%$  (evaluator), though if read from the original figure, the values produced would have an estimated precision of  $\pm 10\%$ . The values so produced would be regarded as **tentative**.

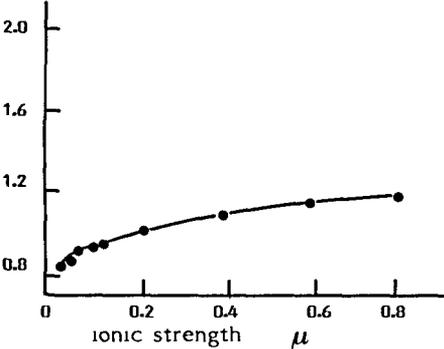
## REFERENCES

- (1) Marsh, J.R.; Weiss, P.J. *J. Ass. Offic. Anal. Chem.* **1967**, *50* 457.  
 (2) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* **1957**, *7*, 374.  
 (3) Hou, J.P.; Poole, J.W. *J. Pharm. Sci.* **1969**, *58*, 1510.



<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo- (ampicillin; ampicillin anhydrate); <math>C_{16}H_{19}N_3O_4S</math>; [69-53-4]</p> <p>(2) Methanol; <math>CH_4O</math>; [67-56-1]</p> <p>(3) Potassium chloride; <math>KCl</math>; [7447-40-7]</p> <p>(4) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Hou, J.P.; Poole, J.W. <i>J. Pharm. Sci.</i> <u>1969</u>, <u>58</u>, 1510-5</p>																						
<p>VARIABLES:</p> <p>Ionic strength at 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>																						
<p>EXPERIMENTAL VALUES:</p> <div style="display: flex; align-items: center;"> <div style="flex: 1;"> <p>solubility of ampicillin in a 20 % (v/v) mixture of methanol in water [g 100cm<sup>-3</sup>]</p> </div> <div style="flex: 2;"> <table border="1" style="margin-left: auto; margin-right: auto;"> <caption>Data points from the solubility graph</caption> <thead> <tr> <th>Ionic strength <math>\mu</math></th> <th>Solubility [g 100cm<sup>-3</sup>]</th> </tr> </thead> <tbody> <tr><td>0.0</td><td>0.85</td></tr> <tr><td>0.02</td><td>0.88</td></tr> <tr><td>0.04</td><td>0.90</td></tr> <tr><td>0.06</td><td>0.92</td></tr> <tr><td>0.08</td><td>0.94</td></tr> <tr><td>0.10</td><td>0.96</td></tr> <tr><td>0.15</td><td>1.00</td></tr> <tr><td>0.40</td><td>1.05</td></tr> <tr><td>0.60</td><td>1.10</td></tr> <tr><td>0.80</td><td>1.15</td></tr> </tbody> </table> <p style="text-align: center;">Ionic strength <math>\mu</math></p> </div> </div>		Ionic strength $\mu$	Solubility [g 100cm <sup>-3</sup> ]	0.0	0.85	0.02	0.88	0.04	0.90	0.06	0.92	0.08	0.94	0.10	0.96	0.15	1.00	0.40	1.05	0.60	1.10	0.80	1.15
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<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of ampicillin anhydrate and 50 cm<sup>3</sup> of a 20% v/v methanol-water mixture were placed in a 120 cm<sup>3</sup> bottle and rotated mechanically in a constant temperature bath for about 2 hours at 25°C. Ionic strength was maintained by adding appropriate amounts of potassium chloride. Samples were taken from the supernatants and filtered through Milipore filters, then diluted with water to make final concentrations of about 1-4 mg cm<sup>-3</sup>. The ampicillin anhydrate content was determined by a modified iodometric procedure (1).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Ampicillin anhydrate was supplied by Wyeth Labs. Its purity was greater than 98%. Methanol and potassium chloride were reagent grade.</p> <p>Water was deionized, distilled and freshly boiled, with a pH of 6.75 at 25°C.</p> <p>ESTIMATED ERROR:</p> <p>Nothing specified</p> <p>REFERENCES:</p> <p>(1) Weiss, P.J. <i>Antibiotics and Chemotherapy</i> <u>1959</u>, <u>9</u>, 660-6.</p>																						

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo- (ampicillin; ampicillin anhydrate); <math>C_{16}H_{19}N_3O_4S</math>; [69-53-4]</p> <p>(2) Ethanol; <math>C_2H_6O</math>; [64-17-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <i>50</i>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin anhydrate in ethanol at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.39 \text{ mg cm}^{-3}</math>. (<math>1.12 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hours at <math>60^\circ\text{C}</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Ampicillin anhydrate was provided by Ayerst Labs, Inc., its purity was not specified.</p> <p>Ethanol was probably of U.S.P. or A.C.S. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo- (ampicillin; ampicillin anhydrate); <math>C_{16}H_{19}N_3O_4S</math>; [69-53-4]</p> <p>(2) Ethanol; <math>C_2H_6O</math>; [64-17-5]</p> <p>(3) Potassium chloride; <math>KCl</math>; [7747-40-7]</p> <p>(4) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Hou, J.P.; Poole, J.W. <i>J. Pharm. Sci.</i> <u>1969</u>, <b>58</b>, 1510-5</p>
<p>VARIABLES:</p> <p>Ionic strength at 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <div style="display: flex; align-items: center; justify-content: center;"> <div style="margin-right: 20px;"> <p>solubility of ampicillin [g 100cm<sup>-3</sup>]</p> </div>  </div>	
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<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo- (ampicillin; ampicillin anhydrate); <math>C_{16}H_{19}N_3O_4S</math>; [69-53-4]</p> <p>(2) 2-Propanol (isopropanol); <math>C_3H_8O</math>; [67-63-0]</p> <p>(3) Potassium chloride; <math>KCl</math>; [7747-40-7]</p> <p>(4) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Hou, J.P.; Poole, J.W. <i>J. Pharm. Sci.</i> 1969, 58, 1510-5</p>																
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<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin anhydrate in isoamyl alcohol at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.13 \text{ mg cm}^{-3}</math>. (<math>3.58 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hours at <math>60^\circ\text{C}</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Ampicillin anhydrate was provided by Ayerst Labs, Inc., its purity was not specified.</p> <p>Isoamyl alcohol was probably of A.C.S. or U.S.P grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p>

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<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin anhydrate in cyclohexane at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.05 \text{ mg cm}^{-3}</math>. (<math>1.37 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
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<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin anhydrate in ligroin at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.01 \text{ mg cm}^{-3}</math>. (<math>2.86 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hours at <math>60^\circ\text{C}</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Ampicillin anhydrate was provided by Ayerst Labs, Inc., its purity was not specified.</p> <p>Ligroin was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p>







<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo- (ampicillin; ampicillin anhydrate); $C_{16}H_{19}N_3O_4S$ ; [69-53-4] (2) 1-Butanol,3-methyl acetate (isoamyl acetate); $C_7H_{14}O_2$ ; [123-92-2]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. 1967, 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of ampicillin anhydrate in isoamyl acetate at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.03 \text{ cm}^{-3}</math>. (<math>8.59 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
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<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo- (ampicillin; ampicillin anhydrate); <math>C_{16}H_{19}N_3O_4S</math>; [69-53-4]</p> <p>(2) 2-Butanone (methyl ethyl ketone); <math>C_4H_8O</math>; [78-93-3]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin anhydrate in methyl ethyl ketone at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.05 \text{ mg cm}^{-3}</math>. (<math>1.49 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hours at <math>60^\circ\text{C}</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Ampicillin anhydrate was provided by Ayerst Labs, Inc., its purity was not specified.</p> <p>Methyl ethyl ketone was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo- (ampicillin; ampicillin anhydrate); $C_{16}H_{19}N_3O_4S$ ; [69-53-4] (2) Ethane, 1,1'-oxybis- (diethyl ether); $C_4H_{10}O$ ; [60-29-7]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1967</b> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of ampicillin anhydrate in diethyl ether at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.02 \text{ mg cm}^{-3}</math>. (<math>6.30 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hours at <math>60^\circ\text{C}</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Ampicillin anhydrate was provided by Ayerst Labs, Inc., its purity was not specified.</p> <p>Diethyl ether was probably of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <b>REFERENCES.</b>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo- (ampicillin; ampicillin anhydrate); $C_{16}H_{19}N_3O_4S$ ; [69-53-4] (2) Ethane, dichloro- (ethylene chloride); $C_2H_4Cl_2$ ; [1300-21-6]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1967</b> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of ampicillin anhydrate in ethylene chloride at <math>21 \pm 1^\circ C</math> was reported as:  <math>9.16 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ C</math>. The residue was further dried for 3 hours at <math>60^\circ C</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Ampicillin anhydrate was provided by Ayerst Labs, Inc., its purity was not specified.</p> <p>Ethylene chloride was probably of A.C.S. or U.S.P. grade.</p>
	<b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p>
	<b>REFERENCES:</b>



<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo- (ampicillin; ampicillin anhydrate); <math>C_{16}H_{19}N_3O_4S</math>; [69-53-4]</p> <p>(2) 1,4-Dioxane; <math>C_4H_8O_2</math>; [123-91-1]</p> <p>(3) Potassium chloride; KCl; [7447-40-7]</p> <p>(4) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Hou, J.P.; Poole, J.W. <i>J. Pharm. Sci.</i> <b>1969</b>, <b>58</b>, 1510-5</p>																						
<p>VARIABLES:</p> <p>Ionic strength at 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>																						
<p>EXPERIMENTAL VALUES:</p> <div style="display: flex; align-items: center;"> <div style="flex: 1;"> <p>Solubility of ampicillin in a 20% (v/v) mixture of 1,4-dioxane in water [<math>g\ 100cm^{-3}</math>]</p> </div> <div style="flex: 2;"> <table border="1" style="margin-top: 10px;"> <caption>Estimated data points from the graph</caption> <thead> <tr> <th>Ionic strength <math>\mu</math></th> <th>Solubility [<math>g\ 100cm^{-3}</math>]</th> </tr> </thead> <tbody> <tr><td>0.0</td><td>1.35</td></tr> <tr><td>0.02</td><td>1.40</td></tr> <tr><td>0.04</td><td>1.45</td></tr> <tr><td>0.06</td><td>1.50</td></tr> <tr><td>0.08</td><td>1.55</td></tr> <tr><td>0.10</td><td>1.60</td></tr> <tr><td>0.15</td><td>1.70</td></tr> <tr><td>0.40</td><td>1.85</td></tr> <tr><td>0.60</td><td>1.90</td></tr> <tr><td>0.80</td><td>1.95</td></tr> </tbody> </table> </div> </div>		Ionic strength $\mu$	Solubility [ $g\ 100cm^{-3}$ ]	0.0	1.35	0.02	1.40	0.04	1.45	0.06	1.50	0.08	1.55	0.10	1.60	0.15	1.70	0.40	1.85	0.60	1.90	0.80	1.95
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<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of ampicillin anhydrate in chloroform at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.10 \text{ mg cm}^{-3}</math>. (<math>2.72 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ C</math>. The residue was further dried for 3 hours at <math>60^\circ C</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<b>SOURCE AND PURITY OF MATERIALS.</b>  <p>Ampicillin anhydrate was provided by Ayerst Labs, Inc., its purity was not specified.</p> <p>Chloroform was probably of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b>





<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo- (ampicillin; ampicillin anhydrate); $C_{16}H_{19}N_3O_4S$ ; [69-53-4] (2) Formamide; $CH_3NO$ ; [75-12-7]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of ampicillin anhydrate in formamide at <math>21 \pm 1^\circ C</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.70 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Ampicillin anhydrate was provided by Ayerst Labs, Inc., its purity was not specified.</p> <p>Formamide was probably of A.C.S. or U.S.P. grade.</p>
	<b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p>
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<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of ampicillin anhydrate in ethylene glycol at $21 \pm 1^\circ\text{C}$ was reported as: $18.42 \text{ mg cm}^{-3}$ . ( $5.27 \times 10^{-2} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $21 \pm 1^\circ\text{C}$ ). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four $\text{cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle and evaporated by heating at $100^\circ\text{C}$ . The residue was further dried for 3 hours at $60^\circ\text{C}$ in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed ( $\pm 0.01 \text{ mg}$ ).	<b>SOURCE AND PURITY OF MATERIALS.</b> Ampicillin anhydrate was provided by Ayerst Labs, Inc., its purity was not specified.  Ethylene glycol was probably of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ\text{C}$ (authors).  <b>REFERENCES.</b>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo- (ampicillin; ampicillin anhydrate); $C_{16}H_{19}N_3O_4S$ ; [69-53-4] (2) 1,2-Propanediol (propylene glycol); $C_3H_8O_2$ ; [57-55-6]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u> , <u>50</u> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of ampicillin anhydrate in propylene glycol at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>2.23 \text{ mg cm}^{-3}</math>. (<math>6.38 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $21 \pm 1^\circ\text{C}$ ). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four $\text{cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle and evaporated by heating at $100^\circ\text{C}$ . The residue was further dried for 3 hours at $60^\circ\text{C}$ in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed ( $\pm 0.01 \text{ mg}$ ).	<b>SOURCE AND PURITY OF MATERIALS:</b>  Ampicillin anhydrate was provided by Ayerst Labs, Inc., its purity was not specified.  Propylene glycol was probably of A.C.S. or U.S.P. grade.  <b>ESTIMATED ERROR:</b>  Solubility precision: none specified Temperature precision: $\pm 1^\circ\text{C}$ (authors).  <b>REFERENCES:</b>



<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo- (ampicillin; ampicillin anhydrate); <math>C_{16}H_{19}N_3O_4S</math>; [69-53-4]</p> <p>(2) Methane,sulfinylbis- (dimethyl sulfoxide); <math>C_2H_6OS</math>; [67-68-5]</p> <p>(3) Potassium chloride; KCl; [7747-40-7]</p> <p>(4) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Hou, J.P.; Poole, J.W. <i>J. Pharm. Sci.</i> <b>1969</b>, <b>58</b>, 1510-5</p>																
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<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo- (ampicillin; ampicillin anhydrate); <math>C_{16}H_{19}N_3O_4S</math>; [69-53-4]</p> <p>(2) Furan, tetrahydro- (tetrahydrofuran); <math>C_4H_8O</math>; [109-99-9]</p> <p>(3) Potassium chloride; KCl; [7447-40-7]</p> <p>(4) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Hou, J.P.; Poole, J.W. <i>J. Pharm. Sci.</i> <b>1969</b>, <b>58</b>, 1510-5</p>																		
<p>VARIABLES:</p> <p>Ionic strength at 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>																		
<p>EXPERIMENTAL VALUES:</p> <div style="display: flex; align-items: center;"> <div style="flex: 1;"> <p>Solubility of ampicillin in a 20% (v/v) mixture of tetrahydrofuran in water [g 100cm<sup>-3</sup>]</p> </div> <div style="flex: 2;"> <table border="1"> <caption>Data points estimated from the graph</caption> <thead> <tr> <th>Ionic strength, <math>\mu</math></th> <th>Solubility [g 100cm<sup>-3</sup>]</th> </tr> </thead> <tbody> <tr><td>0.0</td><td>1.3</td></tr> <tr><td>0.02</td><td>1.35</td></tr> <tr><td>0.05</td><td>1.4</td></tr> <tr><td>0.1</td><td>1.45</td></tr> <tr><td>0.2</td><td>1.6</td></tr> <tr><td>0.4</td><td>1.75</td></tr> <tr><td>0.6</td><td>1.85</td></tr> <tr><td>0.8</td><td>1.9</td></tr> </tbody> </table> </div> </div>		Ionic strength, $\mu$	Solubility [g 100cm <sup>-3</sup> ]	0.0	1.3	0.02	1.35	0.05	1.4	0.1	1.45	0.2	1.6	0.4	1.75	0.6	1.85	0.8	1.9
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0.6	1.85																		
0.8	1.9																		
<p>AUXILIARY INFORMATION</p>																			
<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of ampicillin anhydrate and 50 cm<sup>3</sup> of a 20% v/v tetrahydrofuran-water mixture were placed in a 120 cm<sup>3</sup> bottle and rotated mechanically in a constant temperature bath for about 2 hours at 25°C. Ionic strength was maintained by adding appropriate amounts of potassium chloride. Samples were taken from the supernatants and filtered through Milipore filters, then diluted with water to make final concentrations of about 1-4 mg cm<sup>-3</sup>. The ampicillin anhydrate content was determined by a modified iodometric procedure (1).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Ampicillin anhydrate was supplied by Wyeth Labs. Its purity was greater than 98%. Tetrahydrofuran and potassium chloride were reagent grade.</p> <p>Water was deionized, distilled and freshly boiled, with a pH of 6.75 at 25°C.</p> <p>ESTIMATED ERROR:</p> <p>Nothing specified</p> <p>REFERENCES.</p> <p>(1) Weiss, P.J. <i>Antibiotics and Chemotherapy</i> <b>1959</b>, <b>9</b>, 660-6.</p>																		

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); <math>C_{16}H_{19}N_3O_4 \cdot 3H_2O</math>; [7177-48-2]</p> <p>(2) Aqueous solvents</p>	<p>EVALUATOR:</p> <p>Eric Tomlinson. Department of Pharmacy, University of Amsterdam, The Netherlands. December 1983.</p>
<p>CRITICAL EVALUATION:</p> <p>The solubilities of ampicillin trihydrate in various aqueous mixtures have been reported by seven groups (1-7). Austin et al (1) first reported the solubility in water at 303 K to be <math>1.7 \times 10^{-2} \text{ mol dm}^{-3}</math> (units - evaluator). A method of solubility determination was not given, the sample of antibiotic was described as being pure. Later, Marsh and Weiss (2) reported the solubility in water at <math>294 \pm 1 \text{ K}</math> to be <math>1.87 \times 10^{-2} \text{ mol dm}^{-3}</math> (units - evaluator). The purity of sample was not specified, although the source was a reputable pharmaceutical company (Ayerst Laboratories). Poole et al (3) gave the solubility in water at <math>310.2 \pm 0.5 \text{ K}</math> as <math>1.90 \times 10^{-2} \text{ mol dm}^{-3}</math> (units - evaluator), again, only the commercial source of the sample was given. Hill et al (4) have reported the solubility of ampicillin trihydrate in water at <math>310.2 \pm 0.5 \text{ K}</math> to be <math>1.70 \times 10^{-2} \text{ mol dm}^{-3}</math>. The ampicillin content was assayed for using an acid degradation method. The precision in the solubility determination may be estimated as <math>\pm 5\%</math> (evaluator). Because of the nature of preparation of the sample of antibiotic, and the reasonable temperature control, this value only is designated as <b>recommended</b>.</p> <p>The influence of pH on the solubility of ampicillin trihydrate has been studied by a number of groups. Tsuji et al (5) examined the pH - solubility behavior at constant ionic strength (<math>\mu = 0.5 - \text{KCl}</math>) and temperature (310 K) using HCl or KOH to regulate the pH. Their results were presented graphically, and exhibited a U-shaped curve, with a minimum solubility between about pH 3.5 and pH 5.5. The original data have been obtained directly from the authors (8), and are given in the appropriate compilation sheet. The precision in solubility determination and the temperature can be estimated as <math>\pm 5\%</math> and <math>\pm 1 \text{ K}</math>, respectively (evaluator). The authors fitted the experimental data using:</p> $C_T = C_o [(a_{H^+}/K_1) + 1 + (K_2/a_{H^+})]$ <p>where <math>C_T</math> is the total solubility, <math>C_o</math> the intrinsic solubility of the amphoteric ampicillin, <math>a_{H^+}</math> the hydrogen ion activity, and <math>K_1</math> and <math>K_2</math> the dissociation constants for 2-carboxylic acid and the conjugated acid of the alpha-amino group, respectively. The authors have stated (8) that the intrinsic solubility of ampicillin trihydrate calculated in this manner is <math>2.23 \times 10^{-2} \text{ mol dm}^{-3}</math>, which accords with their experimentally obtained values at pH's 3.75 and 4.46 of <math>2.48 \times 10^{-2} \text{ mol dm}^{-3}</math> and <math>2.16 \times 10^{-2} \text{ mol dm}^{-3}</math>, respectively. Being an ampholyte, ampicillin trihydrate showed increased solubility both in acid (below pH 2.5) and in alkali (above pH 7.0). It is recalled here that Hou and Poole have determined the pH-apparent rate profile of ampicillin anhydrate at 308 K in buffers of total ionic strength 0.5. They found that although the half life of the anhydrate at pH 4.85 is about 200 hours, this falls to about 30 hours at pH's 3.0 and 7.0, and to about 10 hours at pH 1.5 (9). This probably applies to the trihydrate form also, and means that solubility values determined below pH 2.0 and above pH 8, must be regarded as doubtful. Thus the data of Tsuji et al, outside these pH values are regarded as <b>doubtful</b>, although at other pH's their values may be given a <b>tentative</b> designation. A similar consideration applies to the values reported by Marsh and Weiss (2) for the solubility in 0.1 N HCl and 0.1 N NaOH at <math>294 \pm 1 \text{ K}</math> of greater than <math>4.9 \times 10^{-2} \text{ mol dm}^{-3}</math>. However the value of <math>8.7 \times 10^{-2} \text{ mol dm}^{-3}</math> (units - evaluator) at <math>310.2 \pm 0.5 \text{ K}</math> in 0.053 N HCl (4), which has a precision of determination of <math>\pm 5\%</math> (evaluator) is regarded as being <b>tentative</b>. Tsuji et al have determined the effect of <math>0.05 \text{ mol dm}^{-3}</math> sodium dodecylsulfate and <math>0.04 \text{ mol dm}^{-3}</math> cholic acid at pH 4.91 (i.e. the isoelectric point) and at 310 K (estimated precision <math>\pm 1 \text{ K}</math>, evaluator) on the aqueous solubility of ampicillin trihydrate. These are <math>3.5 \times 10^{-2} \text{ mol dm}^{-3}</math> and <math>2.6 \times 10^{-2} \text{ mol dm}^{-3}</math>, respectively. These values are estimated to have a precision of <math>\pm 5\%</math> (evaluator), and are designated as <b>tentative</b>.</p> <p>The values from a further study by Braun and Moll (6) on solubility in different gastric juices is <b>rejected</b> since the purity and source of the sample used were not specified.</p> <p>(continued)</p>	

## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate);  $C_{16}H_{19}N_3O_4S \cdot 3H_2O$ ; [7177-48-2]
- (2) Water;  $H_2O$ ; [7732-18-5]

## EVALUATOR:

Eric Tomlinson.  
Department of Pharmacy,  
University of Amsterdam,  
The Netherlands.  
December 1983.

## CRITICAL EVALUATION: continued

Poole and Bahal (7) have studied the influence of temperature on the solubility of ampicillin trihydrate in water. Over the temperature interval 293 K to 323 K (temperature precision estimated as  $\pm 1$  K, evaluator) they report a constant heat of solution of  $22 \text{ kJ mol}^{-1}$  (units, evaluator). They report their results graphically, from which the following Table may be constructed:

Temperature K	Solubility ( $\text{mol dm}^{-3}$ ) <sup>a</sup>
293	$1.6 \times 10^{-2}$
303	$2.0 \times 10^{-2}$
313	$2.5 \times 10^{-2}$
323	$3.2 \times 10^{-2}$

(<sup>a</sup> units, evaluator)

These workers used iodometric titration to assay the amount of penicillin in their sample. The values given in the table are estimated to have a precision of  $\pm 10\%$  (evaluator). However since the purity of the sample was not specified (although the source was given) these values must be regarded as highly tentative.

## REFERENCES

- (1) Austin, K.W.B.; Marshall, A.C.; Smith, H. *Nature* 1965, **208**, 999.
- (2) Marsh, J.R.; Weiss, P.J. *J. Ass. Offic. Anal. Chem.* 1967, **50**, 457.
- (3) Poole, J.W.; Owen, G.; Silverio, J.; Freyhof, J.N.; Rosenman, S.B. *Curr. Ther. Res. Clin. Exp.* 1968, **10**, 292.
- (4) Hill, S.A.; Jones, K.H.; Seager, H.; taskis, C.B. *J. Pharm. Pharmacol.* 1975, **27**, 594.
- (5) Tsuji, A.; Nakashima, E.; Hamano, S.; Yamana, T. *J. Pharm. Sci.* 1978, **67**, 1059.
- (6) Braun, A.; Moll, F. *Acta Pharm. Technol.* 1980, **26**, 258.
- (7) Poole, J.W.; Bahal, C.K. *J. Pharm. Sci.* 1968, **57**, 1945.
- (8) Tsuji, A. Personal communication.
- (9) Hou, J.P.; Poole, J.W. *J. Pharm. Sci.* 1969, **58**, 1510.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); $C_{16}H_{19}N_3O_4S \cdot 3H_2O$ ; [7177-48-2] (2) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Austin, K.W.B.; Marshall, A.C.; Smith, H. <i>Nature</i> <u>1965</u> , <b>208</b> , 999-1000.
<b>VARIABLES:</b> One Temperature: 30°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of ampicillin trihydrate in water at 30°C was reported as:          0.70 per cent<sup>a</sup> (<math>1.70 \times 10^{-2}</math> mol dm<sup>-3</sup> solution - compiler).</p> <p><sup>a</sup>probably w/v percent (compiler)</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Nothing specified	<b>SOURCE AND PURITY OF MATERIALS:</b> Pure ampicillin trihydrate was obtained by separating the crystals below 50°C. Its source is not specified.  The purity of water used was not specified.  <b>ESTIMATED ERROR:</b> Nothing specified  <b>REFERENCES:</b>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); $C_{16}H_{19}N_3O_4S \cdot 3H_2O$ ; [7177-48-2] (2) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of ampicillin trihydrate in water at <math>21 \pm 1^\circ C</math> was reported as:  <math>7.56 \text{ mg cm}^{-3}</math>. (<math>1.87 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ C</math>. The residue was further dried for 3 hours at <math>60^\circ C</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Ampicillin trihydrate was from Ayerst Labs, Inc. Its purity was not specified.</p> <p>Water was probably of U.S.P. or A.C.S. grade (1).</p>
	<b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p>
	<b>REFERENCES:</b> (1) Weiss, P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <b>7</b> , 374-7.





<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); $C_{16}H_{19}N_3O_4S \cdot 3H_2O$ ; [7177-48-2] (2) Hydrochloric acid; HCl; [7647-01-0] (3) Potassium hydroxide; KOH; [1310-58-3] (4) Potassium chloride; KCl; [7447-40-7] (5) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Tsuji, A.; Nakashima, E.; Hamano, S.; Yamana, T. <i>J. Pharm. Sci.</i> <b>1978</b> , <i>67</i> , 1059-66.				
<b>VARIABLES:</b>  pH at 37°C	<b>PREPARED BY:</b>  A. Regosz				
<b>EXPERIMENTAL VALUES:</b>					
Solubility					
pH <sup>a</sup>	$10^2 \text{ mol dm}^{-3a}$	$\text{mg cm}^{-3b}$	pH <sup>a</sup>	$10^2 \text{ mol dm}^{-3a}$	$\text{mg cm}^{-3b}$
1.87	22.30	89.96	4.49	2.33	9.40
2.16	11.30	45.58	4.78	2.28	9.20
2.22	9.41	37.96	5.16	2.28	9.20
2.36	8.14	21.84	5.54	2.10	8.47
2.55	5.97	24.08	6.00	2.45	9.88
2.67	4.24	17.10	6.55	2.89	11.66
3.09	3.22	12.99	6.95	3.85	15.53
3.37	2.49	10.04	7.00	4.87	19.65
3.75	2.48	10.00	7.26	5.58	22.51
	2.23 - C <sub>o</sub>	8.99	7.50	11.20	45.18
4.46	2.16	8.71	7.50	8.20	33.08
			7.80	19.80	79.87
<p><sup>a</sup> Experimental results obtained from the author (A. Tsuji).</p> <p><sup>b</sup> Calculated by compiler.</p> <p>C<sub>o</sub> - the intrinsic solubility estimated from the solubility at the iso-electric point - is defined in equation [1].</p>					
<b>AUXILIARY INFORMATION</b>					
<b>METHOD/APPARATUS/PROCEDURE:</b>			<b>SOURCE AND PURITY OF MATERIALS:</b>		
<p>An excess of ampicillin trihydrate was added to a glass-stoppered flask, followed by addition of <math>0.5 \text{ mol dm}^{-3}</math> KCl aqueous solution to a const ionic strength (<math>\mu = 0.5</math>). The suspension was then adjusted to the appropriate pH with standard hydrochloric acid or potassium hydroxide solution. The flask was placed in a constant temperature water bath at 37°C and mechanically shaken for 2 hours. A sample was taken through a 0.45 micron Sartorius membrane filter, the pH value was measured, and the sample was assayed after dilution with distilled water. The content of ampicillin was determined by iodometric titration and by UV spectrophotometric measurement at 260 nm.</p>			<p>Ampicillin trihydrate (pure powder) was supplied by Sankyo Co., Tokyo, Japan, its purity not specified.</p> <p>All other chemicals were reagent grade and were used without further purification. Water was distilled.</p>		
			<b>ESTIMATED ERROR:</b> Nothing specified; however if the solubility is reproducible to 0.5 unit in the last significant figure, the precision in the solubility value is better than 1%. Temperature precision: probably $\pm 1^\circ\text{C}$ (compiler).		
			<b>REFERENCES:</b>		

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); <math>C_{16}H_{19}N_3O_4S \cdot 3H_2O</math>; [7177-48-2]</p> <p>(2) Hydrochloric acid; HCl; [7647-01-0]</p> <p>(3) Potassium hydroxide; KOH; [1310-58-3]</p> <p>(4) Potassium chloride; KCl; [7447-40-7]</p> <p>(5) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Tsujii, A.; Nakashima, E.; Hamano, S.; Yamana, T. <i>J. Pharm. Sci.</i> 1978, 67, 1059-66.</p>																																																																
<p>VARIABLES:</p> <p>pH at 37°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>																																																																
<p>COMMENTS AND ADDITIONAL DATA:</p> <p>In the figure, the points are the experimental values<sup>a</sup>. The solid curve was generated from equation [1].</p> $C_T = C_o \left( \frac{a_{H^+}}{K_1} + 1 + \frac{K_2}{a_{H^+}} \right) \quad [1]$ <p>where <math>C_T</math> is the total solubility, <math>C_o</math> is the intrinsic solubility of amphoteric ampicillin, (of the electrically neutral zwitterion), <math>a_{H^+}</math> is the hydrogen ion activity of the solution, and <math>K_1</math> and <math>K_2</math> are dissociation constants for 2-carboxylic acid and the conjugated acid of the <math>\alpha</math>-amino group, respectively.</p> <div style="display: flex; justify-content: space-around; align-items: flex-start;"> <div data-bbox="684 560 960 608"> <p>Solubility [<math>10^2 \text{ mol dm}^{-3}</math>]</p> </div> <div data-bbox="697 618 1204 1072"> <table border="1"> <caption>Estimated data points from the solubility graph</caption> <thead> <tr> <th>pH</th> <th>Solubility [<math>10^2 \text{ mol dm}^{-3}</math>]</th> </tr> </thead> <tbody> <tr><td>2.0</td><td>20</td></tr> <tr><td>2.2</td><td>12</td></tr> <tr><td>2.4</td><td>8</td></tr> <tr><td>2.6</td><td>6</td></tr> <tr><td>2.8</td><td>4.5</td></tr> <tr><td>3.0</td><td>3.5</td></tr> <tr><td>3.2</td><td>3</td></tr> <tr><td>3.4</td><td>2.8</td></tr> <tr><td>3.6</td><td>2.6</td></tr> <tr><td>3.8</td><td>2.5</td></tr> <tr><td>4.0</td><td>2.5</td></tr> <tr><td>4.2</td><td>2.5</td></tr> <tr><td>4.4</td><td>2.5</td></tr> <tr><td>4.6</td><td>2.5</td></tr> <tr><td>4.8</td><td>2.5</td></tr> <tr><td>5.0</td><td>2.5</td></tr> <tr><td>5.2</td><td>2.5</td></tr> <tr><td>5.4</td><td>2.5</td></tr> <tr><td>5.6</td><td>2.5</td></tr> <tr><td>5.8</td><td>2.5</td></tr> <tr><td>6.0</td><td>2.5</td></tr> <tr><td>6.2</td><td>2.5</td></tr> <tr><td>6.4</td><td>2.5</td></tr> <tr><td>6.6</td><td>2.5</td></tr> <tr><td>6.8</td><td>2.5</td></tr> <tr><td>7.0</td><td>2.5</td></tr> <tr><td>7.2</td><td>2.5</td></tr> <tr><td>7.4</td><td>2.5</td></tr> <tr><td>7.6</td><td>2.5</td></tr> <tr><td>7.8</td><td>2.5</td></tr> <tr><td>8.0</td><td>2.5</td></tr> </tbody> </table> <p>pH at constant ionic strength [<math>\mu = 0.5</math>]</p> </div> </div>		pH	Solubility [ $10^2 \text{ mol dm}^{-3}$ ]	2.0	20	2.2	12	2.4	8	2.6	6	2.8	4.5	3.0	3.5	3.2	3	3.4	2.8	3.6	2.6	3.8	2.5	4.0	2.5	4.2	2.5	4.4	2.5	4.6	2.5	4.8	2.5	5.0	2.5	5.2	2.5	5.4	2.5	5.6	2.5	5.8	2.5	6.0	2.5	6.2	2.5	6.4	2.5	6.6	2.5	6.8	2.5	7.0	2.5	7.2	2.5	7.4	2.5	7.6	2.5	7.8	2.5	8.0	2.5
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<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); $C_{16}H_{19}N_3O_4S \cdot 3H_2O$ ; [7177-48-2] (2) Hydrochloric acid; HCl; [7647-01-0] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Hill, S.A.; Jones, K.H.; Seager, H.; Taskis, C.B. <i>J. Pharm. Pharmacol.</i> <u>1975</u> , <b>27</b> , 594-8.
<b>VARIABLES:</b> One temperature: 37°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of ampicillin trihydrate in 0.053 N hydrochloric acid (pH 1.2) at <math>37 \pm 0.5^\circ\text{C}</math> was reported as:</p> <p style="text-align: center;"><math>35.1 \text{ mg cm}^{-3}</math>. (<math>8.7 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>An excess of ampicillin trihydrate was stirred in 0.053 N HCl solution for about 3 hours at (<math>37 \pm 0.5^\circ\text{C}</math>). A sample was taken from the supernatant and assayed for ampicillin content using an acid degradation method (1).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Ampicillin trihydrate was from a batch purified for analytical reference, its source not specified.          The identity of the sample was investigated by X-ray diffraction and infrared spectroscopy.</p> <p>Water was distilled.</p> <hr/> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 0.5^\circ\text{C}</math> (authors).</p> <hr/> <b>REFERENCES:</b> (1) Smith, J.W.G.; De Grey, G.E.; Patel, V.J. <i>Analyst</i> <u>1967</u> , <b>92</b> , 247-52.

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); <math>C_{16}H_{19}N_3O_4 \cdot 3H_2O</math>; [7177-48-2]</p> <p>(2) Sulfuric acid monododecyl ester sodium salt (Sodium dodecyl sulfate); <math>C_{12}H_{25}O_4SNa</math>; [151-21-3]</p> <p>(3) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Tsuji, A.; Nakashima, E.; Hamano, S.; Yamana, T. <i>J. Pharm. Sci.</i> <u>1978</u>, <b>67</b>, 1059-66.</p>
<p>VARIABLES:</p> <p>One temperature: 37°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility<sup>a</sup> of ampicillin trihydrate at 37°C in aqueous solution containing 0.04 mol dm<sup>-3</sup> of sodium dodecyl sulfate was reported as:</p> <p style="text-align: center;"><math>3.50 \times 10^{-2}</math> mol dm<sup>-3</sup>. (14.10 mg cm<sup>-3</sup> - compiler).</p> <p><sup>a</sup> The solubility value was estimated from the solubility at the isoelectric point.</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of ampicillin trihydrate in water containing 0.04 mol dm<sup>-3</sup> sodium dodecyl sulfate were placed in a glass-stoppered flask, and mechanically shaken for about 2 hours in a constant temperature water bath at 37°C. A sample was taken through a 0.45 micron membrane filter and assayed for ampicillin trihydrate using iodometric titration and by spectrophotometric measurement at 260 nm.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Ampicillin trihydrate (pure powder) was supplied by Sankyo Co., Tokyo, Japan, its purity not specified.</p> <p>All other chemicals were reagent grade and were used without further purification. Water was distilled.</p> <p>ESTIMATED ERROR:</p> <p>Nothing specified</p> <p>REFERENCES:</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); $C_{16}H_{19}N_3O_4S \cdot 3H_2O$ ; [7177-48-2] (2) Cholan-24-oic acid, 3,7,12-trihydroxy- (cholic acid); $C_{24}H_{40}O_5$ ; [81-25-4] (3) Water; $H_2O$ ; [7732-18-3]	<b>ORIGINAL MEASUREMENTS:</b> Tsuji, A.; Nakashima, E.; Hamano, S.; Yamana, T. <i>J. Pharm. Sci.</i> <u>1978</u> , <b>67</b> , 1059-66.
<b>VARIABLES:</b> One temperature: 37°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility <sup>a</sup> of ampicillin trihydrate at 37°C in aqueous solution containing 0.04 mol dm <sup>-3</sup> of cholic acid was reported as: $2.63 \times 10^{-2} \text{ mol dm}^{-3}. \text{ (10.61 mg cm}^{-3} \text{ - compiler).}$  <sup>a</sup> The solubility value was estimated from the solubility at the isoelectric point.	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> An excess of ampicillin trihydrate in water containing 0.04 mol dm <sup>-3</sup> of cholic acid were placed in a glass-stoppered flask, and mechanically shaken for about 2 hours in a constant temperature water bath at 37°C. A sample was taken through a 0.45 micron membrane filter and assayed for ampicillin trihydrate using iodometric titration and by spectrophotometric measurement at 260 nm.	<b>SOURCE AND PURITY OF MATERIALS:</b> Ampicillin trihydrate (pure powder) was supplied by Sankyo Co., Tokyo, Japan, its purity not specified. All other chemicals were reagent grade and were used without further purification. Water was distilled.
<b>ESTIMATED ERROR:</b> Nothing specified	
<b>REFERENCES:</b>	

<p>COMPONENTS:</p> <p>(1) 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); <math>C_{16}H_{19}N_3O_4S \cdot 3H_2O</math>; [7177-48-2]</p> <p>(2) Hydrochloric acid; HCl; [7647-01-0]</p> <p>(3) Phosphoric acid, trisodium salt; <math>Na_3PO_4</math>; [7601-54-9]</p> <p>(4) Sodium chloride; NaCl; [7647-14-5]</p> <p>(5) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Braun, A.; Moll, F. <i>Acta Pharm. Technol.</i> <u>1980</u>, <b>26</b>, 258-60.</p>																
<p>VARIABLES:</p> <p>One temperature: 37°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>																
<p>EXPERIMENTAL VALUES:</p> <p>The authors determined the maximal solubility of ampicillin trihydrate in synthetic gastric fluid<sup>a</sup> (without pepsin), and compared the results with those obtained for solubility in human natural gastric fluid.</p> <table border="1" data-bbox="247 685 1138 911"> <thead> <tr> <th colspan="4" style="text-align: center;">Solubility</th> </tr> <tr> <th colspan="2" style="text-align: center;">Synthetic gastric fluid<sup>a</sup> (without pepsin)</th> <th colspan="2" style="text-align: center;">Human natural gastric fluid</th> </tr> <tr> <th style="text-align: center;"><math>10^2 \text{ mg cm}^{-3}</math></th> <th style="text-align: center;"><math>10^2 \text{ mol dm}^{-3b}</math></th> <th style="text-align: center;"><math>10^2 \text{ mg cm}^{-3}</math></th> <th style="text-align: center;"><math>10^2 \text{ mol dm}^{-3b}</math></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">406</td> <td style="text-align: center;">1.01</td> <td style="text-align: center;">415</td> <td style="text-align: center;">1.03</td> </tr> </tbody> </table> <p><sup>a</sup> According to USP XIX the composition of synthetic gastric fluid is: HCl(35%) - 7.0 cm<sup>3</sup>, NaCl - 2.0 g, pepsin - 3.2 g, distilled water to 1000 cm<sup>3</sup>.</p> <p><sup>b</sup> Calculated by compiler.</p>		Solubility				Synthetic gastric fluid <sup>a</sup> (without pepsin)		Human natural gastric fluid		$10^2 \text{ mg cm}^{-3}$	$10^2 \text{ mol dm}^{-3b}$	$10^2 \text{ mg cm}^{-3}$	$10^2 \text{ mol dm}^{-3b}$	406	1.01	415	1.03
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<p style="text-align: center;">AUXILIARY INFORMATION</p>																	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of ampicillin trihydrate (pure powder) was added to a 250 cm<sup>3</sup> flask, followed by addition of 100 cm<sup>3</sup> of synthetic or natural human gastric fluid. The fluid was stirred at a speed of 55 r.p.m. at 37°C for about 1 hour. The fluid was then buffered to pH 4.6 using aqueous <math>Na_3PO_4</math> solution and filtered through a Sartorius SM 11307 filter. The content of the antibiotic in the clear filtrate was determined spectrophotometrically at 320 nm (1).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>The form of the ampicillin used was not described, though was probably the trihydrate.</p> <p>The source and purity of the antibiotic and chemicals were not specified.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision; ±1% (compiler). Temperature precision: ±1°C (compiler).</p> <p>REFERENCES:</p> <p>(1) Smith, H.W.G.; De Grey, G.E.; Patel, V.J. <i>Analyst</i> <u>1967</u>, <b>92</b>, 247.</p>																

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); <math>C_{16}H_{19}N_3O_4S \cdot 3H_2O</math>; [7177-48-2]</p> <p>(2) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Poole, J.W.; Bahal, C.K. <i>J. Pharm. Sci.</i> <u>1968</u>, <b>57</b>, 1945-8.</p>										
<p>VARIABLES:</p> <p>Temperature</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>										
<p>EXPERIMENTAL VALUES:</p> <p>The apparent equilibrium solubilities of ampicillin trihydrate in distilled water were determined over the temperature range 20° to 50°C. Van 't Hoff plots gave a reasonably good linear relationship. The authors estimated graphically the transition temp for the trihydrate-anhydrous crystal system, at which the solubility of the two forms is equal, to be 42°C. The heat of solution was calculated from the slope of the van 't Hoff plot to be 5.4 kcal mol<sup>-1</sup>.</p> <div data-bbox="861 458 1241 944" style="text-align: right;"> <table border="1" style="margin-left: auto; margin-right: auto;"> <caption>Data points from the Solubility vs. <math>K^{-1} \times 10^3</math> plot</caption> <thead> <tr> <th><math>K^{-1} \times 10^3</math></th> <th>Solubility [mg cm<sup>-3</sup>]</th> </tr> </thead> <tbody> <tr> <td>3.1</td> <td>15</td> </tr> <tr> <td>3.2</td> <td>10</td> </tr> <tr> <td>3.3</td> <td>8</td> </tr> <tr> <td>3.4</td> <td>6</td> </tr> </tbody> </table> </div>		$K^{-1} \times 10^3$	Solubility [mg cm <sup>-3</sup> ]	3.1	15	3.2	10	3.3	8	3.4	6
$K^{-1} \times 10^3$	Solubility [mg cm <sup>-3</sup> ]										
3.1	15										
3.2	10										
3.3	8										
3.4	6										
<p>AUXILIARY INFORMATION</p>											
<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of ampicillin trihydrate (2 g) was added to 100 cm<sup>3</sup> of water previously equilibrated to the desired temperature. The bottles were rotated in a constant temperature water bath maintained at the indicated temperature. Samples withdrawn at intervals were filtered through a Milipore filter and diluted immediately to avoid any precipitation. The content of the ampicillin was determined by iodometric titration.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>The trihydrate form of ampicillin was prepared from the anhydrous form using the method of Austin et al. (1). IR spectra and differential thermal analysis curves were obtained for the antibiotic.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: <math>\pm 3\%</math> (compiler).  Temperature precision: <math>\pm 1^\circ C</math> (compiler).</p> <p>REFERENCES:</p> <p>(1) Austin, K.W.P.; Marshall, A.C.; Smith, H. <i>Nature</i> <u>1965</u>, <b>208</b>, 999.</p>										

## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-,trihydrate (ampicillin trihydrate);  $C_{16}H_{19}N_3O_4S_3H_2O$ ; [7177-48-2]
- (2) All non aqueous solvents

## EVALUATOR:

Eric Tomlinson.  
Department of Pharmacy,  
University of Amsterdam,  
The Netherlands.  
December 1983.

## CRITICAL EVALUATION:

Marsh and Weiss have determined the solubilities of ampicillin trihydrate in 21 different non aqueous solvents at  $294 \pm 1$  K. These workers studied a sample of the antibiotic provided by Ayerst Laboratories, its purity was not specified. The amount of penicillin dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than  $20 \text{ mg cm}^{-3}$ . All values reported were uncorrected for solvent blank, which was generally less than  $0.05 \text{ mg total}$ . All data according to Marsh and Weiss have been recalculated to SI units (compiler), and are given in the Table.

Solvent <sup>a</sup>	Solubility (at $294 \pm 1$ K), ( $\text{mol dm}^{-3}$ ) <sup>b</sup>
methanol	$1.65 \times 10^{-2}$
ethanol	$6.29 \times 10^{-3}$
cyclohexane	$1.69 \times 10^{-4}$
benzene	$7.9 \times 10^{-5}$
ligroin	$9.4 \times 10^{-5}$
isooctane	$5.5 \times 10^{-5}$
carbon tetrachloride	$6.2 \times 10^{-4}$
ethyl acetate	$5.58 \times 10^{-4}$
isoamyl acetate	$1.93 \times 10^{-2}$
acetone	$2.22 \times 10^{-2}$
methyl ethyl ketone	$6.92 \times 10^{-5}$
diethylether	$7.4 \times 10^{-4}$
ethylene chloride	$1.69 \times 10^{-3}$
1,4-dioxane	$6.87 \times 10^{-4}$
chloroform	$1.86 \times 10^{-5}$
carbon disulfide	$5.45 \times 10^{-5}$
pyridine	$3.01 \times 10^{-2}$
formamide	c
ethylene glycol	$4.74 \times 10^{-2}$
propylene glycol	$1.03 \times 10^{-2}$
dimethyl sulfoxide	c

(<sup>a</sup> All solvents are probably of U.S.P. or A.C.S. grade as previous (2); <sup>b</sup> units calculated by evaluator; <sup>c</sup> solubility greater than  $4.90 \times 10^{-2} \text{ mol dm}^{-3}$ ).

All these values have an estimated precision of  $\pm 5\%$  (evaluator). Because of the unstated purity of the sample, and since the values in the Table are unconfirmed, the reported solubilities are designated as being highly tentative, except for where the solubility is reported as being greater than  $4.90 \times 10^{-2} \text{ mol dm}^{-3}$ , (which are regarded as being doubtful).

## REFERENCES

- (1) Marsh, J.R.; Weiss, P.J. *J. Ass. Offic. Anal. Chem.* 1967, 50 457.  
(2) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* 1957, 7, 374.

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); <math>C_{16}H_{19}N_3O_4S \cdot 3H_2O</math>; [7177-48-2]</p> <p>(2) Methanol; <math>CH_4O</math>; [67-56-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u>, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin trihydrate in MeOH at <math>21 \pm 1^\circ C</math> was reported as:  <math>6.65 \text{ mg cm}^{-3}</math>. (<math>1.65 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ C</math>. The residue was further dried for 3 hours at <math>60^\circ C</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Ampicillin trihydrate was from Ayerst Labs, Inc. Its purity was not specified.</p> <p>Methanol was probably of U.S.P. or A.C.S. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p>

<p>COMPONENTS:          (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); <math>C_{16}H_{19}N_3O_4S \cdot 3H_2O</math>; [7177-48-2]          (2) Ethanol; <math>C_2H_6O</math>; [64-17-5]</p>	<p>ORIGINAL MEASUREMENTS:          Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u>, <u>50</u>, 457-62.</p>
<p>VARIABLES:          One temperature: 21°C</p>	<p>PREPARED BY:          A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin trihydrate in ethanol at <math>21 \pm 1^\circ C</math> was reported as:  <math>2.54 \text{ mg cm}^{-3}</math>. (<math>6.29 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ C</math>. The residue was further dried for 3 hours at <math>60^\circ C</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<p>SOURCE AND PURITY OF MATERIALS.</p> <p>Ampicillin trihydrate was from Ayerst Labs, Inc. Its purity was not specified.</p> <p>Ethanol was probably of U.S.P. or A.C.S. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-,trihydrate (ampicillin trihydrate); $C_{16}H_{19}N_3O_4S \cdot 3H_2O$ ; [7177-48-2] (2) Cyclohexane; $C_6H_{12}$ ; [110-82-7]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. 1967, 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of ampicillin trihydrate in cyclohexane at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.07 \text{ mg cm}^{-3}</math>. (<math>1.69 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ C</math>. The residue was further dried for 3 hours at <math>60^\circ C</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Ampicillin trihydrate was from Ayerst Labs, Inc. Its purity was not specified.</p> <p>Cyclohexane was probably of A.C.S. or U.S.P. grade.</p> <hr/> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <hr/> <b>REFERENCES:</b>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); <math>C_{16}H_{19}N_3O_4S \cdot 3H_2O</math>; [7177-48-2]</p> <p>(2) Benzene; <math>C_6H_6</math>; [71-43-2]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> 1967, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin trihydrate in benzene at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.03 \text{ mg cm}^{-3}</math>. (<math>7.93 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ C</math>. The residue was further dried for 3 hours at <math>60^\circ C</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Ampicillin trihydrate was from Ayerst Labs, Inc. Its purity was not specified.</p> <p>Benzene was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-,trihydrate (ampicillin trihydrate); <math>C_{16}H_{19}N_3O_4S \cdot 3H_2O</math>; [7177-48-2]</p> <p>(2) Petroleum ether (ligroin)</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin trihydrate in ligroin at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.04 \text{ mg cm}^{-3}</math>. (<math>9.42 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hours at <math>60^\circ\text{C}</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Ampicillin trihydrate was from Ayerst Labs, Inc. Its purity was not specified.</p> <p>Ligroin was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES.</p>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); $C_{16}H_{19}N_3O_4 \cdot 3H_2O$ ; [7177-48-2] (2) Methane, tetrachloro- (carbon tetrachloride); $CCl_4$ ; [56-23-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1967</b> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of ampicillin trihydrate in carbon tetrachloride at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.03 \text{ mg cm}^{-3}</math>. (<math>6.20 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ C</math>. The residue was further dried for 3 hours at <math>60^\circ C</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Ampicillin trihydrate was from Ayerst Labs, Inc. Its purity was not specified.</p> <p>Carbon tetrachloride was probably of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES.</b>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); $C_{16}H_{19}N_3O_4S \cdot 3H_2O$ ; [7177-48-2] (2) 1-Butanol, 3-methyl acetate (isoamyl acetate); $C_7H_{14}O_2$ ; [123-92-2]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of ampicillin trihydrate in isoamyl acetate at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.08 \text{ mg cm}^{-3}</math>. (<math>1.93 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ C</math>. The residue was further dried for 3 hours at <math>60^\circ C</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Ampicillin trihydrate was from Ayerst Labs, Inc. Its purity was not specified.</p> <p>Isoamyl acetate was probably of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p>
	<b>REFERENCES:</b>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-,trihydrate (ampicillin trihydrate); <math>C_{16}H_{19}N_3O_4S \cdot 3H_2O</math>; [7177-48-2]</p> <p>(2) 2-Propanone (acetone); <math>C_3H_6O</math>; [67-64-1]</p>	<p>ORIGINAL MEASUREMENTS: Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. 1967, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY: A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin trihydrate in acetone at <math>21 \pm 1^\circ C</math> was reported as: 8.95 mg <math>cm^{-3}</math>. (<math>2.22 \times 10^{-2}</math> mol <math>dm^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>cm^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>cm^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>cm^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01</math> mg) weighing bottle and evaporated by heating at <math>100^\circ C</math>. The residue was further dried for 3 hours at <math>60^\circ C</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01</math> mg).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Ampicillin trihydrate was from Ayerst Labs, Inc. Its purity was not specified.</p> <p>Acetone was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); $C_{16}H_{19}N_3O_4S \cdot 3H_2O$ ; [7177-48-2] (2) 2-Butanone (methyl ethyl ketone); $C_4H_8O$ ; [78-93-3]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of ampicillin trihydrate in methyl ethyl ketone at <math>21 \pm 1^\circ\text{C}</math> was reported as: <math>2.79 \text{ mg cm}^{-3}</math>. (<math>6.92 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hours at <math>60^\circ\text{C}</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Ampicillin trihydrate was from Ayerst Labs, Inc. Its purity was not specified.</p> <p>Methyl ethyl ketone was probably of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); $C_{16}H_{19}N_3O_4 \cdot 3H_2O$ ; [7177-48-2] (2) Ethane, dichloro- (ethylene chloride); $C_2H_4Cl_2$ ; [1300-21-6]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of ampicillin trihydrate in ethylene chloride at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.07 \text{ mg cm}^{-3}</math>. (<math>1.69 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ C</math>. The residue was further dried for 3 hours at <math>60^\circ C</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Ampicillin trihydrate was from Ayerst Labs, Inc. Its purity was not specified.</p> <p>Ethylene chloride was probably of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); <math>C_{16}H_{19}N_3O_4S \cdot 3H_2O</math>; [7177-48-2]</p> <p>(2) 1,4-Dioxane; <math>C_4H_8O_2</math>; [123-91-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> 1967, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin trihydrate in 1,4-Dioxane at <math>21 \pm 1^\circ C</math> was reported as:  <math>2.77 \text{ mg cm}^{-3}</math>. (<math>6.87 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ C</math>. The residue was further dried for 3 hours at <math>60^\circ C</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Ampicillin trihydrate was from Ayerst Labs, Inc. Its purity was not specified.</p> <p>1,4-Dioxane was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); <math>C_{16}H_{19}N_3O_4S \cdot 3H_2O</math>; [7177-48-2]</p> <p>(2) Methane, trichloro- (chloroform); <math>CHCl_3</math>; [67-66-3]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1967</b>, <i>50</i>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin trihydrate in chloroform at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.08 \text{ mg cm}^{-3}</math>. (<math>1.86 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ C</math>. The residue was further dried for 3 hours at <math>60^\circ C</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Ampicillin trihydrate was from Ayerst Labs, Inc. Its purity was not specified.</p> <p>Chloroform was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); $C_{16}H_{19}N_3O_4 \cdot 3H_2O$ ; [7177-48-2] (2) Pyridine; $C_5H_5N$ ; [110-86-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of ampicillin trihydrate in pyridine at <math>21 \pm 1^\circ C</math> was reported as:  <math>12.13 \text{ mg cm}^{-3}</math>. (<math>3.01 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ C</math>. The residue was further dried for 3 hours at <math>60^\circ C</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Ampicillin trihydrate was from Ayerst Labs, Inc. Its purity was not specified.</p> <p>Pyridine was probably of A.C.S. or U.S.P. grade.</p> <hr/> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <hr/> <b>REFERENCES:</b>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); $C_{16}H_{19}N_3O_4S \cdot 3H_2O$ ; [7177-48-2] (2) Formamide; $CH_3NO$ ; [75-12-7]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1967</b> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of ampicillin trihydrate in formamide at <math>21 \pm 1^\circ C</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.90 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Ampicillin trihydrate was from Ayerst Labs, Inc. Its purity was not specified.</p> <p>Formamide was probably of A.C.S. or U.S.P. grade.</p> <hr/> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <hr/> <b>REFERENCES.</b>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); $C_{16}H_{19}N_3O_4 \cdot 3H_2O$ ; [7177-48-2] (2) 1,2-Ethanediole (ethylene glycol); $C_2H_6O_2$ ; [107-21-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of ampicillin trihydrate in ethylene glycol at <math>21 \pm 1^\circ C</math> was reported as:  <math>19.13 \text{ cm}^{-3}</math>. (<math>4.74 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ C</math>. The residue was further dried for 3 hours at <math>60^\circ C</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Ampicillin trihydrate was from Ayerst Labs, Inc. Its purity was not specified.</p> <p>Ethylene glycol was probably of A.C.S. or U.S.P. grade.</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); $C_{16}H_{19}N_3O_4S \cdot 3H_2O$ ; [7177-48-2] (2) 1,2-Propanediol (propylene glycol); $C_3H_8O_2$ ; [57-55-6]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. 1967, 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of ampicillin trihydrate in propylene glycol at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>4.14 \text{ mg cm}^{-3}</math>. (<math>1.03 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If any insoluble material was visible the suspension was centrifuged within an hour of preparation. The substantially clear part of the solution was then filtered by vacuum through a medium-porosity sintered glass funnel and the clear filtrate collected in a test tube. Four <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle and evaporated by heating at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hours at <math>60^\circ\text{C}</math> in a vacuum oven at a pressure of 5 mm mercury or less. After cooling the bottle was reweighed (<math>\pm 0.01 \text{ mg}</math>).</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Ampicillin trihydrate was from Ayerst Labs, Inc. Its purity was not specified.</p> <p>Propylene glycol was probably of A.C.S. or U.S.P. grade.</p> <hr/> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <hr/> <b>REFERENCES:</b>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, trihydrate (ampicillin trihydrate); <math>C_{16}H_{19}N_3O_4S \cdot 3H_2O</math>; [7177-48-2]</p> <p>(2) Methane, sulfinylbis- (dimethyl sulfoxide); <math>C_2H_6OS</math>; [67-68-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of ampicillin trihydrate in dimethyl sulfoxide at <math>21 \pm 1^\circ C</math> was reported as greater than:</p> <p style="text-align: center;"><math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.90 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p style="text-align: center;">AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of 0.1 N NaOH were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Ampicillin trihydrate was from Ayerst Labs, Inc. Its purity was not specified.</p> <p>Dimethyl sulfoxide was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p>
	<p>REFERENCES.</p>

## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,20]heptane-2-carboxylic acid, 6-[(amino(4-hydroxyphenyl)acetyl)amino]-3,3-dimethyl-7-oxo, trihydrate (amoxicillin trihydrate);  $C_{16}H_{19}N_3O_5 \cdot 3H_2O$ ; [61336-70-7]
- (2) Hydrochloric acid; HCl; [7647-01-0]
- (3) Potassium hydroxide; KOH; [1310-58-3]
- (4) Potassium chloride; KCl; [7447-40-7]
- (5) Water;  $H_2O$ ; [7732-18-5]

## EVALUATOR:

Eric Tomlinson,  
Department of Pharmacy,  
University of Amsterdam,  
The Netherlands.  
December 1983.

## CRITICAL EVALUATION

The influence of pH on the solubility of amoxicillin trihydrate has been studied by Tsuji et al (1), who examined the pH - solubility behavior at constant ionic strength ( $\mu = 0.5$  - KCl) and temperature (310 K) using HCl or KOH to regulate the pH. Their results were presented graphically, and exhibited a U-shaped curve, with a minimum solubility between about pH 3.5 and pH 6.0. The original data have been obtained directly from the authors (2), and are given in the appropriate compilation sheet. The precision in solubility determination and the temperature can be estimated as  $\pm 5\%$  and  $\pm 1$  K, respectively (evaluator). The authors fitted the experimental data using:

$$C_T = C_o [(a_{H^+}/K_1) + 1 + (K_2/a_{H^+})]$$

where  $C_T$  is the total solubility,  $C_o$  the intrinsic solubility of the amphoteric amoxicillin,  $a_{H^+}$  the hydrogen ion activity, and  $K_1$  and  $K_2$  the dissociation constants for 2-carboxylic acid and the conjugated acid of the alpha-amino group, respectively. The authors have stated (2) that the intrinsic solubility of amoxicillin trihydrate calculated in this manner is  $1.30 \times 10^{-2}$  mol dm<sup>-3</sup>, which agrees with their experimentally obtained values at pH's 4.48, 4.71 and 4.97. Being an ampholyte, amoxicillin trihydrate showed increased solubility both in acid (below pH 2.5) and in alkali (above pH 7.0). It is recalled here that Hou and Poole (3) have determined the pH-apparent rate profile of ampicillin anhydrate at 308 K in buffers of total ionic strength 0.5. They found that although the half life of ampicillin anhydrate at pH 4.85 is about 200 hours, this falls to about 30 hours at pH's 3.0 and 7.0, and to about 10 hours at pH 1.5. This probably applies to amoxicillin trihydrate also, and means that solubility values determined below pH 2.0 and above pH 8, must be regarded as doubtful. Thus the data of Tsuji et al, outside these pH values are regarded as **doubtful**, although at other pH's their values may be given a **tentative** designation.

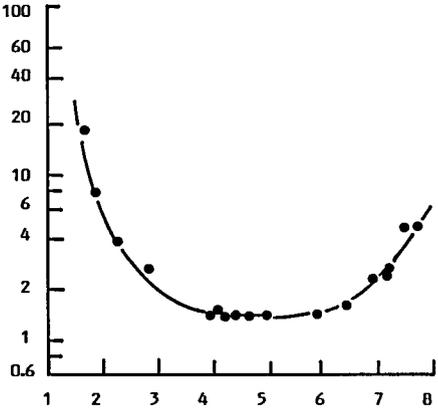
Tsuji et al have further determined the effect of 0.04 mol dm<sup>-3</sup> sodium dodecylsulfate at the isoelectric point and at 310 K (estimated precision  $\pm 1$  K, evaluator) on the aqueous solubility of amoxicillin trihydrate. This is  $1.6 \times 10^{-2}$  mol dm<sup>-3</sup>. This value is estimated to have a precision of  $\pm 5\%$  (evaluator), and is designated as **tentative**.

Finally, Tsuji et al (1) have studied the influence of temperature on the aqueous solubility of amoxicillin trihydrate. Over the temperature interval 293 K to 323 K (temperature precision estimated as  $\pm 1$  K, evaluator) they found a constant heat of solution of 25.9 kJ mol<sup>-1</sup>.

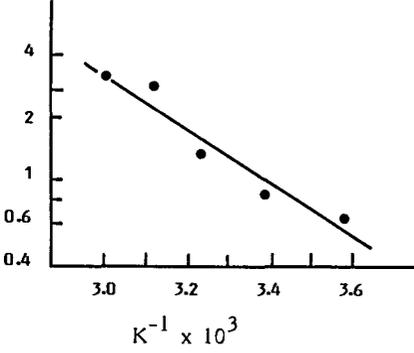
## REFERENCES

- (1) Tsuji, A.; Nakashima, E.; Hamano, S.; Yamana, T. *J. Pharm. Sci.* **1978**, *67*, 1059.
- (2) Tsuji, A. Personal communication.
- (3) Hou, J.P.; Poole, J.W. *J. Pharm. Sci.* **1969**, *58*, 1510.

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(amino(4-hydroxyphenyl)acetyl)amino]-3,3-dimethyl-7-oxo, trihydrate (amoxicillin trihydrate); <math>C_{16}H_{19}N_3O_5 \cdot 3H_2O</math>; [61336-70-7]</p> <p>(2) Hydrochloric acid; HCl; [7647-01-0]</p> <p>(3) Potassium hydroxide; KOH; [1310-58-3]</p> <p>(4) Potassium chloride; KCl; [7447-40-7]</p> <p>(5) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Tsuji, A.; Nakashima, E.; Hamano, S.; Yamana, T. <i>J. Pharm. Sci.</i> <u>1978</u>, <b>67</b>, 1059-66.</p>																																																																		
<p>VARIABLES:</p> <p>pH at 37°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>																																																																		
<p>EXPERIMENTAL VALUES:</p> <table border="1" data-bbox="171 544 1211 911"> <thead> <tr> <th colspan="3">Solubility</th> <th colspan="3">Solubility</th> </tr> <tr> <th>pH<sup>a</sup></th> <th><math>10^2 \text{ mol dm}^{-3a}</math></th> <th><math>\text{mg cm}^{-3}</math></th> <th>pH<sup>a</sup></th> <th><math>10^2 \text{ mol dm}^{-3a}</math></th> <th><math>\text{mg cm}^{-3}</math></th> </tr> </thead> <tbody> <tr> <td>1.72</td> <td>17.30</td> <td>72.56</td> <td>4.71</td> <td>1.30</td> <td>5.45</td> </tr> <tr> <td>1.94</td> <td>7.70</td> <td>32.29</td> <td></td> <td>1.30 - <math>C_o</math></td> <td>5.45</td> </tr> <tr> <td>2.42</td> <td>3.44</td> <td>14.43</td> <td>4.97</td> <td>1.29</td> <td>5.41</td> </tr> <tr> <td>2.89</td> <td>2.36</td> <td>9.90</td> <td>5.98</td> <td>1.35</td> <td>5.66</td> </tr> <tr> <td>4.05</td> <td>1.31</td> <td>5.49</td> <td>6.50</td> <td>1.51</td> <td>6.33</td> </tr> <tr> <td>4.16</td> <td>1.34</td> <td>5.62</td> <td>6.87</td> <td>2.14</td> <td>8.97</td> </tr> <tr> <td>4.27</td> <td>1.24</td> <td>5.20</td> <td>7.19</td> <td>2.46</td> <td>10.32</td> </tr> <tr> <td>4.37</td> <td>1.27</td> <td>5.33</td> <td>7.19</td> <td>2.46</td> <td>10.32</td> </tr> <tr> <td>4.48</td> <td>1.30</td> <td>5.45</td> <td>7.64</td> <td>4.60</td> <td>19.29</td> </tr> </tbody> </table> <p><sup>a</sup> Experimental values obtained from the author (A. Tsuji).</p> <p><sup>b</sup> Calculated by compiler.</p> <p>The <math>C_o</math> value (intrinsic solubility) estimated from the solubility at the isoelectric point is defined by equation [1].</p> <p>(continued over)</p>		Solubility			Solubility			pH <sup>a</sup>	$10^2 \text{ mol dm}^{-3a}$	$\text{mg cm}^{-3}$	pH <sup>a</sup>	$10^2 \text{ mol dm}^{-3a}$	$\text{mg cm}^{-3}$	1.72	17.30	72.56	4.71	1.30	5.45	1.94	7.70	32.29		1.30 - $C_o$	5.45	2.42	3.44	14.43	4.97	1.29	5.41	2.89	2.36	9.90	5.98	1.35	5.66	4.05	1.31	5.49	6.50	1.51	6.33	4.16	1.34	5.62	6.87	2.14	8.97	4.27	1.24	5.20	7.19	2.46	10.32	4.37	1.27	5.33	7.19	2.46	10.32	4.48	1.30	5.45	7.64	4.60	19.29
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<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of amoxicillin trihydrate was added to a glass-stoppered flask, followed by addition of <math>0.5 \text{ mol dm}^{-3}</math> KCl aqueous solution to a constant ionic strength (<math>I = 0.5</math>). The suspension was then adjusted to the appropriate pH with standard hydrochloric acid or potassium hydroxide solution. The flask was placed in a constant temperature water bath at 37°C and mechanically shaken for 2 hr. A sample was taken through a 0.45 micron Sartorius membrane filter, the pH was measured, and the sample was assayed after appropriate dilution with distilled water. The amount of amoxicillin was determined by iodometric titration and by UV spectrophotometric measurement at 260 nm.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Amoxicillin trihydrate was supplied by Fujisawa Pharmaceutical Co., Osaka, Japan, and had a potency of <math>850 \mu\text{g mg}^{-1}</math>.</p> <p>All other chemicals were reagent grade and were used without further purification. Distilled water was used.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: probably <math>\pm 1^\circ\text{C}</math> (compiler)</p> <p>REFERENCES:</p>																																																																		

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(amino(4-hydroxyphenyl)acetyl)amino]-3,3-dimethyl-7-oxo, trihydrate (amoxicillin trihydrate); <math>C_{16}H_{19}N_3O_5 \cdot 3H_2O</math>; [61336-70-7]</p> <p>(2) Hydrochloric acid; HCl; [7647-01-0]</p> <p>(3) Potassium hydroxide; KOH; [1310-58-3]</p> <p>(4) Potassium chloride; KCl; [7447-40-7]</p> <p>(5) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Tsuji, A.; Nakashima, E.; Hamano, S.; Yamana, T. <i>J. Pharm. Sci.</i> <b>1978</b>, <i>67</i>, 1059-66.</p>
<p>VARIABLES:</p> <p>pH at 37°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>COMMENTS AND/OR ADDITIONAL DATA:</p> <p>In the figure at the right, the points are the experimental results<sup>a</sup>. The solid curve was generated from equation [1].</p> $C_T = C_o \left( \frac{a_{H^+}}{K_1} + 1 + \frac{K_2}{a_{H^+}} \right) \quad [1]$ <p>where <math>C_T</math> is the total solubility, <math>C_o</math> is the intrinsic solubility of amphoteric amoxicillin with the electrically neutral zwitterion, <math>a_{H^+}</math> is the hydrogen-ion activity of the solution, and <math>K_1</math> and <math>K_2</math> are dissociation constants for 2-carboxylic acid and the conjugated acid of <math>\alpha</math>-amino group, respectively.</p> <div style="text-align: right;"> <p>Solubility [<math>10^2 \times \text{mol dm}^{-3}</math>]</p>  <p>pH at constant ionic strength [<math>\mu = 0.5</math>]</p> </div>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>ESTIMATED ERROR:</p> <p>REFERENCES:</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(amino(4-hydroxyphenyl)acetyl)amino]-3,3-dimethyl-7-oxo, trihydrate (amoxicillin trihydrate); $C_{16}H_{19}N_3O_5 \cdot 3H_2O$ ; [61336-70-7] (2) Sulfuric acid monododecyl ester sodium salt (Sodium dodecyl sulfate); $C_{12}H_{25}O_4SNa$ ; [151-21-3] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Tsuji, A.; Nakashima, E.; Hamano, S.; Yamana, T. <i>J. Pharm. Sci.</i> <b>1978</b> , <i>67</i> , 1059-66.
<b>VARIABLES:</b> One temperature: 37°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of amoxicillin trihydrate at 37°C 0.04 mol dm<sup>-3</sup> sodium dodecyl sulfate aqueous solution was reported as:</p> $1.6 \times 10^{-2} \text{ mol dm}^{-3a} \quad (6.7 \text{ mg cm}^{-3} - \text{compiler}).$ <p><sup>a</sup> The value was estimated from the solubility near the isoelectric point - (authors).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  An excess of amoxicillin trihydrate and water containing sodium dodecyl sulfate were placed in a glass-stoppered flask and mechanically shaken for about 2 hr in a constant temperature water bath at 37°C. Samples were taken through a 0.45 micron Sartorius membrane filter, and their pH values measured. The sample was assayed for amoxicillin, after appropriate dilution, by iodometric titration and by UV spectrophotometric measurement at 260 nm.	<b>SOURCE AND PURITY OF MATERIALS:</b>  Amoxicillin trihydrate was supplied by Fujisawa Pharmaceutical Co., Osaka, Japan, and had a potency of 850 µg mg <sup>-1</sup> .  All other chemicals were reagent grade and were used without further purification. Distilled water was used.
<b>ESTIMATED ERROR:</b>  Solubility precision: none specified Temperature precision: probably ±1°C (compiler)	
<b>REFERENCES.</b>	

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(amino(4-hydroxyphenyl)acetyl)amino]-3,3-dimethyl-7-oxo, trihydrate (amoxicillin trihydrate); <math>C_{16}H_{19}N_3O_5S \cdot 3H_2O</math>; [61336-70-7]</p> <p>(2) Potassium chloride; KCl; [7447-40-7]</p> <p>(3) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Tsuji, A.; Nakashima, E.; Hamano, S.; Yamana, T. <i>J. Pharm. Sci.</i> <b>1978</b>, <i>67</i>, 1059-66.</p>
<p>VARIABLES:</p> <p>reciprocal of absolute temperature</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>The authors determined the apparent equilibrium solubilities of amoxicillin trihydrate in <math>0.5 \text{ mol dm}^{-3}</math> KCl solution at various temperatures. Van 't Hoff plots gave a reasonably good linear relationship (figure at the right).</p> <p>The value of the heat of solution was calculated from the slope of the van 't Hoff plot to be <math>6.2 \text{ kcal mol}^{-1}</math>.</p> <div style="text-align: center;">  <p>Solubility [<math>10^2 \times \text{mol dm}^{-3}</math>]</p> <p><math>K^{-1} \times 10^3</math></p> </div>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>The apparent equilibrium solubilities were determined between <math>20^\circ\text{C}</math> and <math>50^\circ\text{C}</math> in <math>0.5 \text{ mol dm}^{-3}</math> KCl solution. No procedure was described. The antibiotic content of samples was determined by iodometric titration and UV spectroscopic measurement at <math>260 \text{ nm}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Amoxicillin trihydrate was supplied by Fujisawa Pharmaceutical Co., Osaka, Japan, and had a potency of <math>850 \mu\text{g mg}^{-1}</math>.</p> <p>Potassium chloride was reagent grade. Distilled water was used.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: probably <math>\pm 1^\circ\text{C}</math> (compiler)</p> <p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]hept-2-yl-5-tetrazole,6-[D-2-amino-2-(4-aminophenyl)-acetamido]3,3-dimethyl-7-oxo, trihydrate; (CP-38,371); C<sub>16</sub>H<sub>20</sub>N<sub>8</sub>O<sub>5</sub>S<sub>2</sub>H<sub>2</sub>O; [56852-63-2]</p> <p>(2) Hydrochloric acid; HCl; [7647-01-0]</p> <p>(3) Sodium hydrochloride; NaOH; [1310-73-2]</p> <p>(4) Water; H<sub>2</sub>O; [7732-18-5]</p>	<p>EVALUATOR:</p> <p>Eric Tomlinson. Department of Pharmacy, University of Amsterdam, The Netherlands.</p> <p>December 1983.</p>
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#### CRITICAL EVALUATION

Bogardus and Palepu have studied the influence of pH on the aqueous solubility of a development compound (CP-38,371) synthesized in Pfizer Central Research laboratories. This was studied as the trihydrate. The compilation sheets show that this compound acts similarly to other amphoteric penicillins, in that it exhibits a minimum solubility between pH 4.5 and pH 6.0, with large increases in solubility at pHs outside this range. Although these workers published their results graphically, the original data have been obtained from the authors (2), and are appended.

The authors used very short equilibrium times to minimize any possible degradation, and they were able to confirm with high performance liquid chromatography less than 5 % degradation throughout the pH range 2-4.

CP-38,371 differs from other aminopenicillins in the substitution of the penicillanic acid carboxyl group with a tetrazole and addition of a primary amino group at the 4-position of the aromatic ring. Because of the additional amino group, the solubility of this compound rises more sharply as pH decreases than is found for other aminopenicillins.

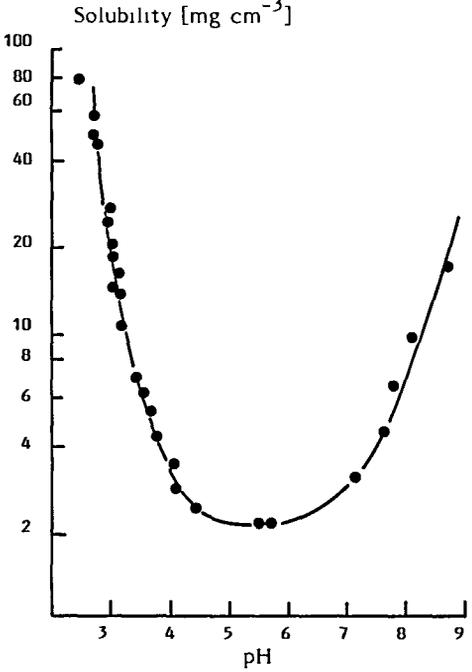
Bogardus and Palepu (1) stated that the measured solubility of CP-38,371 in water (pH 5.47) was  $0.47 \times 10^{-2} \text{ mol dm}^{-3}$  (units, evaluator) which is slightly higher than the intrinsic solubility of  $0.46 \times 10^{-2} \text{ mol dm}^{-3}$ , calculated (for pH 5.6) using a fitting procedure utilizing (amongst others) knowledge of the ionization constants. As stated by the authors this is to be expected with the amphoteric nature of the compound and the nearness of two of the ionization constants to the isoelectric pH of 5.6.

All the values reported by Bogardus (2) and given in the compilation sheet have a precision in measurement of  $\pm 2\%$  (evaluator), though because of the fact that this is the only study reported on this compound, and because of some possibility for degradation (especially at low pH), these values are regarded as being tentative.

#### REFERENCES

- (1) Bogardus, J.B.; Palepu, N.R. *Int. J. Pharmaceutics* 1979, *4*, 159.
- (2) Bogardus, J.B. Personal communication.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]hept-2-yl-5-tetrazole,6-[D-2-amino-2-(4-amino-phenyl)-acetamido]-3,3-dimethyl-7-oxo, trihydrate; (CP-38,371); $C_{16}H_{20}N_8O_2S \cdot 3H_2O$ ; [56852-63-2] (2) Hydrochloric acid; HCl; [7647-01-0] (3) Sodium hydroxide; NaOH; [1310-73-2] (4) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Bogardus, J.B.; Palepu, N.R. <i>Int. J. Pharm.</i> 1979, 4, 159-70.																																																																																																
<b>VARIABLES:</b> pH at 25°C	<b>PREPARED BY:</b> A. Regosz																																																																																																
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<b>METHOD APPARATUS/PROCEDURE:</b> Suspensions of the antibiotic were equilibrated for about 0.5 hr at temp (25 ± 0.2°C) in ampules using a vibratory mixer immersed in a water bath. The suspensions were then adjusted to the appropriate pH with standard HCl or NaOH solution. A sample was filtered through a 1.2 micron membrane filter. The amount of the solute in the filtrate was determined by high performance liquid chromatography using a Waters Microbondapak C-18 column. The mobile phase was 0.01 mol dm <sup>-3</sup> phosphate buffer at pH 5.5 with 5% v/v acetonitrile. The antibiotic was detected by UV absorption at 254 nm.	<b>SOURCE AND PURITY OF MATERIALS:</b> CP-38,371 was synthesized in the Pfizer Central Research Laboratories. The amphoteric form was isolated by aqueous recrystallization as the trihydrate. Purity was approx. 97%, calculated on the anhydrous basis. The major impurity was the corresponding penicilloic acid.																																																																																																
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<p>VARIABLES:</p> <p>pH at 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>COMMENTS AND/OR ADDITIONAL DATA:</p> <p>In the figure at the right, the points are the experimental results<sup>8</sup>. The solid theoretical line was calculated from equation [1].</p> $S_T = C_o \left( 1 + \frac{[H^+]}{K_2} + \frac{[H^+]^2}{K_1 \cdot K_2} + \frac{K_3}{[H^+]} \right) \quad [1]$ <p>where <math>S_T</math> is the total solubility, <math>C_o</math> is the intrinsic solubility of amphoteric antibiotic, <math>[H^+]</math> is concentration of the hydrogenion. <math>K_1</math>, <math>K_2</math> and <math>K_3</math> are dissociation constants for carboxylic and <math>\alpha</math>-amino groups, respectively.</p> <div style="text-align: right;">  </div>	
<p>AUXILIARY INFORMATION</p>	
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## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(amino-1,4-cyclohexadien-1-ylacetyl)amino]-3,3-dimethyl-7-oxo, (epicillin anhydrate); C<sub>16</sub>H<sub>21</sub>N<sub>3</sub>O<sub>5</sub>S; [26774-90-3]
- (2) Hydrochloric acid; HCl; [7647-01-0]
- (3) Potassium hydroxide; KOH; [1310-58-3]
- (4) Potassium chloride; KCl; [7447-40-7]
- (5) Water; H<sub>2</sub>O; [7732-18-5]

## EVALUATOR:

Eric Tomlinson,  
Department of Pharmacy,  
University of Amsterdam,  
The Netherlands.  
December 1983.

## CRITICAL EVALUATION:

The influence of pH on the solubility of epicillin anhydrate has been studied by Tsuji et al (1), who examined the pH - solubility behavior at constant ionic strength ( $\mu = 0.5$  - KCl) and temperature (310 K) using HCl or KOH to regulate the pH. Their results were presented graphically, and exhibited a U-shaped curve, with a minimum solubility at pH 4.47. The original data have been obtained directly from the authors (2), and are given in the appropriate compilation sheet. The precision in solubility determination and the temperature can be estimated as  $\pm 5\%$  and  $\pm 1$  K, respectively (evaluator). The authors fitted the experimental data using:

$$C_T = C_o [(a_{H^+}/K_1) + 1 + (K_2/a_{H^+})]$$

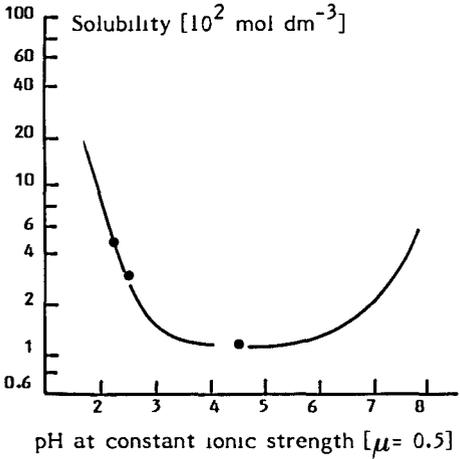
where  $C_T$  is the total solubility,  $C_o$  the intrinsic solubility of the amphoteric epicillin,  $a_{H^+}$  the hydrogen ion activity, and  $K_1$  and  $K_2$  the dissociation constants for 2-carboxylic acid and the conjugated acid of the alpha-amino group, respectively. The authors have stated (2) that the intrinsic solubility of epicillin anhydrate calculated in this manner is  $1.20 \times 10^{-2}$  mol dm<sup>-3</sup>, which agrees with their experimentally obtained value at pH 4.47. Being an ampholyte, epicillin anhydrate showed increased solubility in acid (below pH 2.5) and was calculated in alkali (above pH 6.0) to have a similar behavior. It is recalled here that Hou and Poole (3) have determined the pH-apparent rate profile of ampicillin anhydrate at 308 K in buffers of total ionic strength 0.5. They found that although the half life of ampicillin anhydrate at pH 4.85 is about 200 hours, this falls to about 30 hours at pH's 3.0 and 7.0, and to about 10 hours at pH 1.5. This probably applies to epicillin anhydrate also, and means that any solubility values determined below pH 2.0 and above pH 8.0 and using long equilibration times, must be regarded as doubtful. For the present data of Tsuji et al, where all data are within these values, the reported solubilities are regarded as being **tentative**.

Tsuji et al have further determined the effect of  $0.04$  mol dm<sup>-3</sup> sodium dodecylsulfate at the isoelectric point and at 310 K (estimated precision  $\pm 1$  K, evaluator) on the aqueous solubility of epicillin anhydrate. The found solubility is reported as  $2.0 \times 10^{-2}$  mol dm<sup>-3</sup>. This value is estimated to have a precision of  $\pm 5\%$  (evaluator), and is designated as **tentative**.

The values from a further study by Braun and Moll (4) on solubility in different gastric juices are **rejected** since the purity and source of the sample used is not specified.

## REFERENCES

- (1) Tsuji, A.; Nakashima, E.; Hamano, S.; Yamana, T. *J. Pharm. Sci.* **1978**, *67*, 1059.
- (2) Tsuji, A. Personal communication.
- (3) Hou, J.P.; Poole, J.W. *J. Pharm. Sci.* **1969**, *58*, 1510.
- (4) Braun, A.; Moll, F. *Acta Pharm. Technol.* **1980**, *26*, 258.

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(amino-1,4-cyclohexadien-1-ylacetyl)amino]-3,3-dimethyl-7-oxo, (epicillin anhydrate); <math>C_{16}H_{21}N_3O_4S</math>; [26774-90-3]</p> <p>(2) Hydrochloric acid; HCl; [7647-01-0]</p> <p>(3) Potassium hydroxide; KOH; [1310-58-3]</p> <p>(4) Potassium chloride; KCl; [7447-40-7]</p> <p>(5) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Tsuji, A.; Nakashima, E.; Hamano, S.; Yamana, T. <i>J. Pharm. Sci.</i> <b>1978</b>, <i>67</i>, 1059-66.</p>																	
<p>VARIABLES:</p> <p>pH at 37°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>																	
<p>EXPERIMENTAL VALUES:</p> <table border="1" data-bbox="171 466 665 668"> <thead> <tr> <th rowspan="2">pH<sup>a</sup></th> <th colspan="2">Solubility</th> </tr> <tr> <th><math>10^2 \text{ mol dm}^{-3a}</math></th> <th><math>\text{mg cm}^{-3b}</math></th> </tr> </thead> <tbody> <tr> <td>2.24</td> <td>4.50</td> <td>15.81</td> </tr> <tr> <td>2.51</td> <td>2.90</td> <td>10.19</td> </tr> <tr> <td>4.47</td> <td>1.20</td> <td>4.22</td> </tr> <tr> <td></td> <td><math>1.20 - C_0</math></td> <td>4.22</td> </tr> </tbody> </table> <p>In the figure at the right, the points are the experimental values<sup>a</sup>. The solid curve was generated from equation [1].</p> $C_T = C_0 \left( \frac{a_{H^+}}{K_1} + 1 + \frac{K_2}{a_{H^+}} \right) \quad [1]$ <p>where <math>C_T</math> is the total solubility, <math>C_0</math> is the intrinsic solubility of amphoteric epicillin with the electrically neutral zwitterion, <math>a_{H^+}</math> is the hydrogen-ion activity of the solution, and <math>K_1</math> and <math>K_2</math> are dissociation constant for 2-carboxylic acid and the conjugated acid of <math>\alpha</math>-amino group, respectively.</p> <p><sup>a</sup> Numerical date obtained from the author (A. Tsuji).  <sup>b</sup> Calculated by compiler. The <math>C_0</math> value (intrinsic solubility) estimated from the solubility at the isoelectric point is defined by Eqn [1].</p> 		pH <sup>a</sup>	Solubility		$10^2 \text{ mol dm}^{-3a}$	$\text{mg cm}^{-3b}$	2.24	4.50	15.81	2.51	2.90	10.19	4.47	1.20	4.22		$1.20 - C_0$	4.22
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<p>AUXILIARY INFORMATION</p>																		
<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of epicillin anhydrate was added to a glass-stoppered flask, followed by addition of <math>0.5 \text{ mol dm}^{-3}</math> KCl aqueous solution to a constant ionic strength (<math>I = 0.5</math>). The suspension was then adjusted to the appropriate pH with standard HCl or KOH solution. The flask was placed in a constant temperature bath at 37°C and mechanically shaken for 2 hr. A sample was taken through a 0.45 micron Sartorius membrane filter, the pH was measured, and the sample was assayed after appropriate dilution, if necessary with distilled water. The amount of epicillin was determined by iodometric titration and by UV spectrophotometric measurement at 250 nm.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Epicillin anhydrate was supplied by Sankyo Co., Tokyo, Japan, its purity was not specified.</p> <p>All other chemicals were reagent grade and were used without further purification. Distilled water was used.</p>																	
	<p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified          Temperature precision: probably <math>\pm 1^\circ\text{C}</math> (compiler)</p>																	
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<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(amino-1,4-cyclohexadien-1-ylacetyl)amino]-3,3-dimethyl-7-oxo, (epicillin anhydrate); <math>C_{16}H_{21}N_3O_4S</math>; [26774-90-3]</p> <p>(2) Hydrochloric acid; HCl; [6747-01-0]</p> <p>(3) Phosphoric acid, trisodium salt; <math>Na_3PO_4</math>; [7601-54-9]</p> <p>(4) Sodium chloride; NaCl; [7647-14-5]</p> <p>(5) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Braun, A.; Moll, P. <i>Acta Pharm. Technol.</i> <b>1980</b>, <i>26</i>, 258-60.</p>																
<p>VARIABLES:</p> <p>One temperature: 37°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>																
<p>EXPERIMENTAL VALUES:</p> <p>The authors determined maximal solubility of epicillin in synthetic gastric juice<sup>a</sup> (without pepsin) and compared the results with those obtained for solubility in human natural gastric juice.</p> <table border="1" data-bbox="262 564 1167 831"> <thead> <tr> <th colspan="4" style="text-align: center;">Solubility</th> </tr> <tr> <th colspan="2" style="text-align: center;">Synthetic gastric juice<sup>a</sup> (without pepsin)</th> <th colspan="2" style="text-align: center;">Human natural gastric juice</th> </tr> <tr> <th style="text-align: center;"><math>10^2 \text{ mg cm}^{-3}</math></th> <th style="text-align: center;"><math>10^2 \text{ mol dm}^{-3b}</math></th> <th style="text-align: center;"><math>10^2 \text{ mg cm}^{-3}</math></th> <th style="text-align: center;"><math>10^2 \text{ mol dm}^{-3b}</math></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">500</td> <td style="text-align: center;">1.42</td> <td style="text-align: center;">456</td> <td style="text-align: center;">1.30</td> </tr> </tbody> </table> <p><sup>a</sup> According to USP XIX composition of the synthetic gastric fluid, simulated is: HCl(35%) - 7.0 <math>\text{cm}^3</math>, NaCl - 2.0 g, pepsin - 3.2 g, distilled water to 1000 <math>\text{cm}^3</math>.</p> <p><sup>b</sup> Calculated by compiler.</p>		Solubility				Synthetic gastric juice <sup>a</sup> (without pepsin)		Human natural gastric juice		$10^2 \text{ mg cm}^{-3}$	$10^2 \text{ mol dm}^{-3b}$	$10^2 \text{ mg cm}^{-3}$	$10^2 \text{ mol dm}^{-3b}$	500	1.42	456	1.30
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<p style="text-align: center;">AUXILIARY INFORMATION</p>																	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of antibiotic was added to a 250 <math>\text{cm}^3</math> flask, followed by addition of 100 <math>\text{cm}^3</math> of synthetic or natural gastric juice. The fluid was stirred at a speed of 55 r.p.m. at a temperature of 37°C for about 1 hr. The fluid was then buffered to pH 4.6 using <math>Na_3PO_4</math> solution and filtered through a Sartorius SM 11307 filter. The amount of antibiotic in the filtrate was determined spectrophotometrically at 320 nm (1).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Source and purity of the epicillin and chemicals used were not specified.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: probably <math>\pm 1^\circ\text{C}</math> (compiler).</p> <p>REFERENCES:</p> <p>(1) Smith, H.W.G.; De Grey, G.E.; Patel, V.J. <i>Analyst</i> <b>1967</b>, <i>92</i>, 247.</p>																

## COMPONENTS:

(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium);  $C_{17}H_{19}N_2KO_5S$ ; [132-93-4]

(2) All solvents

## EVALUATOR:

Eric Tomlinson.  
Department of Pharmacy,  
University of Amsterdam,  
The Netherlands.

December 1983.

## CRITICAL EVALUATION:

Marsh and Weiss have determined the solubilities of phenethicillin potassium in 23 different non aqueous solvents and in various aqueous solvents at  $294^{\pm}1$  K (1). These workers studied a sample of the antibiotic provided by Bristol Laboratories, its purity was not specified. The amount of penicillin dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than  $20 \text{ mg cm}^{-3}$ . All values reported were uncorrected for solvent blank, which was generally less than  $0.05 \text{ mg total}$ . All data according to Marsh and Weiss have been recalculated to SI units (evaluator). Solubilities in non aqueous solvents are given in the Table.

Solvent <sup>a</sup>	Solubility (at $294^{\pm}1$ K), ( $\text{mol dm}^{-3}$ ) <sup>b</sup>
methanol	c
ethanol	$3.04 \times 10^{-2}$
cyclohexane	$2.24 \times 10^{-4}$
benzene	$2.5 \times 10^{-5}$
ligroin	$2.5 \times 10^{-5}$
isooctane	$2.5 \times 10^{-5}$
carbon tetrachloride	$5.5 \times 10^{-5}$
ethyl acetate	$5.5 \times 10^{-4}$
isoamyl acetate	$3.43 \times 10^{-4}$
acetone	$2.36 \times 10^{-4}$
methyl ethyl ketone	$1.44 \times 10^{-5}$
diethylether	$3.0 \times 10^{-5}$
ethylene chloride	$4.5 \times 10^{-5}$
1,4-dioxane	$2.65 \times 10^{-3}$
chloroform	$2.43 \times 10^{-4}$
carbon disulfide	$7.0 \times 10^{-5}$
pyridine	$3.78 \times 10^{-4}$
formamide	c
ethylene glycol	c
propylene glycol	c
dimethyl sulfoxide	c
isopropanol	$1.35 \times 10^{-3}$
isoamyl alcohol	$8.40 \times 10^{-4}$

(<sup>a</sup> All solvents are probably of U.S.P. or A.C.S. grade as previous (2); <sup>b</sup> units calculated by evaluator; <sup>c</sup> solubility greater than  $5.0 \times 10^{-2} \text{ mol dm}^{-3}$ ).

Marsh and Weiss have reported the solubility of phenethicillin potassium in water, 0.1 N HCl and 0.1 N NaOH to be greater than  $5.0 \times 10^{-2} \text{ mol dm}^{-3}$ ,  $1.79 \times 10^{-2} \text{ mol dm}^{-3}$ , and greater than  $5.0 \times 10^{-2} \text{ mol dm}^{-3}$ , respectively (units - evaluator).

All these values for solubility in both aqueous and non aqueous solvents have an estimated precision of  $\pm 5\%$  (evaluator). Because of the unstated purity of the sample, and since the values reported are unconfirmed, these solubilities are designated as being highly tentative, except for where the solubility is reported as being greater than  $5.0 \times 10^{-2} \text{ mol dm}^{-3}$ , (which are regarded as being doubtful).

## REFERENCES

- (1) Marsh, J.R.; Weiss, P.J. *J. Ass. Offic. Anal. Chem.* **1967**, *50*, 457.
- (2) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* **1957**, *7*, 374.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); $C_{17}H_{19}N_2KO_5S$ ; [132-93-4] (2) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of phenethicillin potassium in water at <math>21 \pm 1^\circ C</math> was reported as greater than:  <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.0 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.</p> <p>Water was probably of U.S.P. or A.C.S. grade (1).</p>
	<b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).
	<b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); $C_{17}H_{19}N_2KO_5$ ; [132-93-4] (2) Hydrochloric acid; HCl; [7647-01-0] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of phenethicillin potassium in 0.1 N HCl solution at $21 \pm 1^\circ C$ was reported as: $7.22 \text{ mg cm}^{-3}$ . ( $1.79 \times 10^{-2} \text{ mol dm}^{-3}$ - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD / APPARATUS / PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a 15 $\text{cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $21 \pm 1^\circ C$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 $\text{cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ C$ . The residue was further dried for 3 hr at $60^\circ C$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b> Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified. The purity of hydrochloric acid was not specified. Water was probably of U.S.P. or A.C.S. grade (1).  <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <b>7</b> , 374-7.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); $C_{17}H_{19}N_2KO_5$ ; [132-93-4] (2) Sodium hydroxide; NaOH; [1310-73-2] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of phenethicillin potassium in 0.1 N NaOH solution at <math>21 \pm 1^\circ C</math> was reported as greater than:</p> <p style="text-align: center;"><math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.0 \times 10^{-2} \text{ mol dm}^{-3}</math> - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD / APPARATUS / PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.</p> <p>The purity of sodium hydroxide was not specified. Water was probably of U.S.P. or A.C.S. grade (1).</p>
<b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).	
<b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <b>7</b> , 374-7.	

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); $C_{17}H_{19}N_2KO_5$ ; [132-93-4] (2) Methanol; $CH_4O$ ; [67-56-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of phenethicillin potassium in methanol at <math>21 \pm 1^\circ C</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.0 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.</p> <p>Methanol was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); <math>C_{17}H_{19}N_2KO_5</math>; [132-93-4]</p> <p>(2) Ethanol; <math>C_2H_6O</math>; [64-17-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <i>50</i>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of phenethicillin potassium in ethanol at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>12.23 \text{ mg cm}^{-3}</math>. (<math>3.04 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.</p> <p>Ethanol was probably of U.S.P. or A.C.S. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <i>7</i>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); <math>C_{17}H_{19}N_2KO_5</math>; [132-93-4]</p> <p>(2) Cyclohexane; <math>C_6H_{12}</math>; [110-82-7]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of phenethicillin potassium in cyclohexane at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.09 \text{ mg cm}^{-3}</math>. (<math>2.24 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD/APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.</p> <p>Cyclohexane was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); $C_{17}H_{19}N_2KO_5S$ ; [132-93-4] (2) Benzene; $C_6H_6$ ; [71-43-2]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of phenethicillin potassium in benzene at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.01 \text{ mg cm}^{-3}</math>. (<math>2.48 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.</p> <p>Benzene was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).
<b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <b>7</b> , 374-7.	

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); <math>C_{17}H_{19}N_2KO_5S</math>; [132-93-4]</p> <p>(2) Petroleum ether (ligroin)</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of phenethicillin potassium in ligroin at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.01 \text{ mg cm}^{-3}</math>. (<math>2.48 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD / APPARATUS / PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.</p> <p>Ligroin was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); $C_{17}H_{19}N_2KO_5$ ; [132-93-4] (2) Pentane, 2,2,4-trimethyl- (isooctane); $C_8H_{18}$ ; [540-84-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of phenethicillin potassium in isooctane at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.01 \text{ mg cm}^{-3}</math>. (<math>2.48 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.</p> <p>Isooctane was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <i>7</i>, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); $C_{17}H_{19}N_2KO_5$ ; [132-93-4] (2) Methane, tetrachloro- (carbon tetrachloride); $CCl_4$ ; [56-23-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u> , 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of phenethicillin potassium in carbon tetrachloride at $21 \pm 1^\circ C$ was reported as: $0.02 \text{ mg cm}^{-3}$ . ( $5.47 \times 10^{-5} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $21 \pm 1^\circ C$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ C$ . The residue was further dried for 3 hr at $60^\circ C$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b> Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified. Carbon tetrachloride was probably of A.C.S. or U.S.P. grade (1).  <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <u>Antibiotics and Chemotherapy</u> <u>1957</u> , 7, 374-7.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); $C_{17}H_{19}N_2KO_5$ ; [132-93-4] (2) Acetic acid, ethyl ester (ethyl acetate); $C_4H_8O_2$ ; [141-78-6]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of phenethicillin potassium in ethyl acetate at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.02 \text{ mg cm}^{-3}</math>. (<math>5.47 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.</p> <p>Ethyl acetate was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); $C_{17}H_{19}N_2KO_5$ ; [132-93-4] (2) 2-Propanone (acetone); $C_3H_6O$ ; [67-64-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of phenethicillin potassium in acetone at $21 \pm 1^\circ\text{C}$ was reported as: $0.10 \text{ mg cm}^{-3}$ . ( $2.36 \times 10^{-4} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.</p> <p>Acetone was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ\text{C}$ (authors).
<b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <b>7</b> , 374-7.	

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); $C_{17}H_{19}N_2KO_5$ ; [132-93-4] (2) 2-Butanone (methyl ethyl ketone); $C_4H_8O$ ; [78-93-3]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of phenethicillin potassium in methyl ethyl ketone at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.06 \text{ mg cm}^{-3}</math>. (<math>1.44 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.          Methyl ethyl ketone was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); $C_{17}H_{19}N_2KO_5S$ ; [132-93-4] (2) Ethane, 1,1'-oxybis- (diethyl ester); $C_4H_{10}O$ ; [60-29-7]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of phenethicillin potassium in diethyl ether at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.01 \text{ mg cm}^{-3}</math>. (<math>2.98 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.</p> <p>Diethyl ester was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <i>7</i> , 374-7.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); $C_{17}H_{19}N_2KO_5S$ ; [132-93-4] (2) Ethane, dichloro- (ethylene chloride); $C_2H_4Cl_2$ ; [1300-21-6]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of phenethicillin potassium in ethylene chloride at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.02 \text{ mg cm}^{-3}</math>. (<math>4.47 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.</p> <p>Ethylene chloride was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); $C_{17}H_{19}N_2KO_5$ ; [132-93-4] (2) 1,4-Dioxane; $C_4H_8O_2$ ; [123-91-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of phenethicillin potassium in 1,4-dioxane at <math>21 \pm 1^\circ C</math> was reported as:  <math>1.07 \text{ mg cm}^{-3}</math>. (<math>2.65 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.          1,4-Dioxane was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); $C_{17}H_{19}N_2KO_5$ ; [132-93-4] (2) Methane, trichloro- (chloroform); $CHCl_3$ ; [67-66-3]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of phenethicillin potassium in chloroform at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.10 \text{ mg cm}^{-3}</math>. (<math>2.43 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.</p> <p>Chloroform was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.

<p><b>COMPONENTS:</b>  (1) 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); <math>C_{17}H_{19}N_2KO_5</math>; [132-93-4]  (2) Carbon disulfide; <math>CS_2</math>; [75-15-0]</p>	<p><b>ORIGINAL MEASUREMENTS:</b>  Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u>, 50, 457-62.</p>
<p><b>VARIABLES:</b>  One temperature: 21°C</p>	<p><b>PREPARED BY:</b>  A. Regosz</p>
<p><b>EXPERIMENTAL VALUES:</b></p> <p>Solubility of phenethicillin potassium in carbon disulfide at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.03 \text{ mg cm}^{-3}</math>. (<math>6.96 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p style="text-align: center;"><b>AUXILIARY INFORMATION</b></p>	
<p><b>METHOD/APPARATUS/PROCEDURE:</b></p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p><b>SOURCE AND PURITY OF MATERIALS:</b></p> <p>Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.</p> <p>Carbon disulfide was probably of A.C.S. or U.S.P. grade (1).</p> <p><b>ESTIMATED ERROR:</b></p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p><b>REFERENCES:</b>  (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <u>Antibiotics and Chemotherapy</u> <u>1957</u>, 7, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); $C_{17}H_{19}N_2KO_5$ ; [132-93-4] (2) Pyridine; $C_6H_5N$ ; [110-86-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of phenethicillin potassium in pyridine at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.15 \text{ mg cm}^{-3}</math>. (<math>3.78 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.</p> <p>Pyridine was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); $C_{17}H_{19}N_2KO_5$ ; [132-93-4] (2) 1,2-Ethanediol (ethylene glycol); $C_2H_6O_2$ ; [107-21-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u> , 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of phenethicillin potassium in ethylene glycol at <math>21 \pm 1^\circ\text{C}</math> was reported as greater than:</p> <p style="text-align: center;"><math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.0 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ\text{C}</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.</p> <p>Ethylene glycol was probably of A.C.S. or U.S.P. grade (1).</p> <hr/> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <hr/> <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <u>Antibiotics and Chemotherapy</u> <u>1957</u> , 7, 374-7.

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); <math>C_{17}H_{19}N_2KO_5</math>; [132-93-4]</p> <p>(2) 1,2-Propanediol (propylene glycol); <math>C_3H_8O_2</math>; [57-55-6]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of phenethicillin potassium in propylene glycol at <math>21 \pm 1^\circ\text{C}</math> was reported as greater than:</p> <p style="text-align: center;"><math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.0 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ\text{C}</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.</p> <p>Propylene glycol was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); $C_{17}H_{19}N_2KO_5$ ; [132-93-4] (2) Methane, sulfinylbis- (dimethyl sulfoxide); $C_2H_6OS$ ; [67-68-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of phenethicillin potassium in dimethyl sulfoxide at <math>21 \pm 1^\circ\text{C}</math> was reported as greater than:</p> <p style="text-align: center;"><math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>5.0 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $21 \pm 1^\circ\text{C}$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b>  Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.  Dimethyl sulfoxide was probably of A.C.S. or U.S.P. grade (1).  <b>ESTIMATED ERROR:</b>  Solubility precision: none specified Temperature precision: $\pm 1^\circ\text{C}$ (authors).  <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <b>7</b> , 374-7.

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); <math>C_{17}H_{19}N_2KO_5</math>; [132-93-4]</p> <p>(2) 2-Propanol (isopropanol); <math>C_3H_8O</math>; [67-63-0]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. 1967, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of phenethicillin potassium in isopropanol at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.54 \text{ mg cm}^{-3}</math>. (<math>1.35 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD/APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.</p> <p>Isopropanol was probably of U.S.P. or A.C.S. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. Antibiotics and Chemotherapy 1957, 7, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino], monopotassium salt (phenethicillin potassium); <math>C_{17}H_{19}N_2KO_5</math>; [132-93-4]</p> <p>(2) 1-Butanol, 3-methyl- (isoamyl alcohol); <math>C_5H_{12}O</math>; [123-51-3]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of phenethicillin potassium in isoamyl alcohol at <math>21 \pm 1^\circ\text{C}</math> was reported as:</p> <p style="text-align: center;"><math>0.34 \text{ mg cm}^{-3}</math>. (<math>8.40 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD/APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Potassium phenethicillin was provided by Bristol Laboratories; its purity was not specified.</p> <p>Isoamyl alcohol was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

## COMPONENTS:

(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(2,6-dimethoxybenzoyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (methicillin sodium);  $C_{17}H_{19}N_2O_6SNa$ ; [132-92-3]

(2) All solvents

## EVALUATOR:

Eric Tomlinson,  
Department of Pharmacy,  
University of Amsterdam,  
The Netherlands.

December 1983.

## CRITICAL EVALUATION:

Marsh and Weiss have determined the solubilities of methicillin sodium in 23 different non aqueous solvents and in various aqueous solvents at  $294 \pm 1$  K (1). These workers studied a sample of the antibiotic provided by Bristol Laboratories, its purity was not specified. The amount of penicillin dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than  $20 \text{ mg cm}^{-3}$ . All values reported were uncorrected for solvent blank, which was generally less than  $0.05 \text{ mg total}$ . All data according to Marsh and Weiss have been recalculated to SI units (evaluator). Solubilities in non aqueous solvents are given in the Table.

Solvent <sup>a</sup>	Solubility (at $294 \pm 1$ K), ( $\text{mol dm}^{-3}$ ) <sup>b</sup>
methanol	c
ethanol	c
cyclohexane	$1.2 \times 10^{-5}$
benzene	0
ligroin	0
isooctane	$5.52 \times 10^{-4}$
carbon tetrachloride	0
ethyl acetate	$1.19 \times 10^{-4}$
isoamyl acetate	$3.35 \times 10^{-4}$
acetone	$6.41 \times 10^{-4}$
methyl ethyl ketone	$2.61 \times 10^{-4}$
diethylether	$5.5 \times 10^{-5}$
ethylene chloride	$2.03 \times 10^{-4}$
1,4-dioxane	$1.29 \times 10^{-3}$
chloroform	$1.51 \times 10^{-3}$
carbon disulfide	$8.7 \times 10^{-5}$
pyridine	c
formamide	c
ethylene glycol	c
propylene glycol	c
dimethyl sulfoxide	c
isopropanol	$1.63 \times 10^{-2}$
isoamyl alcohol	$1.09 \times 10^{-2}$

(<sup>a</sup> All solvents are probably of U.S.P. or A.C.S. grade as previous (2); <sup>b</sup> units calculated by evaluator; <sup>c</sup> solubility greater than  $4.97 \times 10^{-2} \text{ mol dm}^{-3}$ ).

Marsh and Weiss have reported the solubility of methicillin sodium in water, 0.1 N HCl and 0.1 N NaOH to be greater than  $4.97 \times 10^{-2} \text{ mol dm}^{-3}$ ,  $3.82 \times 10^{-2} \text{ mol dm}^{-3}$ , and greater than  $4.97 \times 10^{-2} \text{ mol dm}^{-3}$ , respectively (units - evaluator).

All these values for solubility in both aqueous and non aqueous solvents have an estimated precision of  $\pm 5\%$  (evaluator). Because of the unstated purity of the sample, and since the values reported are unconfirmed, these solubilities are designated as being highly tentative, except for where the solubility is reported as being greater than  $4.97 \times 10^{-2} \text{ mol dm}^{-3}$ , (which are regarded as being doubtful). Values reported as being  $0 \text{ mol dm}^{-3}$  are rejected since the sensitivity of the assay used is not sufficient for this value to be viewed with any certainty.

## REFERENCES

- (1) Marsh, J.R.; Weiss, P.J. *J. Ass. Offic. Anal. Chem.* 1967, 50, 457.  
 (2) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* 1957, 7, 374.

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(2,6-dimethoxybenzoyl)amino]-3,3-dimethyl-7-oxo-,monosodium salt (methicillin sodium); <math>C_{17}H_{19}N_2O_6SNa</math>; [132-92-3]</p> <p>(2) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> 1967, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of methicillin sodium in water at <math>21 \pm 1^\circ C</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.97 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD/APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Methicillin sodium was provided by Bristol Laboratories; its purity was not specified.</p> <p>Water was probably of U.S.P. or A.C.S. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> 1957, 7, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(2,6-dimethoxybenzoyl)amino]-3,3-dimethyl-7-oxo-,monosodium salt (methicillin sodium); <math>C_{17}H_{19}N_2O_6SNa</math>; [132-92-3]</p> <p>(2) Hydrochloric acid; HCl; [7647-01-0]</p> <p>(3) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u>, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of methicillin sodium in 0.1 N HCl solution at <math>21 \pm 1^\circ C</math> was reported as:  <math>15.39 \text{ mg cm}^{-3}</math>. (<math>3.82 \times 10^{-2} \text{ mol dm}^{-3}</math> - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Methicillin sodium was provided by Bristol Laboratories; its purity was not specified.</p> <p>The purity of hydrochloric acid was not specified. Water was probably of U.S.P. or A.C.S. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <u>Antibiotics and Chemotherapy</u> <u>1957</u>, 7, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(2,6-dimethoxybenzoyl)amino]-3,3-dimethyl-7-oxo-,monosodium salt (methicillin sodium); $C_{17}H_{19}N_2O_6SNa$ ; [132-92-3] (2) Sodium hydroxide; NaOH; [1310-73-2] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1967</b> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of methicillin sodium in 0.1 N NaOH solution at <math>21 \pm 1^\circ C</math> was reported as greater than:</p> <p style="text-align: center;"><math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.97 \times 10^{-2} \text{ mol dm}^{-3}</math> - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $21 \pm 1^\circ C$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b>  Methicillin sodium was provided by Bristol Laboratories; its purity was not specified.  The purity of sodium hydroxide was not specified. Water was probably of U.S.P. or A.C.S. grade (1).  <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <b>1957</b> , <i>7</i> , 374-7.





<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(2,6-dimethoxybenzoyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (methicillin sodium); $C_{17}H_{19}N_2O_6SNa$ ; [132-92-3] (2) Cyclohexane; $C_6H_{12}$ ; [110-82-7]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of methicillin sodium in cyclohexane at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.005 \text{ mg cm}^{-3}</math>. (<math>1.24 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Methicillin sodium was provided by Bristol Laboratories; its purity was not specified.</p> <p>Cyclohexane was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(2,6-dimethoxybenzoyl)amino]-3,3-dimethyl-7-oxo-,monosodium salt (methicillin sodium); $C_{17}H_{19}N_2O_6SNa$ ; [132-92-3] (2) Benzene; $C_6H_6$ ; [71-43-2]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of methicillin sodium in benzene at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.0 \text{ mg cm}^{-3}</math>. (<math>0.0 \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Methicillin sodium was provided by Bristol Laboratories; its purity was not specified.</p> <p>Benzene was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(2,6-dimethoxybenzoyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (methicillin sodium); $C_{17}H_{19}N_2O_6SNa$ ; [132-92-3] (2) Pentane,2,2,4-trimethyl- (isooctane); $C_8H_{18}$ ; [540-84-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of methicillin sodium in isooctane at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.22 \text{ mg cm}^{-3}</math>. (<math>5.52 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Methicillin sodium was provided by Bristol Laboratories; its purity was not specified.</p> <p>Isooctane was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>





<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(2,6-dimethoxybenzoyl)amino]-3,3-dimethyl-7-oxo-,monosodium salt (methicillin sodium); <math>C_{17}H_{19}N_2O_6SNa</math>; [132-92-3]</p> <p>(2) 1-Butanol,3-methyl acetate (isoamyl acetate); <math>C_7H_{14}O_2</math>; [123-92-2]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <i>50</i>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of methicillin sodium in isoamyl acetate at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.14 \text{ mg cm}^{-3}</math>. (<math>3.35 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD/APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Methicillin sodium was provided by Bristol Laboratories; its purity was not specified.</p> <p>Isoamyl acetate was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <i>7</i>, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(2,6-dimethoxybenzoyl)amino]-3,3-dimethyl-7-oxo-,monosodium salt (methicillin sodium); $C_{17}H_{19}N_2O_6Na$ ; [132-92-3] (2) 2-Propanone (acetone); $C_3H_6O$ ; [67-64-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of methicillin sodium in acetone at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.26 \text{ mg cm}^{-3}</math>. (<math>6.41 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Methicillin sodium was provided by Bristol Laboratories; its purity was not specified.</p> <p>Acetone was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(2,6-dimethoxybenzoyl)amino]-3,3-dimethyl-7-oxo-,monosodium salt (methicillin sodium); $C_{17}H_{19}N_2O_6SNa$ ; [132-92-3] (2) 2-Butanone (methyl ethyl ketone); $C_4H_8O$ ; [78-93-3]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. 1967, 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of methicillin sodium in methyl ethyl ketone at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.11 \text{ mg cm}^{-3}</math>. (<math>2.61 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Methicillin sodium was provided by Bristol Laboratories; its purity was not specified.</p> <p>Methyl ethyl ketone was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ\text{C}$ (authors).
<b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <u>Antibiotics and Chemotherapy</u> 1957, 7, 374-7.	

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(2,6-dimethoxybenzoyl)amino]-3,3-dimethyl-7-oxo-,monosodium salt (methicillin sodium); $C_{17}H_{19}N_2O_6SNa$ ; [132-92-3] (2) Ethane,1,1'-oxybis- (diethyl ether); $C_4H_{10}O$ ; [60-29-7]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1967</b> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of methicillin sodium in diethyl ether at $21 \pm 1^\circ C$ was reported as: $0.022 \text{ mg cm}^{-3}$ . ( $5.47 \times 10^{-5} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $21 \pm 1^\circ C$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ C$ . The residue was further dried for 3 hr at $60^\circ C$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b> Methicillin sodium was provided by Bristol Laboratories; its purity was not specified. Diethyl ether was probably of A.C.S. or U.S.P. grade (1).  <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <b>1957</b> , <i>7</i> , 374-7.







<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(2,6-dimethoxybenzoyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (methicillin sodium); $C_{17}H_{19}N_2O_6SNa$ ; [132-92-3] (2) Carbon disulfide; $CS_2$ ; [75-15-0]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of methicillin sodium in carbon disulfide at $21 \pm 1^\circ C$ was reported as: $0.04 \text{ mg cm}^{-3}$ . ( $8.69 \times 10^{-5} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Methicillin sodium was provided by Bristol Laboratories; its purity was not specified.</p> <p>Carbon disulfide was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>









<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(2,6-dimethoxybenzoyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (methicillin sodium); $C_{17}H_{19}N_2O_6SNa$ ; [132-92-3] (2) Methane,sulfinylbis- (dimethyl sulfoxide); $C_2H_6OS$ ; [67-68-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of methicillin sodium in dimethyl sulfoxide at <math>21 \pm 1^\circ C</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.97 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $21 \pm 1^\circ C$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b>  Methicillin sodium was provided by Bristol Laboratories; its purity was not specified.  Dimethyl sulfoxide was probably of A.C.S. or U.S.P. grade (1).  <b>ESTIMATED ERROR:</b>  Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <b>7</b> , 374-7.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(2,6-dimethoxybenzoyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (methicillin sodium); $C_{17}H_{19}N_2O_6SNa$ ; [132-92-3] (2) 2-Propanol (isopropanol); $C_3H_8O$ ; [67-63-0]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1967</b> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of methicillin sodium in isopropanol at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>6.54 \text{ mg cm}^{-3}</math>. (<math>1.63 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Methicillin sodium was provided by Bristol Laboratories; its purity was not specified.</p> <p>Isopropanol was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ\text{C}$ (authors).
<b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <b>1957</b> , <i>7</i> , 374-7.	

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[(2,6-dimethoxybenzoyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt (methicillin sodium); $C_{17}H_{19}N_2O_6SNa$ ; [132-92-3] (2) 1-Butanol,3-methyl- (isoamyl alcohol); $C_2H_{12}O$ ; [123-51-3]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of methicillin sodium in isoamyl alcohol at <math>21 \pm 1^\circ C</math> was reported as:  <math>4.37 \text{ mg cm}^{-3}</math>. (<math>1.09 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a 15 $\text{cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $21 \pm 1^\circ C$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 $\text{cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ C$ . The residue was further dried for 3 hr at $60^\circ C$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b>  Methicillin sodium was provided by Bristol Laboratories; its purity was not specified.  Isoamyl alcohol was probably of A.C.S. or U.S.P. grade (1).  <b>ESTIMATED ERROR:</b>  Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <i>7</i> , 374-7.

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxybutyl)amino] monopotassium salt (propicillin potassium); <math>C_{18}H_{21}N_2KO_5S</math>; [1245-44-9]</p> <p>(2) Aqueous solvents</p>	<p>EVALUATOR:</p> <p>Eric Tomlinson. Department of Pharmacy, University of Amsterdam, The Netherlands. December 1983.</p>
<p>CRITICAL EVALUATION:</p> <p>The solubility of propicillin potassium in aqueous solvents at <math>310.2 \pm 0.1</math> K has been studied by Tsuji et al (1). The sample studied by these workers was of known potency, and the method used to appraise the solubilities may be regarded as leading to reported values having a precision of <math>\pm 2\%</math> (evaluator). The solubility reported of <math>0.72 \text{ mol dm}^{-3}</math> at <math>310.2 \pm 0.1</math> K at pH 2.00 (HCl) and ionic strength of 0.5, is regarded as being <b>tentative</b>.</p> <p>Tsuji et al also studied the influence of the non ionic surfactant poloxyethylene-23-lauryl ether on the solubility of propicillin potassium. Over the concentration range of surfactant from <math>3.0 \times 10^{-3} \text{ mol dm}^{-3}</math> to <math>2.0 \times 10^{-2} \text{ mol dm}^{-3}</math>, an increase in surfactant concentration was found to lead to a regular increase in penicillin solubility from <math>1.21 \times 10^{-3} \text{ mol dm}^{-3}</math> to <math>4.09 \times 10^{-3} \text{ mol dm}^{-3}</math>. The values given in the compilation sheet are also regarded as being <b>tentative</b>, and as having the same level of precision as indicated above.</p> <p>REFERENCE</p> <p>(1) Tsuji, A.; Miyamoto, E.; Matsuda, M.; Nishimra, K.; Yamana, T. <i>J. Pharm. Sci.</i> <u>1982</u>, <b>71</b>, 1313.</p>	

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxybutyl)amino]monopotassium salt (Propicillin potassium); <math>C_{18}H_{21}N_2KO_5S</math>; [1245-44-9]</p> <p>(2) Hydrochloric acid; HCl; [7647-01-0]</p> <p>(3) Potassium chloride; KCl; [7447-40-7]</p> <p>(4) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Tsuji, A.; Miyamoto, E.; Matsuda, M.; Nishimura, K.; Yamana, T. <i>J. Pharm. Sci.</i> <b>1982</b>, <i>71</i>, 1313-18.</p>
<p>VARIABLES:</p> <p>Temperature: 37°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of propicillin potassium in hydrochloric acid-potassium chloride solution (pH 2.00 and ionic strength 0.5) at <math>37 \pm 1^\circ C</math> was reported as:</p> <p style="text-align: center;"><math>0.72 \text{ mol dm}^{-3}</math></p>	
<p style="text-align: center;">AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of propicillin potassium was added to the hydrochloric acid-potassium chloride solution pH 2.00 and ionic strength 0.5 in a glass-stoppered flask. The flask was placed in thermostated water-bath at <math>37 \pm 0.1^\circ C</math> and shaken mechanically until the antibiotic concentration in the solution showed an equilibrium value. A sample was taken through a 0.45 micron membrane filter and, if necessary, assayed after appropriate dilution with distilled water. The pH of the sample solution was measured before use and at the end of the experiment. The amount of antibiotic in the sample was determined by a spectrophotometric method (1).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Propicillin potassium of potency <math>993 \mu\text{g mg}^{-1}</math> was provided by Takeda Chemical Industries, Osaka, Japan.</p> <p>All other chemicals employed were of reagent grade and were used without further purification.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 0.1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Bundgaard, H.; Ilver, K. <i>J. Pharm. Pharmacol.</i> <b>1972</b>, <i>24</i>, 790-4.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxybutyl)amino] monopotassium salt (Propicillin potassium); <math>C_{18}H_{21}N_2KO_5S</math>; [1245-44-9]</p> <p>(2) Polyoxyethylene-23-lauryl ether</p> <p>(3) Hydrochloric acid; HCl; [7647-01-0]</p> <p>(4) Potassium chloride; KCl; [7447-40-7]</p> <p>(5) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Tsuji, A.; Miyamoto, E.; Matsuda, M.; Nishimura, K.; Yamana, T. <i>J. Pharm. Sci.</i> <b>1982</b>, <b>71</b>, 1313-18.</p>												
<p>VARIABLES:</p> <p>Temperature: 37°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>												
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of Propicillin potassium in the presence of Polyoxyethylene-23-lauryl ether:</p> <table border="1" data-bbox="243 548 1006 813"> <thead> <tr> <th>Concentration of polyoxyethylene-23-lauryl ether <math>10^3 \text{ mol dm}^{-3}</math></th> <th>Solubility of propicillin potassium<sup>a</sup> <math>10^3 \text{ mol dm}^{-3}</math></th> </tr> </thead> <tbody> <tr> <td>3.0</td> <td>1.21</td> </tr> <tr> <td>5.0</td> <td>1.55</td> </tr> <tr> <td>7.0</td> <td>1.89</td> </tr> <tr> <td>10.0</td> <td>2.40</td> </tr> <tr> <td>20.0</td> <td>4.09</td> </tr> </tbody> </table> <p><sup>a</sup> value at <math>37 \pm 0.1^\circ\text{C}</math>, pH 2.00, and ionic strength = 0.5</p>		Concentration of polyoxyethylene-23-lauryl ether $10^3 \text{ mol dm}^{-3}$	Solubility of propicillin potassium <sup>a</sup> $10^3 \text{ mol dm}^{-3}$	3.0	1.21	5.0	1.55	7.0	1.89	10.0	2.40	20.0	4.09
Concentration of polyoxyethylene-23-lauryl ether $10^3 \text{ mol dm}^{-3}$	Solubility of propicillin potassium <sup>a</sup> $10^3 \text{ mol dm}^{-3}$												
3.0	1.21												
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7.0	1.89												
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20.0	4.09												
<p>AUXILIARY INFORMATION</p>													
<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of propicillin potassium was added to the hydrochloric acid-potassium chloride solution pH 2.00 and ionic strength 0.5 containing appropriate amount of polyoxyethylene-23-lauryl ether in a glass-stoppered flask. The flask was placed in thermostated water-bath at <math>37 \pm 0.1^\circ\text{C}</math> and shaken mechanically until the antibiotic concentration in the solution showed an equilibrium value. A sample was taken through a 0.45 micron membrane filter and, if necessary, assayed after appropriate dilution with distilled water. The pH of the sample solution was measured before use and at the end of the experiment. The amount of antibiotic in the sample was determined by a spectrophotometric method (1).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Propicillin potassium of potency 933 <math>\mu\text{g mg}^{-1}</math> was provided by Takeda Chemical Industries, Osaka, Japan.</p> <p>Polyoxyethylene-23-lauryl ether was obtained from a commercial source and used without further purification.</p> <p>All other chemicals employed were of reagent grade and used without further purification.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm .1^\circ\text{C}</math>(authors).</p> <p>REFERENCES:</p> <p>(1) Bundgaard, H.; Ilver, K. <i>J. Pharm. Pharmacol.</i> <b>1972</b>, <b>24</b>, 790-4.</p>												

## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (dicloxacillin sodium monohydrate); C<sub>19</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>5</sub>Na.H<sub>2</sub>O; [13412-64-1]
- (2) All solvents

## EVALUATOR:

Eric Tomlinson.  
Department of Pharmacy,  
University of Amsterdam,  
The Netherlands.  
December 1983.

## CRITICAL EVALUATION:

Marsh and Weiss have determined the solubilities of dicloxacillin sodium monohydrate in 23 different non aqueous solvents and in various aqueous solvents at 294<sup>±</sup>1 K (1). These workers studied a sample of the antibiotic provided by Ayerst Laboratories, its purity was not specified. The amount of penicillin dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than 20 mg cm<sup>-3</sup>. All values reported were uncorrected for solvent blank, which was generally less than 0.05 mg total. All data according to Marsh and Weiss have been recalculated to SI units (evaluator). Solubilities in non aqueous solvents are given in the Table.

Solvent <sup>a</sup>	Solubility (at 294 <sup>±</sup> 1 K), (mol dm <sup>-3</sup> ) <sup>b</sup>
methanol	c
ethanol	c
cyclohexane	5.5 x 10 <sup>-5</sup>
benzene	2.9 x 10 <sup>-5</sup>
ligroin	2.0 x 10 <sup>-5</sup>
isooctane	0
carbon tetrachloride	0
ethyl acetate	2.74 x 10 <sup>-3</sup>
isoamyl acetate	2.90 x 10 <sup>-3</sup>
acetone	2.63 x 10 <sup>-2</sup>
methyl ethyl ketone	1.91 x 10 <sup>-2</sup>
diethylether	1.80 x 10 <sup>-4</sup>
ethylene chloride	4.47 x 10 <sup>-3</sup>
1,4-dioxane	8.96 x 10 <sup>-3</sup>
chloroform	1.07 x 10 <sup>-3</sup>
carbon disulfide	3.9 x 10 <sup>-5</sup>
pyridine	1.25 x 10 <sup>-2</sup>
formamide	c
ethylene glycol	c
propylene glycol	c
dimethyl sulfoxide	c
isopropanol	1.87 x 10 <sup>-2</sup>
isoamyl alcohol	2.43 x 10 <sup>-2</sup>

(<sup>a</sup> All solvents are probably of U.S.P. or A.C.S. grade as previous (2); <sup>b</sup> units calculated by evaluator; <sup>c</sup> solubility greater than 3.90 x 10<sup>-2</sup> mol dm<sup>-3</sup>).

Marsh and Weiss have reported the solubility of dicloxacillin sodium monohydrate in water, 0.1 N HCl and 0.1 N NaOH to be greater than 3.90 x 10<sup>-2</sup> mol dm<sup>-3</sup>, 9.22 x 10<sup>-2</sup> mol dm<sup>-3</sup>, and greater than 3.90 x 10<sup>-2</sup> mol dm<sup>-3</sup>, respectively (units - evaluator). The only other value reported is that due to Knott et al (3) who examined the solubility of this penicillin in water at 298 K, their reported value of 0.29 mol dm<sup>-3</sup> is regarded as being **highly doubtful** since neither the method of determination, nor the purity of the sample, nor the source and purity of the water were given.

All the values for solubility in both aqueous and non aqueous solvents due to Marsh and Weiss have an estimated precision of  $\pm$  5% (evaluator). Because of the unstated purity of the sample, and since the values reported are unconfirmed, these solubilities are designated as being **highly tentative**, except for where the solubility is reported as being greater than 3.90 x 10<sup>-2</sup> mol dm<sup>-3</sup>, (which are regarded as being **doubtful**). Values reported as being 0 mol dm<sup>-3</sup> are **rejected** since the sensitivity of the assay used is not sufficient for this value to be viewed with any certainty.

## REFERENCES

- (1) Marsh, J.R.; Weiss, P.J. *J. Ass. Offic. Anal. Chem.* **1967**, *50*, 457.
- (2) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* **1957**, *7*, 374.
- (3) Knott, Th.; Lange, A.; Volkening, R. *Arzneimittel-Forsch.* **1965**, *15*, 331.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (dicloxacillin sodium monohydrate); $C_{19}H_{16}Cl_2N_3O_5SNa \cdot H_2O$ ; [13412-64-1] (2) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Knott, Th; Lange A.; Volkening, R. <i>Arzneimittel-Forsch.</i> 1965, 15, 331-6.
<b>VARIABLES:</b> One temperature: 25°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of dicloxacillin sodium monohydrate in water at 25°C was reported as: $150 \text{ mg cm}^{-3}$ . ( $0.29 \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Nothing specified. The content of the dissolved antibiotic was determined microbiologically.	<b>SOURCE AND PURITY OF MATERIALS:</b> Dicloxacillin sodium monohydrate Dichor-Staphenor, supplied by Bayer, its purity was not specified. The source and purity of the water was not specified.
<b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: none specified	
<b>REFERENCES:</b>	







<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (dicloxacillin sodium monohydrate); $C_{19}H_{16}Cl_2N_3O_5SNa \cdot H_2O$ ; [13412-64-1] (2) Methanol; $CH_4O$ ; [67-56-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of dicloxacillin sodium monohydrate in methanol at <math>21 \pm 1^\circ C</math> was reported as greater than:</p> <p style="text-align: center;"><math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>3.90 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $21 \pm 1^\circ C$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b>  Dicloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.  Methanol was probably of U.S.P. or A.C.S. grade (1,2).  <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <i>7</i> , 374-7. (2) Andrew, M.L.; Weiss, P.J. <i>ibid.</i> , <u>1959</u> , <i>9</i> , 277-9.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (dicloxacillin sodium monohydrate); $C_{19}H_{16}Cl_2N_3O_5SNa \cdot H_2O$ ; [13412-64-1] (2) Ethanol; $C_2H_6O$ ; [64-17-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of dicloxacillin sodium monohydrate in ethanol at $21 \pm 1^\circ C$ was reported as greater than: $20 \text{ mg cm}^{-3}$ . (Greater than $3.90 \times 10^{-2} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a 15 $\text{cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $21 \pm 1^\circ C$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b> Dicloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified. Ethanol was probably of U.S.P. or A.C.S. grade (1,2).  <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <i>7</i> , 374-7. (2) Andrew, M.L.; Weiss, P.J. <i>ibid.</i> , <u>1959</u> , <i>9</i> , 277-9.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (dicloxacillin sodium monohydrate); $C_{19}H_{16}Cl_2N_3O_5SNa \cdot H_2O$ ; [13412-64-1] (2) Cyclohexane; $C_6H_{12}$ ; [110-82-7]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of dicloxacillin sodium monohydrate in cyclohexane at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.028 \text{ mg cm}^{-3}</math>. (<math>5.49 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Dicloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.</p> <p>Cyclohexane was probably of A.C.S. or U.S.P. grade (1,2).</p>
	<b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <b>7</b> , 374-7. (2) Andrew, M.L.; Weiss, P.J. <i>ibid.</i> , <u>1959</u> , <b>9</b> , 277-9.

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (dicloxacillin sodium monohydrate); <math>C_{19}H_{16}Cl_2N_3O_5SNa \cdot H_2O</math>; [13412-64-1]</p> <p>(2) Benzene; <math>C_6H_6</math>; [71-43-2]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of dicloxacillin sodium monohydrate in benzene at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.015 \text{ mg cm}^{-3}</math>. (<math>2.94 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD / APPARATUS / PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Dicloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.</p> <p>Benzene was probably of A.C.S. or U.S.P. grade (1,2).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.  (2) Andrew, M.L.; Weiss, P.J. <i>ibid.</i>, <u>1959</u>, <b>9</b>, 277-9.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (dicloxacillin sodium monohydrate); $C_{19}H_{16}Cl_2N_3O_5SNa \cdot H_2O$ ; [13412-64-1] (2) Petroleum ether (ligroin)	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of dicloxacillin sodium monohydrate in ligroin at $21 \pm 1^\circ C$ was reported as: $0.010 \text{ mg cm}^{-3}$ . ( $1.96 \times 10^{-5} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD / APPARATUS / PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $21 \pm 1^\circ C$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ C$ . The residue was further dried for 3 hr at $60^\circ C$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b> Dicloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified. Ligroin was probably of A.C.S. or U.S.P. grade (1,2).
	<b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors). <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <b>7</b> , 374-7. (2) Andrew, M.L.; Weiss, P.J. <i>ibid.</i> , <u>1959</u> , <b>9</b> , 277-9.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (dicloxacillin sodium monohydrate); $C_{19}H_{16}Cl_2N_3O_5Na \cdot H_2O$ ; [13412-64-1] (2) Pentane,2,2,4-trimethyl- (isooctane); $C_8H_{18}$ ; [540-84-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1967</b> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of dicloxacillin sodium monohydrate in isooctane at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.00 \text{ mg cm}^{-3}</math>. (<math>0.00 \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $21 \pm 1^\circ C$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ C$ . The residue was further dried for 3 hr at $60^\circ C$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b>  Dicloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.  Isooctane was probably of A.C.S. or U.S.P. grade (1,2).
	<b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).
	<b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <b>1957</b> , <i>7</i> , 374-7. (2) Andrew, M.L.; Weiss, P.J. <i>ibid.</i> , <b>1959</b> , <i>9</i> , 277-9.



<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (dicloxacillin sodium monohydrate); <math>C_{19}H_{16}Cl_2N_3O_5Na \cdot H_2O</math>; [13412-64-1]</p> <p>(2) Acetic acid,ethyl ester (ethyl acetate); <math>C_4H_8O_2</math>; [141-78-6]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of dicloxacillin sodium monohydrate in ethyl acetate at <math>21 \pm 1^\circ C</math> was reported as:  <math>1.40 \text{ mg cm}^{-3}</math>. (<math>2.74 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Dicloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.</p> <p>Ethyl acetate was probably of A.C.S. or U.S.P. grade (1,2).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.  (2) Andrew, M.L.; Weiss, P.J. <i>ibid.</i>, <u>1959</u>, <b>9</b>, 277-9.</p>



<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (dicloxacillin sodium monohydrate); <math>C_{19}H_{16}Cl_2N_3O_5Na \cdot H_2O</math>; [13412-64-1]</p> <p>(2) 2-Propanone (acetone); <math>C_3H_6O</math>; [67-64-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> 1967, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of dicloxacillin sodium monohydrate in acetone at <math>21 \pm 1^\circ C</math> was reported as:  <math>13.44 \text{ mg cm}^{-3}</math>. (<math>2.63 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Dicloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.</p> <p>Acetone was probably of A.C.S. or U.S.P. grade (1,2).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES.</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> 1957, 7, 374-7.  (2) Andrew, M.L.; Weiss, P.J. <i>ibid.</i>, 1959, 9, 277-9.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (dicloxacillin sodium monohydrate); $C_{19}H_{16}Cl_2N_3O_5SNa \cdot H_2O$ ; [13412-64-1] (2) 2-Butanone (methyl ethyl ketone); $C_4H_8O$ ; [78-93-3]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of dicloxacillin sodium monohydrate in methyl ethyl ketone at <math>21 \pm 1^\circ C</math> was reported as:</p> <p style="text-align: center;"><math>9.73 \text{ mg cm}^{-3}</math>. (<math>1.91 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD / APPARATUS / PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Dicloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.</p> <p>Methyl ethyl ketone was probably of A.C.S. or U.S.P. grade (1,2).</p> <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <i>7</i> , 374-7. (2) Andrew, M.L.; Weiss, P.J. <i>ibid.</i> , <u>1959</u> , <i>9</i> , 277-9.





<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (dicloxacillin sodium monohydrate); <math>C_{19}H_{16}Cl_2N_3O_5SNa \cdot H_2O</math>; [13412-64-1]</p> <p>(2) 1,4-Dioxane; <math>C_4H_8O_2</math>; [123-91-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1967</b>, <i>50</i>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of dicloxacillin sodium monohydrate in 1,4-dioxane at <math>21 \pm 1^\circ C</math> was reported as:</p> <p style="text-align: center;"><math>4.57 \text{ mg cm}^{-3}</math>. (<math>8.96 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Dicloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.</p> <p>1,4-Dioxane was probably of A.C.S. or U.S.P. grade (1,2).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <b>1957</b>, <i>7</i>, 374-7. (2) Andrew, M.L.; Weiss, P.J. <i>ibid.</i>, <b>1959</b>, <i>9</i>, 277-9.</p>







<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (dicloxacillin sodium monohydrate); $C_{19}H_{16}Cl_2N_3O_5Na.H_2O$ ; [13412-64-1] (2) Formamide; $CH_3NO$ ; [75-12-7]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of dicloxacillin sodium monohydrate in formamide at <math>21 \pm 1^\circ C</math> was reported as greater than:</p> <p style="text-align: center;"><math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>3.90 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $21 \pm 1^\circ C$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b>  Dicloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.  Formamide was probably of A.C.S. or U.S.P. grade (1,2).  <b>ESTIMATED ERROR:</b>  Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <b>7</b> , 374-7. (2) Andrew, M.L.; Weiss, P.J. <i>ibid.</i> , <u>1959</u> , <b>9</b> , 277-9.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (dicloxacillin sodium monohydrate); $C_{19}H_{16}Cl_2N_3O_5SNa \cdot H_2O$ ; [13412-64-1] (2) 1,2-Ethandiol (ethylene glycol); $C_2H_6O_2$ ; [107-21-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of dicloxacillin sodium monohydrate in ethylene glycol at <math>21 \pm 1^\circ C</math> was reported as greater than:</p> <p style="text-align: center;"><math>20 \text{ cm}^{-3}</math>. (Greater than <math>3.90 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ cm}^{-3}</math>.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Dicloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.</p> <p>Ethylene glycol was probably of A.C.S. or U.S.P. grade (1,2).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <b>7</b> , 374-7. (2) Andrew, M.L.; Weiss, P.J. <i>ibid.</i> , <u>1959</u> , <b>9</b> , 277-9.







<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (dicloxacillin sodium monohydrate); $C_{19}H_{16}Cl_2N_3O_5Na \cdot H_2O$ ; [13412-64-1] (2) 1-Butanol, 3-methyl- (isoamyl alcohol); $C_5H_{12}O$ ; [123-51-3]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of dicloxacillin sodium monohydrate in isoamyl alcohol at <math>21 \pm 1^\circ C</math> was reported as: <math>12.42 \text{ mg cm}^{-3}</math>. (<math>2.43 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD / APPARATUS / PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Dicloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.</p> <p>Isoamyl alcohol was probably of A.C.S. or U.S.P. grade (1,2).</p> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <b>7</b> , 374-7. (2) Andrew, M.L.; Weiss, P.J. <i>ibid.</i> , <u>1959</u> , <b>9</b> , 277-9.

## COMPONENTS:

(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (cloxacillin sodium monohydrate);  $C_{19}H_{17}ClN_3O_5SNa \cdot H_2O$ ; [7081-44-9]

(2) All solvents

## EVALUATOR:

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December 1983.

## CRITICAL EVALUATION:

Marsh and Weiss have determined the solubilities of cloxacillin sodium monohydrate in 23 different non aqueous solvents and in various aqueous solvents at 294<sup>±</sup>1 K (1). These workers studied a sample of the antibiotic provided by Ayerst Laboratories, its purity was not specified. The amount of penicillin dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than 20 mg cm<sup>-3</sup>. All values reported were uncorrected for solvent blank, which was generally less than 0.05 mg total. All data according to Marsh and Weiss have been recalculated to SI units (evaluator). Solubilities in non aqueous solvents are given in the Table.

Solvent <sup>a</sup>	Solubility (at 294 <sup>±</sup> 1 K), (mol dm <sup>-3</sup> ) <sup>b</sup>
methanol	c
ethanol	c
cyclohexane	5.9 x 10 <sup>-5</sup>
benzene	9.3 x 10 <sup>-5</sup>
ligroin	0
isooctane	0
carbon tetrachloride	2.1 x 10 <sup>-5</sup>
ethyl acetate	1.26 x 10 <sup>-3</sup>
isoamyl acetate	8.85 x 10 <sup>-4</sup>
acetone	5.72 x 10 <sup>-3</sup>
methyl ethyl ketone	3.72 x 10 <sup>-3</sup>
diethylether	1.81 x 10 <sup>-4</sup>
ethylene chloride	5.46 x 10 <sup>-4</sup>
1,4-dioxane	8.88 x 10 <sup>-3</sup>
chloroform	3.82 x 10 <sup>-3</sup>
carbon disulfide	1.30 x 10 <sup>-4</sup>
pyridine	c
formamide	c
ethylene glycol	c
propylene glycol	c
dimethyl sulfoxide	c
isopropanol	1.92 x 10 <sup>-2</sup>
isoamyl alcohol	1.23 x 10 <sup>-2</sup>

(<sup>a</sup> All solvents are probably of U.S.P. or A.C.S. grade as previous (2); <sup>b</sup> units calculated by evaluator; <sup>c</sup> solubility greater than 4.20 x 10<sup>-2</sup> mol dm<sup>3</sup>).

Marsh and Weiss have reported the solubility of cloxacillin sodium monohydrate in water, 0.1 N HCl and 0.1 N NaOH to be greater than 4.20 x 10<sup>-2</sup> mol dm<sup>-3</sup>, 9.51 x 10<sup>-3</sup> mol dm<sup>-3</sup>, and greater than 4.20 x 10<sup>-2</sup> mol dm<sup>-3</sup>, respectively (units - evaluator).

All these values for solubility in both aqueous and non aqueous solvents have an estimated precision of  $\pm$  5% (evaluator). Because of the unstated purity of the sample, and since the values reported are unconfirmed, these solubilities are designated as being highly tentative, except for where the solubility is reported as being greater than 4.20 x 10<sup>-2</sup> mol dm<sup>-3</sup>, (which are regarded as being doubtful). Values reported as being 0 mol dm<sup>-3</sup> are rejected since the sensitivity of the assay used is not sufficient for this value to be viewed with any certainty.

## REFERENCES

- (1) Marsh, J.R.; Weiss, P.J. *J. Ass. Offic. Anal. Chem.* 1967, 50, 457.
- (2) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* 1957, 7, 374.

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (cloxacillin sodium monohydrate); <math>C_{19}H_{17}ClN_3O_5SNa \cdot H_2O</math>; [7081-44-9]</p> <p>(2) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cloxacillin sodium monohydrate in water at <math>21 \pm 1^\circ C</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.20 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of water were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.</p> <p>Water was probably of U.S.P. or A.C.S. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (cloxacillin sodium monohydrate); <math>C_{19}H_{17}ClN_3O_5Na.H_2O</math>; [7081-44-9]</p> <p>(2) Hydrochloric acid; HCl; [7647-01-0]</p> <p>(3) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1967</b>, <i>50</i>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cloxacillin sodium monohydrate in 0.1 N HCl solution at <math>21 \pm 1^\circ C</math> was reported as:</p> <p style="text-align: center;"><math>4.53 \text{ gm cm}^{-3}</math>. (<math>9.51 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.</p> <p>Purities of hydrochloric acid and water were not specified.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified</p> <p>Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <b>1957</b>, <i>7</i>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (cloxacillin sodium monohydrate); C<sub>19</sub>H<sub>17</sub>ClN<sub>3</sub>O<sub>5</sub>Na.H<sub>2</sub>O; [7081-44-9]</p> <p>(2) Sodium hydroxide; HNaO; [1310-73-2]</p> <p>(3) Water; H<sub>2</sub>O; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cloxacillin sodium monohydrate in 0.1 N NaOH solution at 21 ± 1°C was reported as greater than:</p> <p>20 mg cm<sup>-3</sup>. (Greater than 4.20 x 10<sup>-2</sup> mol dm<sup>-3</sup> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten cm<sup>3</sup> of 0.1 N NaOH were added to about 200 mg of the antibiotic in a 15 cm<sup>3</sup> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (21 ± 1°C). If all of the material appeared to be in solution, the solubility was considered to be greater than 20 mg cm<sup>-3</sup>.</p>	<p>SOURCE AND PURITY OF MATERIALS.</p> <p>Cloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.</p> <p>Purities of sodium hydroxide and water were not specified.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: ±1°C (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (cloxacillin sodium monohydrate); C<sub>19</sub>H<sub>17</sub>ClN<sub>3</sub>O<sub>5</sub>Na·H<sub>2</sub>O; [7081-44-9]</p> <p>(2) Methanol; CH<sub>4</sub>O; [67-56-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <i>50</i>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cloxacillin sodium monohydrate in methanol at 21 ± 1°C was reported as greater than:</p> <p style="text-align: center;">20 mg cm<sup>-3</sup>. (Greater than 4.20 x 10<sup>-2</sup> mol dm<sup>-3</sup> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten cm<sup>3</sup> of solvent were added to about 200 mg of the antibiotic in a 15 cm<sup>3</sup> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (21 ± 1°C). If all of the material appeared to be in solution, the solubility was considered to be greater than 20 mg cm<sup>-3</sup>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.</p> <p>Methanol was probably of U.S.P. or A.C.S. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: ±1°C (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <i>7</i>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (cloxacillin sodium monohydrate); <math>C_{19}H_{17}ClN_3O_5Na \cdot H_2O</math>; [7081-44-9]</p> <p>(2) Ethanol; <math>C_2H_6O</math>; [64-17-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cloxacillin sodium monohydrate in ethanol at <math>21 \pm 1^\circ C</math> was reported as greater than:</p> <p style="text-align: center;"><math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.20 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.</p> <p>Ethanol was probably of U.S.P. or A.C.S. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES.</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonylamino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (cloxacillin sodium monohydrate); <math>C_{19}H_{17}ClN_3O_5SNa \cdot H_2O</math>; [7081-44-9]</p> <p>(2) Cyclohexane; <math>C_6H_{12}</math>; [110-82-7]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cloxacillin sodium monohydrate in cyclohexane at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.028 \text{ mg cm}^{-3}</math>. (<math>5.88 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.</p> <p>Cyclohexane was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (cloxacillin sodium monohydrate); <math>C_{19}H_{17}ClN_3O_5Na \cdot H_2O</math>; [7081-44-9]</p> <p>(2) Benzene; <math>C_6H_6</math>; [71-43-2]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cloxacillin sodium monohydrate in benzen at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.044 \text{ mg cm}^{-3}</math>. (<math>9.25 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.</p> <p>Benzene was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (cloxacillin sodium monohydrate); $C_{19}H_{17}ClN_3O_5SNa \cdot H_2O$ ; [7081-44-9] (2) Pentane, 2,2,4-trimethyl- (isooctane); $C_8H_{18}$ ; [540-84-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of cloxacillin sodium monohydrate in isooctane at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.0 \text{ mg cm}^{-3}</math>. (<math>0.0 \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a 15 $\text{cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $21 \pm 1^\circ C$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 $\text{cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ C$ . The residue was further dried for 3 hr at $60^\circ C$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b>  Cloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.  Isooctane was probably of A.C.S. or U.S.P. grade (1).  <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <i>7</i> , 374-7.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (cloxacillin sodium monohydrate); C <sub>19</sub> H <sub>17</sub> ClN <sub>3</sub> O <sub>5</sub> Na.H <sub>2</sub> O; [7081-44-9] (2) Methane,tetrachloro- (carbon tetrachloride); CCl <sub>4</sub> ; [56-23-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u> , 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of cloxacillin sodium monohydrate in carbon tetrachloride at 21 ± 1°C was reported as:</p> <p style="text-align: center;">0.010 mg cm<sup>-3</sup>. (2.10 x 10<sup>-5</sup> mol dm<sup>-3</sup> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  <p>Ten cm<sup>3</sup> of solvent were added to about 200 mg of the antibiotic in a 15 cm<sup>3</sup> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (21 ± 1°C). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 cm<sup>3</sup> of the clear filtrate were added to a tared (± 0.1 mg) weighing bottle and evaporated at 100°C. The residue was further dried for 3 hr at 60°C in a vacuum oven. After cooling, the residue was reweighed (± 0.1 mg). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (± 0.01 mg) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (± 0.01 mg) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Cloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.</p> <p>Carbon tetrachloride was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: ± 1°C (authors).</p> <b>REFERENCES:</b>  <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <u>Antibiotics and Chemotherapy</u> <u>1957</u>, 7, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (cloxacillin sodium monohydrate); C<sub>19</sub>H<sub>17</sub>ClN<sub>3</sub>O<sub>5</sub>Na.H<sub>2</sub>O; [7081-44-9]</p> <p>(2) Acetic acid,ethyl ester (ethyl acetate); C<sub>4</sub>H<sub>8</sub>O<sub>2</sub>; [141-78-6]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1967</b>, <i>50</i>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cloxacillin sodium monohydrate in ethyl acetate at 21 ± 1°C was reported as: 0.60 mg cm<sup>-3</sup>. (1.26 x 10<sup>-3</sup> mol dm<sup>-3</sup> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD/APPARATUS/PROCEDURE:</p> <p>Ten cm<sup>3</sup> of solvent were added to about 200 mg of the antibiotic in a 15 cm<sup>3</sup> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (21 ± 1°C). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 cm<sup>3</sup> of the clear filtrate were added to a tared (± 0.1 mg) weighing bottle and evaporated at 100°C. The residue was further dried for 3 hr at 60°C in a vacuum oven. After cooling, the residue was reweighed (± 0.1 mg). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (± 0.01 mg) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (± 0.01 mg) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.</p> <p>Ethyl acetate was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: ±1°C (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <b>1957</b>, <i>7</i>, 374-7.</p>





<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (cloxacillin sodium monohydrate); $C_{19}H_{17}ClN_3O_5SNa \cdot H_2O$ ; [7081-44-9] (2) 2-Butanone (methyl ethyl ketone); $C_4H_8O$ ; [78-93-3]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1967</b> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of cloxacillin sodium monohydrate in methyl ethyl ketone at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>1.77 \text{ mg cm}^{-3}</math>. (<math>3.72 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $21 \pm 1^\circ\text{C}$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and $2 \text{ cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ\text{C}$ . The residue was further dried for 3 hr at $60^\circ\text{C}$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b>  Cloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.  Methyl ethyl ketone was probably of A.C.S. or U.S.P. grade (1).
	<b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ\text{C}$ (authors).
	<b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <b>1957</b> , <i>7</i> , 374-7.

<b>COMPONENTS:</b> (1) 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (cloxacillin sodium monohydrate); $C_{19}H_{17}ClN_3O_5Na \cdot H_2O$ ; [7081-44-9] (2) Ethane, 1,1'-oxybis- (diethyl ether); $C_4H_{10}O$ ; [60-29-7]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. 1967, 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of cloxacillin sodium monohydrate in diethyl ether at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.086 \text{ mg cm}^{-3}</math>. (<math>1.81 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Cloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.</p> <p>Diethyl ether was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> 1957, 7, 374-7.</p>













<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (cloxacillin sodium monohydrate); <math>C_{19}H_{17}ClN_3O_5Na \cdot H_2O</math>; [7081-44-9]</p> <p>(2) 1,2-Ethanediol (ethylene glycol); <math>C_2H_6O_2</math>; [107-21-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cloxacillin sodium monohydrate in ethylene glycol at <math>21 \pm 1^\circ C</math> was reported as greater than:</p> <p style="text-align: center;"><math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.20 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD / APPARATUS / PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.</p> <p>Ethylene glycol was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>





<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (cloxacillin sodium monohydrate); <math>C_{19}H_{17}ClN_3O_5SNa \cdot H_2O</math>; [7081-44-9]</p> <p>(2) 2-Propanol (isopropanol); <math>C_3H_8O</math>; [67-63-0]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cloxacillin sodium monohydrate in isopropanol at <math>21 \pm 1^\circ C</math> was reported as:  <math>9.16 \text{ mg cm}^{-3}</math>. (<math>1.92 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.</p> <p>Isopropanol was probably of U.S.P. or A.C.S. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate (cloxacillin sodium monohydrate); <math>C_{19}H_{17}ClN_3O_5SNa \cdot H_2O</math>; [7081-44-9]</p> <p>(2) 1-Butanol,3-methyl- (isoamyl alcohol); <math>C_5H_{12}O</math>; [123-51-3]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cloxacillin sodium monohydrate in isoamyl alcohol at <math>21 \pm 1^\circ C</math> was reported as: <math>5.87 \text{ mg cm}^{-3}</math>. (<math>1.23 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cloxacillin sodium monohydrate was supplied by Ayerst Laboratories, Inc., its purity was not specified.</p> <p>Isoamyl alcohol was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>

## COMPONENTS:

- (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid-3,3-dimethyl-6[[5-methyl-3-phenyl-4-isoxazolyl]carbonyl]amino]-7-oxo-, mono-sodium salt (oxacillin sodium);  
 $C_{19}H_{18}N_3O_5SNa$ ; [1173-88-2]
- (2) All solvents

## EVALUATOR:

Eric Tomlinson.  
 Department of Pharmacy,  
 University of Amsterdam,  
 The Netherlands.  
 December 1983.

## CRITICAL EVALUATION:

Marsh and Weiss have determined the solubilities of oxacillin sodium in 23 different non aqueous solvents and in various aqueous solvents at  $294^{\pm 1}$  K (1). These workers studied a sample of the antibiotic provided by Bristol Laboratories, its purity was not specified. The amount of penicillin dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than  $20 \text{ mg cm}^{-3}$ . All values reported were uncorrected for solvent blank, which was generally less than  $0.05 \text{ mg total}$ . All data according to Marsh and Weiss have been recalculated to SI units (evaluator). Solubilities in non aqueous solvents are given in the Table.

Solvent <sup>a</sup>	Solubility (at $294^{\pm 1}$ K), ( $\text{mol dm}^{-3}$ ) <sup>b</sup>
methanol	c
ethanol	$2.75 \times 10^{-2}$
cyclohexane	$2.79 \times 10^{-4}$
benzene	0
ligroin	$8.3 \times 10^{-5}$
isooctane	0
carbon tetrachloride	0
ethyl acetate	$5.9 \times 10^{-5}$
isoamyl acetate	$4.20 \times 10^{-4}$
acetone	$3.82 \times 10^{-4}$
methyl ethyl ketone	$2.17 \times 10^{-4}$
diethylether	$2.8 \times 10^{-5}$
ethylene chloride	$4.3 \times 10^{-5}$
1,4-dioxane	$1.55 \times 10^{-3}$
chloroform	$1.13 \times 10^{-4}$
carbon disulfide	$5.2 \times 10^{-5}$
pyridine	c
formamide	c
ethylene glycol	c
propylene glycol	c
dimethyl sulfoxide	c
isopropanol	$8.45 \times 10^{-3}$
isoamyl alcohol	$2.03 \times 10^{-3}$

(<sup>a</sup> All solvents are probably of U.S.P. or A.C.S. grade as previous (2); <sup>b</sup> units calculated by evaluator; <sup>c</sup> solubility greater than  $4.72 \times 10^{-2} \text{ mol dm}^{-3}$ ).

Marsh and Weiss have reported the solubility of oxacillin sodium in water, 0.1 N HCl and 0.1 N NaOH to be greater than  $4.72 \times 10^{-2} \text{ mol dm}^{-3}$ ,  $1.23 \times 10^{-2} \text{ mol dm}^{-3}$ , and greater than  $4.72 \times 10^{-2} \text{ mol dm}^{-3}$ , respectively (units - evaluator).

All these values for solubility in both aqueous and non aqueous solvents have an estimated precision of  $\pm 5\%$  (evaluator). Because of the unstated purity of the sample, and since the values reported are unconfirmed, these solubilities are designated as being highly tentative, except for where the solubility is reported as being greater than  $4.72 \times 10^{-2} \text{ mol dm}^{-3}$ , (which are regarded as being doubtful). Values reported as being  $0 \text{ mol dm}^{-3}$  are rejected since the sensitivity of the assay used is not sufficient for this value to be viewed with any certainty.

## REFERENCES

- (1) Marsh, J.R.; Weiss, P.J. *J. Ass. Offic. Anal. Chem.* 1967, 50, 457.  
 (2) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* 1957, 7, 374.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid-3,3-dimethyl-6[[5-methyl-3-phenyl-4-isoxazolyl]carbonyl]amino]-7-oxo-, monosodium salt (oxacillin sodium); $C_{19}H_{18}N_3O_5SNa$ ; [1173-88-2] (2) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of oxacillin sodium in water at <math>21 \pm 1^\circ C</math> was reported as greater than:  <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.72 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Oxacillin sodium was provided by Bristol Laboratories; its purity was not specified.</p> <p>The water was probably of U.S.P. or A.C.S. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid-3,3-dimethyl-6[[[5-methyl-3-phenyl-4-isoxazolyl]carbonyl]amino]-7-oxo-, monosodium salt (oxacillin sodium); $C_{19}H_{18}N_3O_5SNa$ ; [1173-88-2] (2) Hydrochloric acid; HCl; [7647-01-0] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of oxacillin sodium in 0.1 N HCl solution at <math>21 \pm 1^\circ C</math> was reported as:  <math>5.23 \text{ mg cm}^{-3}</math>. (<math>1.23 \times 10^{-2} \text{ mol dm}^{-3}</math> - compiler)</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Oxacillin sodium was provided by Bristol Laboratories; its purity was not specified.</p> <p>The purity of hydrochloric acid was not described. Water was probably of U.S.P. or A.C.S. grade (1).</p> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid-3,3-dimethyl-6[[[(5-methyl-3-phenyl-4-isoxazolyl)carbonyl]amino]-7-oxo-, monosodium salt (oxacillin sodium); $C_{19}H_{18}N_3O_5SNa$ ; [1173-88-2] (2) Methanol; $CH_4O$ ; [67-56-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of oxacillin sodium in methanol at $21 \pm 1^\circ C$ was reported as greater than: $20 \text{ mg cm}^{-3}$ . (Greater than $4.72 \times 10^{-2} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a 15 $\text{cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $21 \pm 1^\circ C$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b> Oxacillin sodium was provided by Bristol Laboratories; its purity was not specified. Methanol was probably of U.S.P. or A.C.S. grade (1).  <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <b>7</b> , 374-7.

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid-3,3-dimethyl-6[[5-methyl-3-phenyl-4-isoxazolyl]carbonyl]amino]-7-oxo-, monosodium salt (oxacillin sodium); <math>C_{19}H_{18}N_3O_5Na</math>; [1173-88-2]</p> <p>(2) Ethanol; <math>C_2H_6O</math>; [64-17-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of oxacillin sodium in ethanol at <math>21 \pm 1^\circ C</math> was reported as:  <math>11.69 \text{ mg cm}^{-3}</math>. (<math>2.75 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD/APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Oxacillin sodium was provided by Bristol Laboratories; its purity was not specified.</p> <p>Ethanol was probably of U.S.P. or A.C.S. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid-3,3-dimethyl-6[[[5-methyl-3-phenyl-4-isoxazolyl]carbonyl]amino]-7-oxo-, monosodium salt (oxacillin sodium); $C_{19}H_{18}N_3O_5SNa$ ; [1173-88-2] (2) Benzene; $C_6H_6$ ; [71-43-2]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of oxacillin sodium in benzene at $21 \pm 1^\circ C$ was reported as: $0.0 \text{ mg cm}^{-3}$ . ( $0.0 \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a 15 $\text{cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $21 \pm 1^\circ C$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 $\text{cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ C$ . The residue was further dried for 3 hr at $60^\circ C$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b> Oxacillin sodium was provided by Bristol Laboratories; its purity was not specified. Benzene was probably of A.C.S. or U.S.P. grade (1).  <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <b>Antibiotics and Chemotherapy</b> <u>1957</u> , <b>7</b> , 374-7.





<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid-3,3-dimethyl-6[[[(5-methyl-3-phenyl-4-isoxazolyl)carbonyl]amino]-7-oxo-, monosodium salt (oxacillin sodium); <math>C_{19}H_{18}N_3O_5SNa</math>; [1173-88-2]</p> <p>(2) Methane,tetrachloro- (carbon tetrachloride); <math>CCl_4</math>; [56-23-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u>, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of oxacillin sodium in carbon tetrachloride at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.0 \text{ mg cm}^{-3}</math>. (<math>0.0 \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD/APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Oxacillin sodium was provided by Bristol Laboratories; its purity was not specified.</p> <p>Carbon tetrachloride was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <u>Antibiotics and Chemotherapy</u> <u>1957</u>, 7, 374-7.</p>







<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid-3,3-dimethyl-6[[5-methyl-3-phenyl-4-isoxazolyl]carbonylamino]-7-oxo-, monosodium salt (oxacillin sodium); $C_{19}H_{18}N_3O_5SNa$ ; [1173-88-2] (2) 2-Butanone (methyl ethyl ketone); $C_4H_8O$ ; [78-93-3]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of oxacillin sodium in methyl ethyl ketone at $21 \pm 1^\circ\text{C}$ was reported as: $0.09 \text{ mg cm}^{-3}$ . ( $2.17 \times 10^{-4} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Oxacillin sodium was provided by Bristol Laboratories; its purity was not specified.</p> <p>Methyl ethyl ketone was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ\text{C}$ (authors).
<b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.	



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid-3,3-dimethyl-6[[5-methyl-3-phenyl-4-isoxazolyl]carbonyl]amino]-7-oxo-, monosodium salt (oxacillin sodium); $C_{19}H_{18}N_3O_5Na$ ; [1173-88-2] (2) Ethane, dichloro- (ethylene chloride); $C_2H_4Cl_2$ ; [1300-21-6]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of oxacillin sodium in ethylene chloride at $21 \pm 1^\circ C$ was reported as: $0.02 \text{ mg cm}^{-3}$ . ( $4.25 \times 10^{-5} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a 15 $\text{cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp ( $21 \pm 1^\circ C$ ). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 $\text{cm}^3$ of the clear filtrate were added to a tared ( $\pm 0.1 \text{ mg}$ ) weighing bottle and evaporated at $100^\circ C$ . The residue was further dried for 3 hr at $60^\circ C$ in a vacuum oven. After cooling, the residue was reweighed ( $\pm 0.1 \text{ mg}$ ). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared ( $\pm 0.01 \text{ mg}$ ) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing ( $\pm 0.01 \text{ mg}$ ) was repeated.	<b>SOURCE AND PURITY OF MATERIALS:</b> Oxacillin sodium was provided by Bristol Laboratories; its purity was not specified. Ethylene chloride was probably of A.C.S. or U.S.P. grade (1).  <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <b>7</b> , 374-7.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid-3,3-dimethyl-6[[[(5-methyl-3-phenyl-4-isoxazolyl)carbonyl]amino]-7-oxo-, monosodium salt (oxacillin sodium); $C_{19}H_{18}N_3O_5SNa$ ; [1173-88-2] (2) 1,4-Dioxane; $C_4H_8O_2$ ; [123-91-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of oxacillin sodium in 1,4-dioxane at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.66 \text{ mg cm}^{-3}</math>. (<math>1.55 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Oxacillin sodium was provided by Bristol Laboratories; its purity was not specified.          1,4-Dioxane was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid-3,3-dimethyl-6[[[(5-methyl-3-phenyl-4-isoxazolyl)carbonyl]amino]-7-oxo-, monosodium salt (oxacillin sodium); $C_{19}H_{18}N_3O_5SNa$ ; [1173-88-2] (2) Carbon disulfide; $CS_2$ ; [75-15-0]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of oxacillin sodium in carbon disulfide at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.02 \text{ mg cm}^{-3}</math>. (<math>5.20 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD / APPARATUS / PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Oxacillin sodium was provided by Bristol Laboratories; its purity was not specified.</p> <p>Carbon disulfide was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid-3,3-dimethyl-6[[[5-methyl-3-phenyl-4-isoxazolyl)carbonyl]amino]-7-oxo-, monosodium salt (oxacillin sodium); $C_{19}H_{18}N_3O_5SNa$ ; [1173-88-2] (2) Pyridine; $C_6H_5N$ ; [110-86-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of oxacillin sodium in pyridine at $21 \pm 1^\circ C$ was reported as greater than: $20 \text{ mg cm}^{-3}$ . (Greater than $4.72 \times 10^{-2} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $21 \pm 1^\circ C$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b> Oxacillin sodium was provided by Bristol Laboratories; its purity was not specified. Pyridine was probably of A.C.S. or U.S.P. grade (1).  <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).  <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <b>7</b> , 374-7.



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid-3,3-dimethyl-6[[[(5-methyl-3-phenyl-4-isoxazolyl)carbonyl]amino]-7-oxo-, monosodium salt (oxacillin sodium); $C_{19}H_{18}N_3O_5SNa$ ; [1173-88-2] (2) 1,2-Ethanediol (ethylene glycol); $C_2H_6O_2$ ; [107-21-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1967</b> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of oxacillin sodium in ethylene glycol at <math>21 \pm 1^\circ\text{C}</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.72 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ\text{C}</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Oxacillin sodium was provided by Bristol Laboratories; its purity was not specified.</p> <p>Ethylene glycol was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <b>1957</b>, <i>7</i>, 374-7.</p>





<p><b>COMPONENTS:</b>  (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid-3,3-dimethyl-6[[5-methyl-3-phenyl-4-isoxazolyl]carbonylamino]-7-oxo-, monosodium salt (oxacillin sodium); <math>C_{19}H_{18}N_3O_5SNa</math>; [1173-88-2]  (2) 2-Propanol (isopropanol); <math>C_3H_8O</math>; [67-63-0]</p>	<p><b>ORIGINAL MEASUREMENTS:</b>  Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <i>50</i>, 457-62.</p>
<p><b>VARIABLES:</b>  One temperature: 21°C</p>	<p><b>PREPARED BY:</b>  A. Regosz</p>
<p><b>EXPERIMENTAL VALUES:</b></p> <p>Solubility of oxacillin sodium in isopropanol at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>3.58 \text{ mg cm}^{-3}</math>. (<math>8.45 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p style="text-align: center;"><b>AUXILIARY INFORMATION</b></p>	
<p><b>METHOD/APPARATUS/PROCEDURE:</b></p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p><b>SOURCE AND PURITY OF MATERIALS:</b></p> <p>Oxacillin sodium was provided by Bristol Laboratories; its purity was not specified.</p> <p>Isopropanol was probably of A.C.S. or U.S.P. grade (1).</p> <p><b>ESTIMATED ERROR:</b></p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p><b>REFERENCES:</b></p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <i>7</i>, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid-3,3-dimethyl-6[[5-methyl-3-phenyl-4-isoxazolyl]carbonylamino]-7-oxo-, monosodium salt (oxacillin sodium); $C_{19}H_{18}N_3O_5SNa$ ; [1173-88-2] (2) 1-Butanol,3-methyl- (isoamyl alcohol); $C_2H_{12}O$ ; [123-51-3]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u> , 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of oxacillin sodium in isoamyl alcohol at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.86 \text{ mg cm}^{-3}</math>. (<math>2.03 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Oxacillin sodium was provided by Bristol Laboratories; its purity was not specified.</p> <p>Isoamyl alcohol was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <u>Antibiotics and Chemotherapy</u> <u>1957</u>, 7, 374-7.</p>

## COMPONENTS:

- (1) 4-Thia-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[(2-ethoxy-1-naphthalenyl)carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt (nafcillin sodium);  $C_{21}H_{21}N_2O_5SNa$ ; [985-16-0]
- (2) All solvents

## EVALUATOR:

Eric Tomlinson,  
Department of Pharmacy,  
University of Amsterdam,  
The Netherlands.  
December 1983.

## CRITICAL EVALUATION:

Marsh and Weiss have determined the solubilities of nafcillin sodium in 23 different non aqueous solvents and in various aqueous solvents at  $294 \pm 1$  K (1). These workers studied a sample of the antibiotic described as a pooled commercial preparation, its purity was not specified. The amount of penicillin dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than  $20 \text{ mg cm}^{-3}$ . All values reported were uncorrected for solvent blank, which was generally less than  $0.05 \text{ mg total}$ . All data according to Marsh and Weiss have been recalculated to SI units (evaluator). Solubilities in non aqueous solvents are given in the Table.

Solvent <sup>a</sup>	Solubility (at $294 \pm 1$ K), ( $\text{mol dm}^{-3}$ ) <sup>b</sup>
methanol	c
ethanol	c
cyclohexane	$8.0 \times 10^{-5}$
benzene	$1.19 \times 10^{-4}$
ligroin	0
isooctane	0
carbon tetrachloride	0
ethyl acetate	c
isoamyl acetate	$1.14 \times 10^{-2}$
acetone	c
methyl ethyl ketone	c
diethylether	$9.35 \times 10^{-4}$
ethylene chloride	c
1,4-dioxane	c
chloroform	c
carbon disulfide	$1.33 \times 10^{-4}$
pyridine	c
formamide	c
ethylene glycol	c
propylene glycol	c
dimethyl sulfoxide	c
isopropanol	c
isoamyl alcohol	c

(<sup>a</sup> All solvents are probably of U.S.P. or A.C.S. grade as previous (2); <sup>b</sup> units calculated by evaluator; <sup>c</sup> solubility greater than  $4.60 \times 10^{-2} \text{ mol dm}^{-3}$ ).

Marsh and Weiss have reported the solubility of nafcillin sodium in water, 0.1 N HCl and 0.1 N NaOH to be greater than  $4.60 \times 10^{-2} \text{ mol dm}^{-3}$ ,  $2.18 \times 10^{-2} \text{ mol dm}^{-3}$ , and greater than  $4.60 \times 10^{-2} \text{ mol dm}^{-3}$ , respectively (units - evaluator).

All these values for solubility in both aqueous and non aqueous solvents have an estimated precision of  $\pm 5\%$  (evaluator). Because of the unstated purity of the sample, and since the values reported are unconfirmed, these solubilities are designated as being highly tentative, except for where the solubility is reported as being greater than  $4.60 \times 10^{-2} \text{ mol dm}^{-3}$ , (which are regarded as being doubtful). Values reported as being  $0 \text{ mol dm}^{-3}$  are rejected since the sensitivity of the assay used is not sufficient for this value to be viewed with any certainty.

## REFERENCES

- (1) Marsh, J.R.; Weiss, P.J. *J. Ass. Offic. Anal. Chem.* 1967, 50, 457.  
(2) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* 1957, 7, 374.









<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[2-(ethoxy-1-naphthalenyl)carbonyl]amino]-3,3-dimethyl-7-oxo,monosodium salt (nafcillin sodium); $C_{21}H_{21}N_2O_5$ SNa; [985-16-0] (2) Ethanol; $C_2H_6O$ ; [64-17-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u> , 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of nafcillin sodium in ethanol at <math>21 \pm 1^\circ\text{C}</math> was reported as greater than:  <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.6 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to, about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $21 \pm 1^\circ\text{C}$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b>  Nafcillin sodium was a pooled commercial preparation; its purity was not specified.  Ethanol was probably of U.S.P. or A.C.S. grade (1).  <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ\text{C}$ (authors).  <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <u>Antibiotics and Chemotherapy</u> <u>1957</u> , 7, 374-7.

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[(2-ethoxy-1-naphthalenyl) carbonyl]amino]-3,3-dimethyl-7-oxo, mono-sodium salt (nafcillin sodium); <math>C_{21}H_{21}N_2O_5</math> SNa; [985-16-0]</p> <p>(2) Cyclohexane; <math>C_6H_{12}</math>; [110-82-7]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <i>50</i>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of nafcillin sodium in cyclohexane at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.04 \text{ mg cm}^{-3}</math>. (<math>8.02 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD/APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Nafcillin sodium was a pooled commercial preparation; its purity was not specified.</p> <p>Cyclohexane was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <i>7</i>, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[(2-ethoxy-1-naphthalenyl) carbonyl]amino]-3,3-dimethyl-7-oxo,monosodium salt (nafcillin sodium); C <sub>21</sub> H <sub>21</sub> N <sub>2</sub> O <sub>5</sub> SNa; [985-16-0] (2) Benzene; C <sub>6</sub> H <sub>6</sub> ; [71-43-2]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. 1967, 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of nafcillin sodium in benzene at 21 ± 1°C was reported as:          0.05 mg cm<sup>-3</sup>. (1.19 x 10<sup>-4</sup> mol dm<sup>-3</sup> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten cm<sup>3</sup> of solvent were added to about 200 mg of the antibiotic in a 15 cm<sup>3</sup> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (21 ± 1°C). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 cm<sup>3</sup> of the clear filtrate were added to a tared (± 0.1 mg) weighing bottle and evaporated at 100°C. The residue was further dried for 3 hr at 60°C in a vacuum oven. After cooling, the residue was reweighed (± 0.1 mg). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (± 0.01 mg) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (± 0.01 mg) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Nafcillin sodium was a pooled commercial preparation; its purity was not specified.</p> <p>Benzene was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: ±1°C (authors).  <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. Antibiotics and Chemotherapy 1957, 7, 374-7.

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[(2-ethoxy-1-naphthalenyl) carbonyl]amino]-3,3-dimethyl-7-oxo,monosodium salt (nafcillin sodium); $C_{21}H_{21}N_2O_5$ SNa; [985-16-0] (2) Petroleum ether (Igroin)	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of nafcillin sodium in Igroin at $21 \pm 1^\circ\text{C}$ was reported as: $0.0 \text{ mg cm}^{-3}$ . ( $0.0 \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Nafcillin sodium was a pooled commercial preparation; its purity was not specified.</p> <p>Igroin was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ\text{C}$ (authors).
<b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.	

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[(2-ethoxy-1-naphthalenyl) carbonyl]amino]-3,3-dimethyl-7-oxo, mono-sodium salt (nafcillin sodium); $C_{21}H_{21}N_2O_5$ SNa; [985-16-0] (2) Pentane, 2,2,4-trimethyl (isooctane); $C_8H_{18}$ ; [540-84-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of nafcillin sodium in isooctane at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.0 \text{ mg cm}^{-3}</math>. (<math>0.0 \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Nafcillin sodium was a pooled commercial preparation; its purity was not specified.</p> <p>Isooctane was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[2-ethoxy-1-naphthalenyl]carbonyl]amino]-3,3-dimethyl-7-oxo, mono-sodium salt (nafcillin sodium); $C_{21}H_{21}N_2O_5$ SNa; [985-16-0] (2) Acetic acid, ethyl ester (ethyl acetate); $C_4H_8O_2$ ; [141-78-6]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> 1967, 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of nafcillin sodium in ethyl acetate at <math>21 \pm 1^\circ\text{C}</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.60 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ\text{C}</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Nafcillin sodium was a pooled commercial preparation; its purity was not specified.</p> <p>Ethyl acetate was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> 1957, 7, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[(2-ethoxy-1-naphthalenyl) carbonyl]amino]-3,3-dimethyl-7-oxo,monosodium salt (nafcillin sodium); $C_{21}H_{21}N_2O_5$ SNa; [985-16-0] (2) 1-Butanol,3-methyl acetate (isoamyl acetate); $C_7H_{14}O_2$ ; [123-92-2]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. 1967, 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of nafcillin sodium in isoamyl acetate at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>4.85 \text{ mg cm}^{-3}</math>. (<math>1.14 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD / APPARATUS / PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Nafcillin sodium was a pooled commercial preparation; its purity was not specified.</p> <p>Isoamyl acetate was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> 1957, 7, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[2-ethoxy-1-naphthalenyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt (nafcillin sodium); $C_{21}H_{21}N_2O_5$ SNa; [985-16-0] (2) 2-Propanone (acetone); $C_3H_6O$ ; [67-64-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of nafcillin sodium in acetone at <math>21 \pm 1^\circ\text{C}</math> was reported as greater than:  <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.6 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD / APPARATUS / PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $21 \pm 1^\circ\text{C}$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b>  Nafcillin sodium was a pooled commercial preparation; its purity was not specified.  Acetone was probably of A.C.S. or U.S.P. grade (1).
	<b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ\text{C}$ (authors).
	<b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <b>7</b> , 374-7.



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[2-ethoxy-1-naphthalenyl]carbonylamino]-3,3-dimethyl-7-oxo, monosodium salt (nafcillin sodium); $C_{21}H_{21}N_2O_5$ SNa; [985-16-0] (2) Ethane, 1,1'-oxybis- (diethyl ether); $C_4H_{10}O$ ; [60-29-7]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u> , 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of nafcillin sodium in diethyl ether at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.41 \text{ mg cm}^{-3}</math>. (<math>9.35 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Nafcillin sodium was a pooled commercial preparation; its purity was not specified.</p> <p>Diethyl ether was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <u>Antibiotics and Chemotherapy</u> <u>1957</u>, 7, 374-7.</p>

<p><b>COMPONENTS:</b></p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[(2-ethoxy-1-naphthalenyl) carbonyl]amino]-3,3-dimethyl-7-oxo, mono-sodium salt (nafcillin sodium); <math>C_{21}H_{21}N_2O_5</math> SNa; [985-16-0]</p> <p>(2) Ethane, dichloro- (ethylene chloride); <math>C_2H_4Cl_2</math>; [1300-21-6]</p>	<p><b>ORIGINAL MEASUREMENTS:</b></p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p><b>VARIABLES:</b></p> <p>One temperature: 21°C</p>	<p><b>PREPARED BY:</b></p> <p>A. Regosz</p>
<p><b>EXPERIMENTAL VALUES:</b></p> <p>Solubility of nafcillin sodium in ethylene chloride at <math>21 \pm 1^\circ\text{C}</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.6 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p><b>AUXILIARY INFORMATION</b></p>	
<p><b>METHOD/APPARATUS/PROCEDURE:</b></p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ\text{C}</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p><b>SOURCE AND PURITY OF MATERIALS:</b></p> <p>Nafcillin sodium was a pooled commercial preparation; its purity was not specified.</p> <p>Ethylene chloride was probably of A.C.S. or U.S.P. grade (1).</p> <p><b>ESTIMATED ERROR:</b></p> <p>Solubility precision: none specified</p> <p>Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p><b>REFERENCES:</b></p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[(2-ethoxy-1-naphthalenyl) carbonyl]amino]-3,3-dimethyl-7-oxo,mono-sodium salt (nafcillin sodium); $C_{21}H_{21}N_2O_5$ SNa; [985-16-0] (2) 1,4-Dioxane; $C_4H_8O_2$ ; [123-91-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of nafcillin sodium in 1,4-dioxane at <math>21 \pm 1^\circ\text{C}</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.6 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD/APPARATUS/PROCEDURE:</b>  Ten $\text{cm}^3$ of solvent were added to about 200 mg of the antibiotic in a $15 \text{ cm}^3$ glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature ( $21 \pm 1^\circ\text{C}$ ). If all of the material appeared to be in solution, the solubility was considered to be greater than $20 \text{ mg cm}^{-3}$ .	<b>SOURCE AND PURITY OF MATERIALS:</b>  Nafcillin sodium was a pooled commercial preparation; its purity was not specified.  1,4-Dioxane was probably of A.C.S. or U.S.P. grade (1).  <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ\text{C}$ (authors).  <b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , 7, 374-7.



<b>COMPONENTS:</b> (1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,6-[[[(2-ethoxy-1-naphthalenyl) carbonyl]amino]-3,3-dimethyl-7-oxo,mono-sodium salt (nafcillin sodium); $C_{21}H_{21}N_2O_5$ SNa; [985-16-0] (2) Carbon disulfide; $CS_2$ ; [75-15-0]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of nafcillin sodium in carbon disulfide at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.06 \text{ mg cm}^{-3}</math>. (<math>1.33 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Nafcillin sodium was a pooled commercial preparation; its purity was not specified.</p> <p>Carbon disulfide was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> Solubility precision: none specified Temperature precision: $\pm 1^\circ C$ (authors).
<b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u> , <b>7</b> , 374-7.	

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[(2-ethoxy-1-naphthalenyl) carbonyl]amino]-3,3-dimethyl-7-oxo, mono-sodium salt (nafcillin sodium); <math>C_{21}H_{21}N_2O_5</math> SNa; [985-16-0]</p> <p>(2) Pyridine; <math>C_5H_5N</math>; [110-86-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1967</b>, <i>50</i>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of nafcillin sodium in pyridine at <math>21 \pm 1^\circ\text{C}</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.6 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ\text{C}</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Nafcillin sodium was a pooled commercial preparation; its purity was not specified.</p> <p>Pyridine was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <b>1957</b>, <i>7</i>, 374-7.</p>



<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[[(2-ethoxy-1-naphthalenyl) carbonyl]amino]-3,3-dimethyl-7-oxo, mono-sodium salt (nafcillin sodium); <math>C_{21}H_{21}N_2O_5</math> SNa; [985-16-0]</p> <p>(2) 1,2-Ethandiol (ethylene glycol); <math>C_2H_6O_2</math>; [107-21-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of nafcillin sodium in ethylene glycol at <math>21 \pm 1^\circ\text{C}</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.6 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ\text{C}</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Nafcillin sodium was a pooled commercial preparation; its purity was not specified.</p> <p>Ethylene glycol was probably of A.C.S. or U.S.P. grade (1).</p>
	<p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p>
	<p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[2-ethoxy-1-naphthalenyl]carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt (nafcillin sodium); <math>C_{21}H_{21}N_2O_5</math> SNa; [985-16-0]</p> <p>(2) 1,2-Propanediol (propylene glycol); <math>C_3H_8O_2</math>; [57-55-6]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of nafcillin sodium in propylene glycol at <math>21 \pm 1^\circ\text{C}</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.6 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ\text{C}</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Nafcillin sodium was a pooled commercial preparation; its purity was not specified.</p> <p>Propylene glycol was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[2-(ethoxy-1-naphthalenyl) carbonyl]amino]-3,3-dimethyl-7-oxo, monosodium salt (nafcillin sodium); <math>C_{21}H_{21}N_2O_5</math> SNa; [985-16-0]</p> <p>(2) Methane, sulfinylbis- (dimethyl sulfoxide); <math>C_2H_6OS</math>; [67-68-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of nafcillin sodium in dimethyl sulfoxide at <math>21 \pm 1^\circ\text{C}</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.6 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ\text{C}</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Nafcillin sodium was a pooled commercial preparation; its purity was not specified.</p> <p>Dimethyl sulfoxide was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>





<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid, 7-amino-3-methyl-8-oxo (7-aminodeacetoxycephalosporanic acid); <math>C_8H_{10}N_2O_3S</math> [22252-43-3]</p> <p>(2) Aqueous solvents</p>	<p>EVALUATOR:</p> <p>Eric Tomlinson, Department of Pharmacy, University of Amsterdam, The Netherlands.</p> <p>December 1983.</p>
<p>CRITICAL EVALUATION:</p> <p>7-aminodeacetoxycephalosporanic acid is an ampholyte possessing a carboxyl group of pK 1.75 and an amino group of pK 4.63 (1), with an isoelectric point at 3.55. Nys et al. (2) have reported two values for its solubility in 0.1 mol dm<sup>-3</sup> HCl at 293<sup>±</sup>5 K (units and precision estimation - evaluator), i.e. the intrinsic solubility measured experimentally (<math>9.2 \times 10^{-4}</math> mol dm<sup>-3</sup>) and that calculated using an equation accounting for the pH and the various dissociations occurring (<math>8.1 \times 10^{-4}</math> mol dm<sup>-3</sup>). The experimentally observed value is regarded as being <b>highly tentative</b> since although these authors reported on the purity and the source of the sample studied, an incomplete description of the method used to determine the solubility was presented.</p> <p>In a later publication (3) Nys et al. reported the solubility of this compound at 298<sup>±</sup>1 K (units and estimation of precision - evaluator) and at constant ionic strength (<math>I = 0.1</math>) as <math>9.4 \times 10^{-4}</math> mol dm<sup>-3</sup> (experimental) and <math>8.9 \times 10^{-4}</math> mol dm<sup>-3</sup> (calculated for the ampholyte zwitter ion). The authors also investigated the dependence between the ionic strength of electrolyte (NH<sub>4</sub>Cl or NaCl) and the solubility of 7-aminodeacetoxycephalosporanic acid at 298<sup>±</sup>1 K. They showed graphically only that there was only a very slight effect on solubility (which is different to that observed with 6-aminopenicillanic acid, where the effect was found to be significant). In addition equimolar concentrations of benzene acetic acid had no observed effect on the solubility. However it was observed that at pH 3.55 there was a three-fold increase in the aqueous solubility when 0.015 mol dm<sup>-3</sup> 7-phenylacetamidodeacetoxycephalosporanic acid was added. These data were presented graphically only. The reported solubility obtained experimentally is regarded as <b>tentative</b> and having an estimated precision of <sup>±</sup>5 percent.</p> <p>REFERENCES</p> <p>(1) Stedman, R.J.; Swered, K.; Hoover, J.R.E. <i>J. Med. Chem.</i> 1964, 7, 17.  (2) Nys, P.S.; Koltsova, E.V.; Shellenberg, N.N.; Savitskaya, E.M.; Levitov, M.M. <i>Antibiotiki, (Moscow)</i> 1977, 21, 391.  (3) Nys, P.S.; Elizarovskaya, L.M.; Shellenberg, N.N.; Savitskaya, E.M. <i>Antibiotiki, (Moscow)</i> 1979, 24, 895.</p>	

<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid, 7-amino-3-methyl-8-oxo, (7-aminodeacetoxycephalosporanic acid); <math>C_8H_{10}N_2O_3S</math>; [22252-43-3]</p> <p>(2) Potassium chloride; KCl; [7447-40-7]</p> <p>(3) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Nys, P.S.; Koltsova, E.V.; Shellenberg, N.N.; Savitskaya, E.M.; Levitov, M.M. <i>Antibiotiki, (Moscow)</i> 1976, 21, 391-4.</p>
<p>VARIABLES:</p> <p>One temperature: 20°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>The author<sup>3</sup> report two values for the solubility of 7-aminodeacetoxycephalosporanic acid in 0.1 mol dm<sup>-3</sup> KCl solution at 20°C.</p> <ol style="list-style-type: none"> <li>Minimal solubility (intrinsic solubility) <math>S_x^0 = 9.2 \times 10^{-4}</math> mol dm<sup>-3</sup> (0.2 mg cm<sup>-3</sup><sup>a</sup>) (estimated experimentally).</li> <li>Characteristic solubility (total solubility) <math>S_{AH\pm}^0 = 8.12 \times 10^{-4}</math> mol dm<sup>-3</sup> (0.33 mg cm<sup>-3</sup><sup>a</sup>) (calculated from equation) [1].</li> </ol> $S_{AH\pm}^0 = S_x^0 \left( \frac{K_1 \cdot C_H^0}{(C_H^0)^2 + K_1 C_H^0 + K_1 \cdot K_2} \right) \quad [1]$ <p>where <math>C_x^0</math> is the concentration of hydrogen ions, <math>K_1</math> and <math>K_2</math> are dissociation constants for 2-carboxylic acid and -amino group, respectively.</p> <p><math>S_x^0</math> value estimated from the solubility at the isoelectric point pH</p> <p><sup>a</sup> Calculated by compiler.</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>The dissociation constants were determined by potentiometric titration. The isoelectric point was determined by electrophoretic method. The amount of the dissolved solute was determined spectrophotometrically at 265 nm and by colorimetric method (410 nm) after reaction with p-dimethylamino-benzaldehyde.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>7-Aminodeacetoxycephalosporanic acid of 99% purity was prepared by enzymatic hydrolysis of 7-phenylacetamidodesacetoxycephalosporanic acid.</p> <p>The potassium chloride was of analytical grade. Distilled water was used.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: ±1°C (compiler).</p> <p>REFERENCES:</p>

<b>COMPONENTS:</b> (1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid, 7-amino-3-methyl-8-oxo, (7-aminodeacetoxycephalosporanic acid); $C_8H_{10}N_2O_3S$ ; [22252-43-3] (2) Ammonium chloride; $NH_4Cl$ ; [12125-02-9] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Nys, P.S.; Elizarovskaya, L.M.; Shellenberg, N.N.; Savitskaya, E.M. <i>Antibiotiki, (Moscow)</i> 1979, 24, 895-902.
<b>VARIABLES:</b>  One temperature: 25°C	<b>PREPARED BY:</b>  A. Regosz
<b>EXPERIMENTAL VALUES:</b>  The authors report two values for the solubility of the ampholyte zwitterion of 7-aminodeacetoxycephalosporanic acid in water at 25°C and constant ionic strength ( $I = 0.1$ ). 1. Minimal solubility (intrinsic solubility) $S_x^0 = 9.35 \times 10^{-4} \text{ mol dm}^{-3}$ ( $0.20 \text{ mg cm}^{-3a}$ ) (estimated experimentally). 2. Characteristic solubility (total solubility) $S_{AH\pm}^0 = 8.90 \times 10^{-4} \text{ mol dm}^{-3}$ ( $0.19 \text{ mg cm}^{-3a}$ ) (calculated from equation) [1]. $S_{AH\pm}^0 = S_x^0 \left( \frac{K_1 \cdot C_H^0}{(C_H^0)^2 + K_1 \cdot C_H^0 + K_1 \cdot K_2} \right) \quad [1]$ where $C_H^0$ is the concentration of hydrogen ions, $K_1$ (COOH) = $5.62 \times 10^{-3} \text{ mol dm}^{-3}$ and $K_2$ ( $NH_3^+$ ) = $1.41 \times 10^{-5} \text{ mol dm}^{-3}$ are dissociations constants.  $S_x^0$ value estimated from the solubility at the isoelectric point (pH = 3.55).  <sup>a</sup> Calculated by compiler.	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  A saturated mixture was prepared by stirring an excess of 7-aminodeacetoxycephalosporanic acid in distilled water at 25°C, maintained the constant ionic strength ( $I = 0.1$ ) by adding appropriate amounts of $NH_4Cl$ . The amount of the dissolved solute was determined by iodometric titration.	<b>SOURCE AND PURITY OF MATERIALS:</b>  The purity of 7-aminodeacetoxycephalosporanic acid was 99%; it was probably prepared by enzymatic hydrolysis of 7-phenylacetamido-deacetoxycephalosporadic acid; its purity was determined iodometrically. The ammonium chloride was of analytical grade. Doubly distilled water was used.  <b>ESTIMATED ERROR:</b>  Solubility precision: none specified Temperature precision: probably $\pm 1^\circ\text{C}$ (compiler).  <b>REFERENCES:</b>

<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid, 7-amino-3-methyl-8-oxo, (7-aminodeacetoxycephalosporanic acid); <math>C_8H_{10}N_2O_3S</math>; [22252-43-3]</p> <p>(2) Benzeneacetic acid; <math>C_8H_8O_2</math>; [103-82-2]</p> <p>(3) Hydrochloric acid; HCl; [7647-01-0]</p> <p>(4) Ammonium chloride; <math>NH_4Cl</math>; [12125-02-9]</p> <p>(5) Sodium chloride; NaCl; [7647-14-5]</p> <p>(6) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Nys, P.S.; Elizarovskaya, L.M.; Shellenberg, N.N.; Savitskaya, E.M. <i>Antibiotiki, (Moscow)</i> 1979, 24, 895-902.</p>																								
<p>VARIABLES:</p> <p>Ionic strength at 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>																								
<p>EXPERIMENTAL VALUES:</p> <div style="display: flex; align-items: center;"> <div style="flex: 1;"> <p>Minimal solubility (<math>S_x^0</math>) of 7-aminodeacetoxycephalosporanic acid [<math>10^3 \text{ mol dm}^{-3}</math>]</p> </div> <div style="flex: 1.5; text-align: center;"> <table border="1" style="margin: 10px auto;"> <caption>Estimated data from the graph</caption> <thead> <tr> <th>Ionic strength (mol dm<sup>-3</sup>)</th> <th>Minimal solubility (<math>S_x^0</math>) [<math>10^3 \text{ mol dm}^{-3}</math>] (Benzene acetic acid)</th> <th>Minimal solubility (<math>S_x^0</math>) [<math>10^3 \text{ mol dm}^{-3}</math>] (7-aminodeacetoxycephalosporanic acid)</th> </tr> </thead> <tbody> <tr><td>0</td><td>1.3</td><td>1.3</td></tr> <tr><td>0.2</td><td>1.4</td><td>1.4</td></tr> <tr><td>0.4</td><td>1.5</td><td>1.5</td></tr> <tr><td>0.6</td><td>1.6</td><td>1.6</td></tr> <tr><td>0.8</td><td>1.7</td><td>1.7</td></tr> <tr><td>1.0</td><td>1.8</td><td>1.8</td></tr> <tr><td>1.2</td><td>1.8</td><td>1.8</td></tr> </tbody> </table> </div> <div style="flex: 1;"> <p>Ionic strength (<math>NH_4Cl</math> or <math>NaCl</math>, <math>\text{mol dm}^{-3}</math>) at 25°C and at <math>pH = pI^a</math></p> <p>△ influence of benzene acetic acid</p> <p>▲ 7-aminodeacetoxycephalosporanic acid</p> </div> </div> <p><sup>a</sup> <math>S_x^0</math> values estimated at the isoelectric point (<math>pI = pH</math> 3.55).</p>		Ionic strength (mol dm <sup>-3</sup> )	Minimal solubility ( $S_x^0$ ) [ $10^3 \text{ mol dm}^{-3}$ ] (Benzene acetic acid)	Minimal solubility ( $S_x^0$ ) [ $10^3 \text{ mol dm}^{-3}$ ] (7-aminodeacetoxycephalosporanic acid)	0	1.3	1.3	0.2	1.4	1.4	0.4	1.5	1.5	0.6	1.6	1.6	0.8	1.7	1.7	1.0	1.8	1.8	1.2	1.8	1.8
Ionic strength (mol dm <sup>-3</sup> )	Minimal solubility ( $S_x^0$ ) [ $10^3 \text{ mol dm}^{-3}$ ] (Benzene acetic acid)	Minimal solubility ( $S_x^0$ ) [ $10^3 \text{ mol dm}^{-3}$ ] (7-aminodeacetoxycephalosporanic acid)																							
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<p>METHOD APPARATUS/PROCEDURE:</p> <p>Accurately weighed samples of 7-aminodeacetoxycephalosporanic acid were suspended in water at 25°C. The suspension was then adjusted to pH 7.5 using 2 N NaOH solution. To the above suspension equimolar amounts of benzeneacetic acid were added. After cooling to 5°C the pH of the suspension was adjusted to <math>pH = pI</math> using 20% HCl solution and equilibrated by shaking for 3 hr. Ionic strength was maintained by adding appropriate amounts of <math>NH_4Cl</math> or NaCl. The amount of the solute was determined by iodometric titration.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>The purity of 7-aminodeacetoxycephalosporanic acid determined iodometrically was 99%; it was probably prepared by enzymatic hydrolysis of 7-phenylacetamidodeacetoxycephalosporanic acid.</p> <p>Benzeneacetic acid was precipitated twice from aqueous and ethanol solution. All other reagents used were of analytical grade. Double distilled water was used.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified</p> <p>Temperature precision: probably <math>\pm 1^\circ C</math> (compiler).</p> <p>REFERENCES:</p>																								

<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid, 7-amino-3-methyl-8-oxo, (7-aminodeacetoxycephalosporanic acid); <math>C_8H_{10}N_2O_3S</math>; [22252-43-3]</p> <p>(2) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid, 3-methyl-8-oxo-7-(2-phenylacetamido) 7-phenylacetamidodeacetoxycephalosporanic acid; <math>C_{16}H_{16}N_2O_4S</math>; [27255-72-7]</p> <p>(3) Hydrochloric acid; [7647-01-0]</p> <p>(4) Sodium hydroxide; NaOH; [1310-73-2]</p> <p>(5) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Nys, P.S.; Elizarovskaya, L.M.; Shellenberg, N.N.; Savitskaya, E.M. <i>Antibiotiki, (Moscow)</i> 1979, 24, 895-902.</p>														
<p>VARIABLES:</p> <p>Concentration of 7-phenylacetamidodeacetoxycephalosporanic acid</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>														
<p>EXPERIMENTAL VALUES:</p> <div style="display: flex; align-items: center;"> <div style="flex: 1;"> <p>Minimal solubility (<math>S_x^0</math>) of 7-aminodeacetoxycephalosporanic acid [<math>\text{mol dm}^{-3} \times 10^3</math>]</p> </div> <div style="flex: 2;"> <table border="1" style="margin-top: 10px;"> <caption>Data points from the graph</caption> <thead> <tr> <th>Concentration of 7-phenylacetamidodeacetoxycephalosporanic acid [<math>\text{mol dm}^{-3} \times 10^3</math>]</th> <th>Minimal solubility (<math>S_x^0</math>)</th> </tr> </thead> <tbody> <tr><td>0</td><td>1.5</td></tr> <tr><td>3</td><td>2.0</td></tr> <tr><td>6</td><td>2.5</td></tr> <tr><td>9</td><td>3.0</td></tr> <tr><td>12</td><td>3.5</td></tr> <tr><td>15</td><td>4.0</td></tr> </tbody> </table> </div> <div style="flex: 1;"> <p>Concentration of 7-phenylacetamidodeacetoxycephalosporanic acid at 25°C and at <math>\text{pH} = \text{pI}^a</math> [<math>\text{mol dm}^{-3} \times 10^3</math>]</p> </div> </div> <p><math>a_{S_x^0}</math> values estimated at the isoelectric point (<math>\text{pI} = \text{pH } 3.05</math>).</p>		Concentration of 7-phenylacetamidodeacetoxycephalosporanic acid [ $\text{mol dm}^{-3} \times 10^3$ ]	Minimal solubility ( $S_x^0$ )	0	1.5	3	2.0	6	2.5	9	3.0	12	3.5	15	4.0
Concentration of 7-phenylacetamidodeacetoxycephalosporanic acid [ $\text{mol dm}^{-3} \times 10^3$ ]	Minimal solubility ( $S_x^0$ )														
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<p>METHOD APPARATUS/PROCEDURE:</p> <p>Accurately weighed samples of 7-aminodeacetoxycephalosporanic acid were suspended in water at 25°C. The suspension was then adjusted to pH 7.5 using 2 N NaOH solution. To the above suspensions, appropriate amounts of 7-phenylacetamidodeacetoxycephalosporanic acid were added; after stirring and cooling to temp 5°C, the suspension was adjusted to <math>\text{pH} = \text{pI}</math> using 20% HCl solution. The suspension was equilibrated by shaking for about 3 hr. The amount of 7-aminodeacetoxycephalosporanic acid was determined by iodometric titration.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>7-Aminodeacetoxycephalosporanic acid was probably prepared by enzymatic hydrolysis of 7-phenylacetamidodeacetoxycephalosporanic acid; its purity (99%) was determined iodometrically.</p> <p>7-phenylacetamidodeacetoxycephalosporanic acid was prepared by transformation of benzylpenicillin, and was purified by repeatedly recrystallization from an isopropanil-hexane mixture. Its purity (99%) was determined iodometrically. All other reagents were of analytical grade. Distilled water was used.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: probably <math>\pm 1^\circ\text{C}</math> (compiler)</p> <p>REFERENCES:</p>														

<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid, 7-amino-3-(hydroxymethyl)-8-oxo-, acetate ester (7-aminoacetoxycephalosporanic acid); <math>C_{10}H_{12}N_2O_5S</math>; [957-68-6]</p> <p>(2) Sodium chloride; NaCl; [7647-14-5]</p> <p>(3) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>EVALUATOR:</p> <p>Eric Tomlinson. Department of Pharmacy, University of Amsterdam, The Netherlands. December 1983.</p>
<p>CRITICAL EVALUATION:</p> <p>7-aminoacetoxycephalosporanic acid is an ampholyte possessing a carboxyl group of <math>pK_1</math> 2.64 and an amino group of <math>pK_2</math> 4.63. Its solubility in water has been reported on only one occasion (1). This group has reported the effect of sodium chloride on the solubility. Both experimental values and values calculated using an equation to account for the concentration of hydrogen ions and the dissociation of the carboxy and amino groups (see compilation sheet) have been reported.</p> <p>The sample of acid used was of 99 per cent purity and had been prepared by enzyme hydrolysis of 7-phenylacetamidodesacetoxycephalosporanic acid. The precision in measurement of solubility can be estimated from reference 1 as being <math>\pm 5</math> %. Measurements were at <math>293 \pm 1</math> K (units and precision estimation - evaluator). The paper gives that the solubility of the compound in water in the presence of <math>0.1 \text{ mol dm}^{-3}</math> NaCl (at pH 3.74, i.e. the isoelectric point) as <math>3.24 \times 10^{-3} \text{ mol dm}^{-3}</math>. This compares to a value of <math>2.64 \times 10^{-3} \text{ mol dm}^{-3}</math> calculated for the ampholyte zwitterion, and is regarded as being tentative.</p> <p>REFERENCE</p> <p>(1) Bulycheva, M.S.; Nys, P.S.; Savitskaya, E.M. <i>Antibiotiki, (Moscow)</i> <u>1977</u>, <b>22</b>, 1073.</p>	

<b>COMPONENTS:</b> (1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid, 7-amino-3-(hydroxymethyl)-8-oxo-, acetate ester (7-aminoacetoxycephalosporanic acid); $C_{10}H_{12}O_5S$ ; [957-68-6] (2) Sodium chloride; NaCl; [7647-14-5] (3) Water; $H_2O$ ; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Bulycheva, M.S.; Nys, P.S.; Savitskaya, E.M. <i>Antibiotiki (Moscow)</i> 1977, 22, 1073-77.
<b>VARIABLES:</b>  Temperature: 20°C	<b>PREPARED BY:</b>  A. Regosz
<b>EXPERIMENTAL VALUES:</b>  The authors report two value for the solubility of 7-aminoacetoxycephalosporanic acid in 0.1 mol dm <sup>-3</sup> NaCl solution at 20° C. <ol style="list-style-type: none"> <li>Intrinsic solubility of the ampholyte (based on experimental data)  <math>S_x^o = 3.24 \times 10^{-3} \text{ mol dm}^{-3}</math> (determined at pH = 3.74) (pl).</li> <li>Observed solubility of the ampholyte zwitterion (based on calculated data)  <math>S_{AH\pm}^o = 2.64 \times 10^{-2} \text{ mol dm}^{-3}</math></li> </ol> The following relationship between solubilities 1 and 2 was derived by the authors: $S_{AH\pm}^o = S_x^o \frac{K_1 \cdot C_H^o}{(C_H^o)^2 + K_1 \cdot C_H^o + K_1 \cdot K_2}$ where $C_H^o$ is the concentration of hydrogen ion, $K_1 (COO^-) = 2.3 \times 10^{-3}$ <sup>a</sup> (pK <sub>1</sub> = 2.64, and $K_2 (NH_3^+) = 1.5 \times 10^{-5}$ <sup>a</sup> (pK <sub>2</sub> = 4.83), are dissociation constants. <p><sup>a</sup> Calculated by compiler, based on the pK<sub>a</sub> values.</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  A saturated solution was prepared by stirring an excess of 7-aminoacetoxycephalosporanic acid and 0.1 mol dm <sup>-3</sup> NaCl at 20°C. The pH was then adjusted to 3.74 (pl) using 0.1 N NaOH solution. After filtering, the concentration of the solute was determined spectrophotometrically at 410 nm based on reaction, in acid solution, with p-dimethylaminobenzaldehyde reagent.	<b>SOURCE AND PURITY OF MATERIALS:</b>  The sources and purities of 7-aminoacetoxycephalosporanic acid and chemicals used in the experiments were not specified.  <b>ESTIMATED ERROR:</b> Solubility precision: ±5% (compiler) Temperature precision: ±1°C (compiler)  <b>REFERENCES:</b>

<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid, 3-methyl-8-oxo-7-(2-phenylacetamido) (7-phenylacetamidodeacetoxycephalosporanic acid); <math>C_{16}H_{16}N_2O_4S</math>; [27255-72-7]</p> <p>(2) Aqueous solvents</p>	<p>EVALUATOR:</p> <p>Eric Tomlinson, Department of Pharmacy, University of Amsterdam, The Netherlands.</p> <p>December 1983.</p>
<p>CRITICAL EVALUATION:</p> <p>7-Phenylacetamidodeacetoxycephalosporanic acid is one of the intermediate products in the transformation of benzylpenicillin into 7-aminodeacetoxycephalosporanic acid (1). Its solubility has been reported by Nys et al in two studies (2,3). In their earlier report they estimated the minimal aqueous solubility at <math>293 \pm 1</math> K (units and precision - evaluator) and at a constant ionic strength of 0.1 to be <math>2.07 \times 10^{-3}</math> mol dm<sup>-3</sup>. However neither a procedure nor the purity of the sample studied was given. In their later study (3) Nys et al used a sample with a purity determined after repeated recrystallization from an isopropanol-hexane mixture to be 99 percent, and gave their procedure of solubility determination. They reported that at <math>298 \pm 1</math> K (units and precision - evaluator) and at a constant ionic strength of 0.1, the minimal solubility of this acid (determined at its isoelectric point of 3.05) was <math>3.14 \times 10^{-3}</math> mol dm<sup>-3</sup>. This latter value is regarded as having a precision of <math>\pm 5</math> percent (evaluator), and may be designated as tentative.</p> <p>REFERENCES</p> <p>(1) Stedman, R.J.; Swered, K.; Hoover, J.R.E. <i>J. Med. Chem.</i> <u>1964</u>, <i>7</i>, 17. (2) Nys, P.S.; Koltsova, E.V.; Shellenberg, N.N.; Zinchenko, E. Ya.; Ryabova, N.M.; Savitskaya, E.M.; Levitov, M.M.; Mezentsev, A.S. <i>Antibiotiki, (Moscow)</i> <u>1976</u>, <i>21</i>, 309. (3) Nys, P.S.; Elizarovskaya, E.M. <i>Antibiotiki, (Moscow)</i> <u>1979</u>, <i>24</i>, 895.</p>	

<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid, 3-methyl-8-oxo-7-(2-phenylacetamido), 7-phenylacetamidodeacetoxycephalosporanic acid; <math>C_{16}H_{16}N_2O_4S</math>; [27255-72-7]</p> <p>(2) Potassium chloride; KCl; [7447-40-7]</p> <p>(3) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Nys, P.S.; Koltsova, E.V.; Shellenberg, N.N.; Zinchenko, E.Ya.; Ryabova, N.M.; Savitskaya, E.M.; Levitov, M.M.; Mezentsev, A.S. <i>Antibiotiki, (Moscow)</i> 1976, 21, 309-12.</p>
<p>VARIABLES:</p> <p>One temperature: 20°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>The authors estimated minimal solubility (intrinsic solubility) of the ampholyte zwitterion of 7-phenylacetamidodeacetoxycephalosporanic acid in water at 20°C and constant ionic strength (<math>I = 0.1</math>), to</p> $S_x^0 = 2.07 \times 10^{-3} \text{ mol dm}^{-3} \text{ (0.69 mg cm}^{-3} \text{ - compiler).}$ <p><math>S_x^0</math> value estimated from the solubility at the isoelectric point (<math>pH = 3.05</math>).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Procedure not described. The constant ionic strength was maintained using 0.1 mol <math>dm^{-3}</math> KCl solution. The amount of the dissolved solute was determined spectrophotometrically at 265 nm.</p>	<p>SOURCE AND PURITY OF MATERIALS.</p> <p>7-Phenylacetamidodeacetoxycephalosporanic acid was prepared by transformation of benzylpenicillin, its purity was not specified.</p> <p>The potassium chloride was of analytical grade. Distilled water was used.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: probably <math>\pm 1^\circ C</math> (compiler)</p> <p>REFERENCES.</p>

<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid, 3-methyl-8-oxo-7-(2-phenylacetamido), 7-phenylacetamidodeacetoxycephalosporanic acid; <math>C_{16}H_{16}N_2O_4S</math>; [27255-72-7]</p> <p>(2) Ammonium chloride; <math>H_4ClN</math>; [12125-02-9]</p> <p>(3) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Nys, P.S.; Elizarovskaya, L.M.; Shellenberg, N.N.; Savitskaya, E.M. <i>Antibiotiki, (Moscow)</i> <u>1979, 24, 895-902.</u></p>
<p>VARIABLES:</p> <p>One temperature: 25°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>The authors report two values for the solubility of the ampholyte zwitterion of 7-phenylacetamidodeacetoxycephalosporanic acid in water at 25°C and constant ionic strength (<math>I = 0.1</math>).</p> <ol style="list-style-type: none"> <li>Minimal solubility (intrinsic solubility) <math>S_x^0 = 3.14 \times 10^{-4} \text{ mol dm}^{-3}</math> (<math>0.10 \text{ mg cm}^{-3a}</math>) (estimated experimentally).</li> <li>Characteristic solubility (total solubility) <math>S_{AH\pm}^0 = 3.10 \times 10^{-4} \text{ mol dm}^{-3}</math> (<math>0.10 \text{ mg cm}^{-3a}</math>) (calculated from equation) [1].</li> </ol> $S_{AH\pm}^0 = S_x^0 \left( \frac{K_1 \cdot C_H^0}{(C_H^0)^2 + K_1 \cdot C_H^0 + K_1 + K_2} \right) \quad [1]$ <p>where <math>C_H^0</math> is the concentration of hydrogen ions, <math>K_1</math> (COOH) = <math>5.62 \times 10^{-4} \text{ mol dm}^{-3}</math>  <math>K_2</math> (<math>NH_3^+</math>) - not given, are dissociation constants.</p> <p><math>S_x^0</math> value estimated from the solubility at the isoelectric point <math>pH = 3.05</math>.</p> <p><sup>a</sup> Calculated by compiler.</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>A saturated mixture was prepared by stirring an excess of 7-phenylacetamidodeacetoxycephalosporanic acid in distilled water at 25°C, maintained the constant ionic strength (<math>I = 0.1</math>) by adding appropriate amounts of <math>NH_4Cl</math>. The amount of the dissolved solute was determined by iodometric titration.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>7-Phenylacetamidodeacetoxycephalosporanic acid was prepared by transformation of benzylpenicillin and was purified by repeatedly recrystallization from isopropanol-hexane mixture; its purity (99%) was determined iodometrically.</p> <p>The ammonium chloride was of analytical grade. Doubly distilled water was used.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: probably <math>\pm 1^\circ\text{C}</math> (compiler)</p> <p>REFERENCES:</p>

## COMPONENTS:

(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino], monosodium salt (cephalothin sodium);  $C_{16}H_{15}N_2O_6S_2Na$ ; [58-71-9]

(2) All solvents

## EVALUATOR:

Eric Tomlinson,  
Department of Pharmacy,  
University of Amsterdam,  
The Netherlands.

December 1983.

## CRITICAL EVALUATION:

Marsh and Weiss have determined the solubilities of cephalothin sodium in 23 different non aqueous solvents and in various aqueous solvents at  $294 \pm 1$  K (1). These workers studied a sample of the antibiotic provided by Eli Lilly and Co, its purity was not specified. The amount of antibiotic dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than  $20 \text{ mg cm}^{-3}$ . All values reported were uncorrected for solvent blank, which was generally less than  $0.02 \text{ mg total}$ . All data according to Marsh and Weiss have been recalculated to SI units (evaluator). Solubilities in non aqueous solvents are given in the Table.

Solvent <sup>a</sup>	Solubility (at $294 \pm 1$ K), (mol $\text{dm}^{-3}$ ) <sup>b</sup>
methanol	$2.85 \times 10^{-2}$
ethanol	$4.25 \times 10^{-2}$
isopropanol	$1.96 \times 10^{-4}$
isoamyl alcohol	$1.79 \times 10^{-4}$
cyclohexane	$1.24 \times 10^{-4}$
benzene	$4.8 \times 10^{-5}$
ligroin	$4.8 \times 10^{-5}$
isooctane	$6.7 \times 10^{-5}$
carbon tetrachloride	$6.0 \times 10^{-5}$
ethyl acetate	$5.3 \times 10^{-5}$
isoamyl acetate	$9.6 \times 10^{-5}$
acetone	$1.55 \times 10^{-4}$
methyl ethyl ketone	$3.6 \times 10^{-5}$
diethylether	$0.5 \times 10^{-5}$
ethylene chloride	$6.0 \times 10^{-3}$
1,4-dioxane	$1.25 \times 10^{-3}$
chloroform	$1.63 \times 10^{-4}$
carbon disulfide	$3.6 \times 10^{-5}$
pyridine	$2.51 \times 10^{-4}$
formamide	c
ethylene glycol	c
propylene glycol	c
dimethyl sulfoxide	c

(<sup>a</sup> All solvents are probably of U.S.P. or A.C.S. grade, as previous (2); <sup>b</sup> units calculated by evaluator; <sup>c</sup> solubility greater than  $4.80 \times 10^{-2} \text{ mol dm}^{-3}$ ).

Marsh and Weiss have reported the solubility of cephalothin sodium in water, 0.1 N HCl and 0.1 N NaOH to be greater than  $4.80 \times 10^{-2} \text{ mol dm}^{-3}$ ,  $9.4 \times 10^{-3} \text{ mol dm}^{-3}$ , and greater than  $4.80 \times 10^{-2} \text{ mol dm}^{-3}$ , respectively (units - evaluator).

All these values for solubility in both aqueous and non aqueous solvents have an estimated precision of  $\pm 5\%$  (evaluator). Because of the unstated purity of the sample, and since the values reported are unconfirmed, these solubilities are designated as being highly tentative, except for where the solubility is reported as being greater than  $4.80 \times 10^{-2} \text{ mol dm}^{-3}$ , (which are regarded as being doubtful).

## REFERENCES

- (1) Marsh, J.R.; Weiss, P.J. *J. Ass. Offic. Anal. Chem.* **1967**, *50*, 457.  
(2) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* **1957**, *7*, 374.





<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino], monosodium salt (cephalothin sodium); <math>C_{16}H_{15}N_2O_6S_2Na</math>; [58-71-9]</p> <p>(2) Sodium hydroxide; <math>HNaO</math>; [1310-73-2]</p> <p>(3) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephalothin sodium in 0.1 N NaOH solution at <math>21 \pm 1^\circ C</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.8 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of 0.1 N NaOH solution were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephalotin sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>The purity of sodium hydroxide was not specified. Water was probably of U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p>



<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino], monosodium salt (cephalothin sodium); <math>C_{16}H_{15}N_2O_6S_2Na</math>; [58-71-9]</p> <p>(2) Ethanol; <math>C_2H_6O</math>; [64-17-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephalothin sodium in ethanol at <math>21 \pm 1^\circ C</math> was reported as:  <math>1.78 \text{ mg cm}^{-3}</math>. (<math>4.25 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephalotin sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Ethanol was probably of U.S.P. or A.C.S. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<b>COMPONENTS:</b> (1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino], monosodium salt (cephalothin sodium); $C_{16}H_{15}N_2O_6S_2Na$ ; [58-71-9] (2) 2-Propanol (isopropanol); $C_3H_8O$ ; [67-63-0]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of cephalothin sodium in isopropanol at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.082 \text{ mg cm}^{-3}</math>. (<math>1.96 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Cephalotin sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Isopropanol was of U.S.P. or A.C.S. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino], monosodium salt (cephalothin sodium); <math>C_{16}H_{15}N_2O_6S_2Na</math>; [58-71-9]</p> <p>(2) 1-Butanol,3-methyl- (isoamyl alcohol); <math>C_5H_{12}O</math>; [123-51-3]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u>, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephalothin sodium in isoamyl alcohol at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.075 \text{ mg cm}^{-3}</math>. (<math>1.79 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephalotin sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Isoamyl alcohol was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <b>Antibiotics and Chemotherapy</b> <u>1957</u>, 7, 374-7.</p>



<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino], monosodium salt (cephalothin sodium); <math>C_{16}H_{15}N_2O_6S_2Na</math>; [58-71-9]</p> <p>(2) Benzene; <math>C_6H_6</math>; [71-43-2]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <i>50</i>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephalothin sodium in benzene at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.020 \text{ mg cm}^{-3}</math>. (<math>4.78 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephalotin sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Benzene was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <i>7</i>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino], monosodium salt (cephalothin sodium); <math>C_{16}H_{15}N_2O_6S_2Na</math>; [58-71-9]</p> <p>(2) Petroleum ether (ligroin)</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1967</b>, <i>50</i>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephalothin sodium in ligroin at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.020 \text{ mg cm}^{-3}</math>. (<math>4.78 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephalotin sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Ligroin was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <b>1957</b>, <i>7</i>, 374-7.</p>





<b>COMPONENTS:</b> (1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino], monosodium salt (cephalothin sodium); $C_{16}H_{15}N_2O_6S_2Na$ ; [58-71-9] (2) Acetic acid, ethyl ester (ethyl acetate); $C_4H_8O_2$ ; [141-78-6]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <i>50</i> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of cephalothin sodium in ethyl acetate at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.022 \text{ mg cm}^{-3}</math>. (<math>5.26 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Cephalotin sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Ethyl acetate was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <i>7</i>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino], monosodium salt (cephalothin sodium); <math>C_{16}H_{15}N_2O_6S_2Na</math>; [58-71-9]</p> <p>(2) 1-Butanol, 3-methyl acetate (isoamyl acetate); <math>C_7H_{14}O_2</math>; [123-92-2]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <i>50</i>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephalothin sodium in isoamyl acetate at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.040 \text{ mg cm}^{-3}</math>. (<math>9.56 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephalotin sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Isoamyl acetate was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p>
	<p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <i>7</i>, 374-7.</p>

<b>COMPONENTS:</b> (1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino], monosodium salt (cephalothin sodium); $C_{16}H_{15}N_2O_6S_2Na$ ; [58-71-9] (2) 2-Propanone (acetone); $C_3H_6O$ ; [67-64-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of cephalothin sodium in acetone at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.065 \text{ mg cm}^{-3}</math>. (<math>1.55 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Cephalotin sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Acetone was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino], monosodium salt (cephalothin sodium); <math>C_{16}H_{15}N_2O_6S_2Na</math>; [58-71-9]</p> <p>(2) 2-Butanone (methyl ethyl ketone); <math>C_4H_8O</math>; [78-93-3]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <i>50</i>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephalothin sodium in methyl ethyl ketone at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.015 \text{ mg cm}^{-3}</math>. (<math>3.56 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephalothin sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Methyl ethyl ketone was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES.</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <i>7</i>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino], monosodium salt (cephalothin sodium); <math>C_{16}H_{15}N_2O_6S_2Na</math>; [58-71-9]</p> <p>(2) Ethane,1,1'-oxybis- (diethyl ether); <math>C_4H_{10}O</math>; [60-29-7]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1967</b>, <i>50</i>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephalothin sodium in diethyl ether at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.002 \text{ mg cm}^{-3}</math>. (<math>4.78 \times 10^{-6} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephalotin sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Diethyl ether was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <b>1957</b>, <i>7</i>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino], monosodium salt (cephalothin sodium); <math>C_{16}H_{15}N_2O_6S_2Na</math>; [58-71-9]</p> <p>(2) Ethane, dichloro- (ethylene chloride); <math>C_2H_4Cl_2</math>; [1300-21-6]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephalothin sodium in ethylene chloride at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.025 \text{ mg cm}^{-3}</math>. (<math>5.98 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephalotin sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Ethylene chloride was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES.</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino], monosodium salt (cephalothin sodium); <math>C_{16}H_{15}N_2O_6S_2Na</math>; [58-71-9]</p> <p>(2) 1,4-Dioxane; <math>C_4H_8O_2</math>; [123-91-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <i>50</i>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephalothin sodium in 1,4-dioxane at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.52 \text{ mg cm}^{-3}</math>. (<math>1.25 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephalotin sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>1,4-Dioxane was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <i>7</i>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino], monosodium salt (cephalothin sodium); <math>C_{16}H_{15}N_2O_6S_2Na</math>; [58-71-9]</p> <p>(2) Methane, trichloro- (chloroform); <math>CHCl_3</math>; [67-66-3]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephalothin sodium in chloroform at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.068 \text{ mg cm}^{-3}</math>. (<math>1.63 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephalothin sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Chloroform was probably of U.S.P. or A.C.S. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES.</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino], monosodium salt (cephalothin sodium); <math>C_{16}H_{15}N_2O_6S_2Na</math>; [58-71-9]</p> <p>(2) Carbon disulfide; <math>CS_2</math>; [75-15-0]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephalothin sodium in carbon disulfide at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.015 \text{ mg cm}^{-3}</math>. (<math>3.59 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephalotin sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Carbon disulfide was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino], monosodium salt (cephalothin sodium); <math>C_{16}H_{15}N_2O_6S_2Na</math>; [58-71-9]</p> <p>(2) Pyridine; <math>C_5H_5N</math>; [110-86-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephalothin sodium in pyridine at <math>21 \pm 1^\circ C</math> was reported as:  <math>0.11 \text{ mg cm}^{-3}</math>. (<math>2.51 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephalotin sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Pyridine was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>



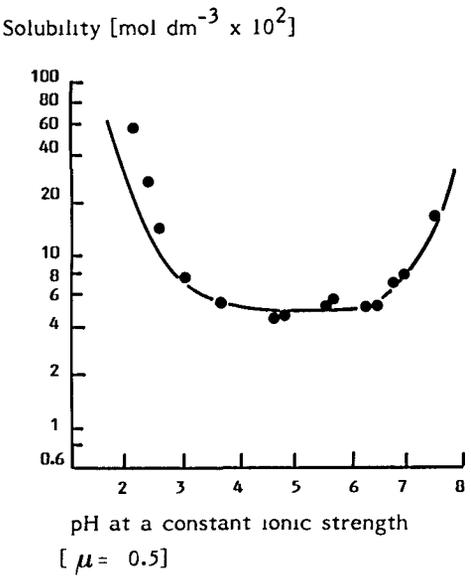
<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino], monosodium salt (cephalothin sodium); <math>C_{16}H_{15}N_2O_6S_2Na</math>; [58-71-9]</p> <p>(2) 1,2-Ethanediol (ethylene glycol); <math>C_2H_6O_2</math>; [107-21-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. 1967, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephalothin sodium in ethylene glycol at <math>21 \pm 1^\circ C</math> was reported as greater than <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.80 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephalotin sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Ethylene glycol was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p>
	<p>REFERENCES:</p>



<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino], monosodium salt (cephalothin sodium); <math>C_{16}H_{15}N_2O_6S_2Na</math>; [58-71-9]</p> <p>(2) Methane,sulfinylbis- (dimethyl sulfoxide); <math>C_2H_6OS</math>; [67-68-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u>, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephalothin sodium in diethyl sulfoxide at <math>21 \pm 1^\circ C</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.80 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephalothin sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Dimethyl sulfoxide was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ C</math> (authors).</p> <p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-7[(aminophenylacetyl)amino]-3-methyl-8-oxo, monohydrate (cephalexin monohydrate) <math>C_{16}H_{17}N_3O_4S \cdot H_2O</math>; [23325-78-2]</p> <p>(2) All aqueous solvents</p>	<p>EVALUATOR:</p> <p>Eric Tomlinson. Department of Pharmacy, University of Amsterdam, The Netherlands. December 1983.</p>
<p>CRITICAL EVALUATION:</p> <p>The influence of pH on the solubility of cephalexin monohydrate has been studied by Tsuji et al (1), who examined the pH - solubility behavior at constant ionic strength (<math>\mu = 0.5</math> - KCl) and temperature (310 K) using HCl or KOH to regulate the pH. Their results were presented graphically, and exhibited a U-shaped curve, with a minimum solubility between pH 4 and 6. The original data have been obtained directly from the authors (2), and are given in the appropriate compilation sheet. The precision in solubility determination and the temperature can be estimated as <math>\pm 5\%</math> and <math>\pm 1</math> K, respectively (evaluator). The authors fitted the experimental data using:</p> $C_T = C_o [(a_{H^+}/K_1) + 1 + (K_2/a_{H^+})]$ <p>where <math>C_T</math> is the total solubility, <math>C_o</math> the intrinsic solubility of the ampholyte, <math>a_{H^+}</math> the hydrogen ion activity, and <math>K_1</math> and <math>K_2</math> the dissociation constants for 2-carboxylic acid and the conjugated acid of the alpha-amino group, respectively. The authors have stated (2) that the intrinsic solubility of cephalexin monohydrate calculated in this manner is <math>4.72 \times 10^{-2}</math> mol dm<sup>-3</sup>, which agrees with their experimentally obtained value at pH 4.75 of <math>4.71 \times 10^{-2}</math> mol dm<sup>-3</sup>. Being an ampholyte, this antibiotic showed increased solubility in acid and in alkali. At low pH values, the observed values were found to be higher than those calculated using the above equation and could be reflecting antibiotic instability at these low pHs (3). For the present data of Tsuji et al, the reported solubilities are regarded as being tentative, except for those at pH 2.5 and below which are regarded as being doubtful.</p> <p>Tsuji et al (1) have studied the influence of temperature on the aqueous solubility of cephalexin monohydrate. Over the temperature interval 293 K to 323 K (temperature precision estimated as <math>\pm 1</math> K, evaluator) they found a constant heat of solution of 5.81 kJ mol<sup>-1</sup>.</p> <p>REFERENCES</p> <p>(1) Tsuji, A.; Nakashima, E.; Hamano, S.; Yamana, T. <i>J. Pharm. Sci.</i> <b>1979</b>, <b>68</b>, 301.  (2) Tsuji, A. Personal communication.  (3) Hou, J.P.; Poole, J.W. <i>J. Pharm. Sci.</i> <b>1969</b>, <b>58</b>, 1510.</p>	

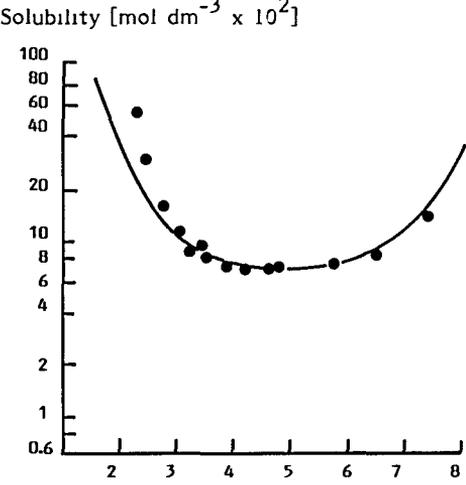
<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-7[(aminophenylacetyl)amino]-3-methyl-8-oxo, monohydrate (cephalexin monohydrate); <math>C_{16}H_{17}N_3O_4S \cdot H_2O</math>; [23325-78-2]</p> <p>(2) Hydrochloric acid; HCl; [7647-01-0]</p> <p>(3) Potassium hydroxide; KOH; [1310-58-3]</p> <p>(4) Potassium chloride; KCl; [7447-40-7]</p> <p>(5) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Tsuji, A.; Nakashima, E.; Yamana, T. J. <i>Pharm. Sci.</i> 1979, 68, 308-11.</p>																																																												
<p>VARIABLES:</p> <p>pH at 37°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>																																																												
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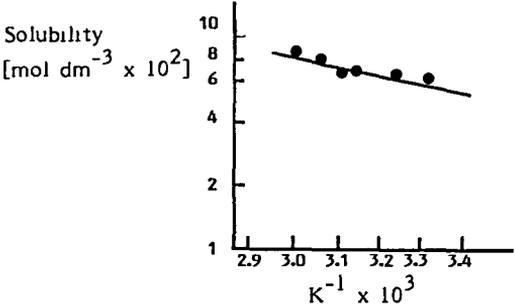
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<p>COMMENTS AND/OR ADDITIONAL DATA:</p> <p>In the figure at the right, the points are the experimental results<sup>a</sup>. The solid line was generated from equation [1].</p> $C_T = C_o \left( \frac{a_{H^+}}{K_1} + 1 + \frac{K_2}{a_{H^+}} \right) \quad [1]$ <p>where <math>C_T</math> is the total solubility, <math>C_o</math> is the intrinsic solubility of amphoteric cephal<sup>o</sup>exine with the electrically neutral zwitterion, <math>a_{H^+}</math> is the hydrogenion activity of the solution, and <math>K_1</math> and <math>K_2</math> are dissociation constants for carboxylic acid and the conjugated acid of the <math>\alpha</math>-amino group, respectively.</p> <div style="text-align: right;">  </div>	
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<p>EXPERIMENTAL VALUES:</p> <p>The authors determined the apparent equilibrium solubilities of cephalexin monohydrate in <math>0.5 \text{ mol dm}^{-3}</math> KCl aqueous solution versus a reciprocal absolute temperature. Van 't Hoff plots gave a reasonable good linear relationship (figure).</p> <p>The value of the heat of solution <math>\Delta H_{\text{soln}}</math> for cephalexin was calculated from the van 't Hoff plot to be <math>5.81 \text{ kJ mol}^{-1}</math>.</p> <div data-bbox="596 754 1103 1068" style="text-align: center;"> <p>Solubility <math>[\text{mol dm}^{-3} \times 10^2]</math></p> <p><math>K^{-1} \times 10^3</math></p> <table border="1"> <caption>Data points from the Van't Hoff plot</caption> <thead> <tr> <th><math>K^{-1} \times 10^3</math></th> <th>Solubility <math>[\text{mol dm}^{-3} \times 10^2]</math></th> </tr> </thead> <tbody> <tr> <td>3.0</td> <td>5.0</td> </tr> <tr> <td>3.1</td> <td>4.8</td> </tr> <tr> <td>3.2</td> <td>4.5</td> </tr> <tr> <td>3.3</td> <td>4.8</td> </tr> <tr> <td>3.4</td> <td>4.2</td> </tr> </tbody> </table> </div>		$K^{-1} \times 10^3$	Solubility $[\text{mol dm}^{-3} \times 10^2]$	3.0	5.0	3.1	4.8	3.2	4.5	3.3	4.8	3.4	4.2
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<p>CRITICAL EVALUATION:</p> <p>The influence of pH on the solubility of cephradine monohydrate has been studied by Tsuji et al (1), who examined the pH - solubility behavior at constant ionic strength (<math>\mu = 0.5</math> - KCl) and temperature (310 K) using HCl or KOH to regulate the pH. Their results were presented graphically, and exhibited a U-shaped curve, with a minimum solubility between pH 4 and 6. The original data have been obtained directly from the authors (2), and are given in the appropriate compilation sheet. The precision in solubility determination and the temperature can be estimated as <math>\pm 5\%</math> and <math>\pm 1</math> K, respectively (evaluator). The authors fitted the experimental data using:</p> $C_T = C_o [(a_{H^+}/K_1) + 1 + (K_2/a_{H^+})]$ <p>where <math>C_T</math> is the total solubility, <math>C_o</math> the intrinsic solubility of the ampholyte, <math>a_{H^+}</math> the hydrogen ion activity, and <math>K_1</math> and <math>K_2</math> the dissociation constants for 2-carboxylic acid and the conjugated acid of the alpha-amino group, respectively. The authors have stated (2) that the intrinsic solubility of cephradine monohydrate calculated in this manner is <math>7.08 \times 10^{-2}</math> mol dm<sup>-3</sup>, which agrees with their experimentally obtained value at pH 4.16 of <math>7.19 \times 10^{-2}</math> mol dm<sup>-3</sup>. Being an ampholyte, this antibiotic showed increased solubility in acid and in alkali. At low pH values, the observed values were found to be higher than those calculated using the above equation and could be reflecting antibiotic instability at these low pHs (3). For the present data of Tsuji et al, the reported solubilities are regarded as being tentative, except for those at pH 2.5 and below which are regarded as being doubtful.</p> <p>Tsuji et al (1) have studied the influence of temperature on the aqueous solubility of cephradine monohydrate. Over the temperature interval 293 K to 323 K (temperature precision estimated as <math>\pm 1</math> K, evaluator) they found a constant heat of solution of 6.60 kJ mol<sup>-1</sup>.</p> <p>REFERENCES</p> <p>(1) Tsuji, A.; Nakashima, E.; Hamano, S.; Yamana, T. <i>J. Pharm. Sci.</i> <u>1978</u>, <b>67</b>, 1059.  (2) Tsuji, A. Personal communication.  (3) Hou, J.P.; Poole, J.W. <i>J. Pharm. Sci.</i> <u>1969</u>, <b>58</b>, 1510.</p>	

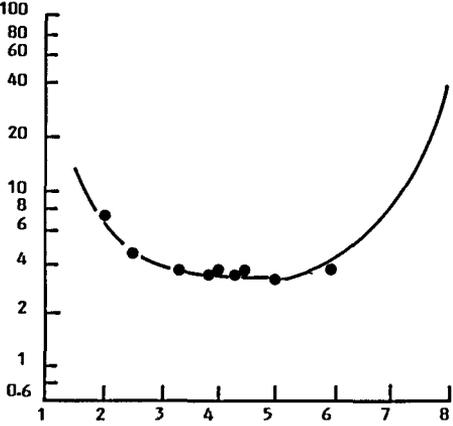
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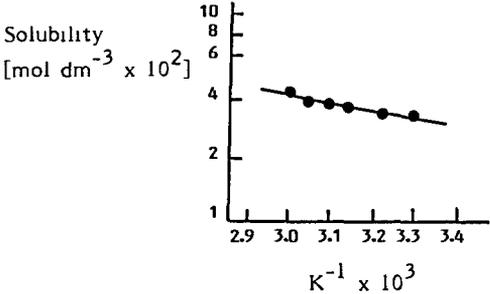
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<p>VARIABLES:</p> <p>pH at 37°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>COMMENTS AND/OR ADDITIONAL DATA:</p> <p>In the figure at the right, the points are the experimental data<sup>a</sup>. The solid line was calculated from equation [1].</p> $C_T = C_o \left( \frac{a_{H^+}}{K_1} + 1 + \frac{K_2}{a_{H^+}} \right) \quad [1]$ <p>where <math>C_T</math> is the total solubility, <math>C_o</math> is the intrinsic solubility of amphoteric cephradine with the electrically neutral zwitterion, <math>a_{H^+}</math> is the hydrogen activity of the solution, and <math>K_1</math> and <math>K_2</math> are the dissociation constants for carboxylic acid and the conjugated acid of the <math>\alpha</math>-amino group, respectively.</p> <div style="text-align: right;">  <p>Solubility [mol dm<sup>-3</sup> x 10<sup>2</sup>]</p> <p>pH at constant ionic strength [<math>\mu = 0.5</math>]</p> </div>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>ESTIMATED ERROR:</p> <p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-7[(amino-1,4-cyclohexadien-1-yl-acetyl)amino]-3-methyl-8-oxo, monohydrate (cephadrine monohydrate); <math>C_{16}H_{19}N_3O_4 \cdot H_2O</math>; [31828-50-9]</p> <p>(2) Potassium chloride; KCl; [7447-40-7]</p> <p>(3) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Tsuji, A.; Nakashima, E.; Yamana, T. <i>J Pharm. Sci.</i> <b>1979</b>, <i>68</i>, 308-11.</p>														
<p>VARIABLES:</p> <p>Reciprocal of absolute temperature</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>														
<p>EXPERIMENTAL VALUES:</p> <p>The authors determined the apparent equilibrium solubilities of cephradine monohydrate in <math>0.5 \text{ mol dm}^{-3}</math> KCl solution versus a reciprocal absolute temperature. Classical van 't Hoff plots gave a reasonably good linear relationship (figure). The value of the heat of solution <math>\Delta H_{\text{sol}}</math> for cephradine was calculated from the van 't Hoff plot to be <math>6.60 \text{ kJ mol}^{-1}</math>.</p> <div style="text-align: center;">  <table border="1" style="margin: 10px auto;"> <caption>Estimated data points from the van't Hoff plot</caption> <thead> <tr> <th><math>K^{-1} \times 10^3</math></th> <th>Solubility <math>[\text{mol dm}^{-3} \times 10^2]</math></th> </tr> </thead> <tbody> <tr><td>3.00</td><td>8.5</td></tr> <tr><td>3.05</td><td>7.8</td></tr> <tr><td>3.10</td><td>7.2</td></tr> <tr><td>3.15</td><td>6.8</td></tr> <tr><td>3.25</td><td>6.5</td></tr> <tr><td>3.35</td><td>6.2</td></tr> </tbody> </table> </div>		$K^{-1} \times 10^3$	Solubility $[\text{mol dm}^{-3} \times 10^2]$	3.00	8.5	3.05	7.8	3.10	7.2	3.15	6.8	3.25	6.5	3.35	6.2
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<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-3[(acetyloxy)methyl]-7[aminophenyl-acetyl]amino]-8-oxo, dihydrate (cephaloglycin dihydrate); <math>C_{18}H_{19}N_3O_6 \cdot 2H_2O</math>; [22202-75-1]</p> <p>(2) All aqueous solvents</p>	<p>EVALUATOR:</p> <p>Eric Tomlinson. Department of Pharmacy, University of Amsterdam, The Netherlands.  December 1983.</p>
<p>CRITICAL EVALUATION:</p> <p>The influence of pH on the solubility of cephaloglycin dihydrate has been studied by Tsuji et al (1), who examined the pH - solubility behavior at constant ionic strength (<math>\mu = 0.5</math> - KCl) and temperature (310 K) using HCl or KOH to regulate the pH. Their results were presented graphically, and exhibited a U-shaped curve, with a minimum solubility between pH 4 and 5. The original data have been obtained directly from the authors (2), and are given in the appropriate compilation sheet. The precision in solubility determination and the temperature can be estimated as <math>\pm 5\%</math> and <math>\pm 1</math> K, respectively (evaluator). The authors fitted the experimental data using:</p> $C_T = C_o [(a_{H^+}/K_1) + 1 + (K_2/a_{H^+})]$ <p>where <math>C_T</math> is the total solubility, <math>C_o</math> the intrinsic solubility of the ampholyte, <math>a_{H^+}</math> the hydrogen ion activity, and <math>K_1</math> and <math>K_2</math> the dissociation constants for 2-carboxylic acid and the conjugated acid of the alpha-amino group, respectively. The authors have stated (2) that the intrinsic solubility of cephaloglycin dihydrate calculated in this manner is <math>3.36 \times 10^{-2}</math> mol dm<sup>-3</sup>, which agrees with their experimentally obtained value at pH 4.01 of <math>3.43 \times 10^{-2}</math> mol dm<sup>-3</sup>. Being an ampholyte, this antibiotic showed increased solubility in acid and in alkali. Unlike for the other cephalosporins studied by these authors, at low pH values, the observed values were found to agree with those calculated using the above equation. For the present data of Tsuji et al, the reported solubilities are regarded as being tentative.</p> <p>Tsuji et al (1) have studied the influence of temperature on the aqueous solubility of cephaloglycin dihydrate. Over the temperature interval 293 K to 323 K (temperature precision estimated as <math>\pm 1</math> K, evaluator) they found a constant heat of solution of 7.82 kJ mol<sup>-1</sup>.</p> <p>REFERENCES</p> <p>(1) Tsuji, A.; Nakashima, E.; Hamano, S.; Yamana, T. <i>J. Pharm. Sci.</i> 1979, 68, 301. (2) Tsuji, A. Personal communication.</p>	



<p>COMPONENTS:</p> <p>(1) 5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid-3[(acetyloxy)methyl]-7[(aminophenylacetyl)amino]-8-oxo, dihydrate (cephaloglycin dihydrate); <math>C_{18}H_{19}N_3O_6S \cdot 2H_2O</math>; [22202-75-1]</p> <p>(2) Hydrochloric acid; HCl; [7647-01-0]</p> <p>(3) Potassium hydroxide; KOH; [1310-58-3]</p> <p>(4) Potassium chloride; KCl; [7447-40-7]</p> <p>(5) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS: (continued) Tsuji, A.; Nakashima, E.; Yamana, T. J. Pharm. Sci. 1979, 68, 308-11.</p>																												
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<p>COMMENTS AND/OR ADDITIONAL DATA:</p> <p>In the figure at the right, the points are the experimental values. The solid line was calculated from equation [1].</p> $C_T = C_o \left( \frac{a_{H^+}}{K_1} + 1 + \frac{K_2}{a_{H^+}} \right) \quad [1]$ <p>where <math>C_T</math> is the total solubility, <math>C_o</math> is the intrinsic solubility of amphoteric cephaloglycin with the electrically neutral zwitterion, <math>a_{H^+}</math> is the hydrogenion activity of the solution, and <math>K_1</math> and <math>K_2</math> are dissociation constants for 2-carboxylic acid and the conjugated acid of the <math>\alpha</math>-amino group, respectively.</p> <div style="text-align: right;"> <p>Solubility [<math>\text{mol dm}^{-3} \times 10^2</math>]</p>  <table border="1" style="margin-left: auto; margin-right: auto;"> <caption>Estimated data points from the solubility graph</caption> <thead> <tr> <th>pH at 37°C</th> <th>Solubility [<math>\text{mol dm}^{-3} \times 10^2</math>]</th> </tr> </thead> <tbody> <tr><td>2.0</td><td>10</td></tr> <tr><td>2.5</td><td>6</td></tr> <tr><td>3.0</td><td>4.5</td></tr> <tr><td>3.5</td><td>3.5</td></tr> <tr><td>4.0</td><td>3.2</td></tr> <tr><td>4.5</td><td>3.2</td></tr> <tr><td>5.0</td><td>3.2</td></tr> <tr><td>5.5</td><td>3.5</td></tr> <tr><td>6.0</td><td>4.5</td></tr> <tr><td>6.5</td><td>10</td></tr> <tr><td>7.0</td><td>20</td></tr> <tr><td>7.5</td><td>40</td></tr> <tr><td>8.0</td><td>80</td></tr> </tbody> </table> <p>pH at 37°C</p> </div>		pH at 37°C	Solubility [ $\text{mol dm}^{-3} \times 10^2$ ]	2.0	10	2.5	6	3.0	4.5	3.5	3.5	4.0	3.2	4.5	3.2	5.0	3.2	5.5	3.5	6.0	4.5	6.5	10	7.0	20	7.5	40	8.0	80
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<p>COMPONENTS:</p> <p>(1) Pyridinium,1-[[2-carboxy-8-oxo-7-[2-thienyl]acetyl]amino-5-Thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]methyl]-hydroxide, inner salt, (6R-trans) (cephaloridine); C<sub>19</sub>H<sub>17</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub>; [50-59-9]</p> <p>(2) All solvents</p>	<p>EVALUATOR:</p> <p>Eric Tomlinson. Department of Pharmacy, University of Amsterdam, The Netherlands. December 1983.</p>
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## CRITICAL EVALUATION:

Marsh and Weiss have determined the solubilities of cephaloridine in 23 different non aqueous solvents and in various aqueous solvents at 294<sup>±</sup>1 K (1). These workers studied a sample of the antibiotic provided by Eli Lilly and Co, its purity was not specified. The amount of antibiotic dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than 20 mg cm<sup>-3</sup>. All values reported were uncorrected for solvent blank, which was generally less than 0.02 mg total. All data according to Marsh and Weiss have been recalculated to SI units (evaluator). Solubilities in non aqueous solvents are given in the Table.

Solvent <sup>a</sup>	Solubility (at 294 <sup>±</sup> 1 K), (mol dm <sup>-3</sup> ) <sup>b</sup>
methanol	7.01 x 10 <sup>-3</sup>
ethanol	4.69 x 10 <sup>-3</sup>
isopropanol	5.05 x 10 <sup>-4</sup>
isoamyl alcohol	7.75 x 10 <sup>-4</sup>
cyclohexane	1.44 x 10 <sup>-5</sup>
benzene	9.6 x 10 <sup>-5</sup>
ligroin	8.4 x 10 <sup>-5</sup>
isooctane	1.20 x 10 <sup>-4</sup>
carbon tetrachloride	1.25 x 10 <sup>-5</sup>
ethyl acetate	8.4 x 10 <sup>-5</sup>
isoamyl acetate	1.08 x 10 <sup>-4</sup>
acetone	4.38 x 10 <sup>-4</sup>
methyl ethyl ketone	2.65 x 10 <sup>-5</sup>
diethylether	2.4 x 10 <sup>-5</sup>
ethylene chloride	2.89 x 10 <sup>-4</sup>
1,4-dioxane	5.82 x 10 <sup>-4</sup>
chloroform	5.82 x 10 <sup>-5</sup>
carbon disulfide	4.8 x 10 <sup>-5</sup>
pyridine	1.78 x 10 <sup>-3</sup>
formamide	c
ethylene glycol	c
propylene glycol	c
dimethyl sulfoxide	c

(<sup>a</sup> All solvents are probably of U.S.P. or A.C.S. grade, as previous (2); <sup>b</sup> units calculated by evaluator; <sup>c</sup> solubility greater than 4.80 x 10<sup>-2</sup> mol dm<sup>-3</sup>).

Marsh and Weiss have reported the solubility of cephaloridine in water, 0.1 N HCl and 0.1 N NaOH to all be greater than 4.80 x 10<sup>-2</sup> mol dm<sup>-3</sup>, (units - evaluator).

All these values for solubility in both aqueous and non aqueous solvents have an estimated precision of  $\pm$  5% (evaluator). Because of the unstated purity of the sample, and since the values reported are unconfirmed, these solubilities are designated as being highly tentative, except for where the solubility is reported as being greater than 4.80 x 10<sup>-2</sup> mol dm<sup>-3</sup>, (which are regarded as being doubtful).

## REFERENCES

- (1) Marsh, J.R.; Weiss, P.J. *J. Ass. Offic. Anal. Chem.* 1967, 50, 457.  
 (2) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* 1957, 7, 374.

<b>COMPONENTS:</b> (1) Pyridinium,1-[[2-carboxy-8-oxo-7-[2-thienyl-acetyl]amino-5-Thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]methyl]-hydroxide, inner salt, (6R-trans) Cephaloridine; C <sub>19</sub> H <sub>17</sub> N <sub>3</sub> O <sub>4</sub> S <sub>2</sub> ; [50-59-9] (2) Water; H <sub>2</sub> O; [7732-18-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. 1967, 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of cephaloridine in water at 21±1°C was reported as greater than:          20 mg cm<sup>-3</sup>. (Greater than 4.8 x 10<sup>-2</sup> mol dm<sup>-3</sup> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  Ten cm <sup>3</sup> of water were added to about 200 mg of the antibiotic in a 15 cm <sup>3</sup> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (21±1°C). If all of the material appeared to be in solution, the solubility was considered to be greater than 20 mg cm <sup>-3</sup> .	<b>SOURCE AND PURITY OF MATERIALS:</b>  Cephaloridine sodium was provided by Eli Lilly and Co.; its purity was not specified.  The water was probably of U.S.P. or A.C.S. grade.  <b>ESTIMATED ERROR:</b>  Solubility precision: none specified Temperature precision: ±1°C (authors).  <b>REFERENCES:</b>





<b>COMPONENTS:</b> (1) Pyridinium,1-[[2-carboxy-8-oxo-7-[2-thienyl-acetyl]amino-5-Thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]methyl]-hydroxide, inner salt, (6R-trans) Cephaloridine; $C_{19}H_{17}N_3O_4S_2$ ; [50-59-9] (2) Methanol; $CH_4O$ ; [67-56-1]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. 1967, 50, 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p style="text-align: center;">Solubility of cephaloridine in methanol at <math>21 \pm 1^\circ C</math> was reported as:  <math>2.912 \text{ mg cm}^{-3}</math>. (<math>7.009 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Cephaloridine sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Methanol was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ C</math> (authors).</p>
	<b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> 1957, 7, 374-7.

<p>COMPONENTS:</p> <p>(1) Pyridinium,1-[[2-carboxy-8-oxo-7-[2-thienyl-acetyl]amino-5-Thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]methyl]-hydroxide, inner salt, (6R-trans) Cephaloridine; <math>C_{19}H_{17}N_3O_4S_2</math>; [50-59-9]</p> <p>(2) Ethanol; <math>C_2H_6O</math>; [64-17-5]</p>	<p>ORIGINAL MEASUREMENTS: Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY: A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephaloridine in ethanol at <math>21 \pm 1^\circ\text{C}</math> was reported as: 1.950 mg <math>\text{cm}^{-3}</math>. (<math>4.693 \times 10^{-3}</math> mol <math>\text{dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1</math> mg) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1</math> mg). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01</math> mg) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01</math> mg) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephaloridine sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Ethanol was probably of U.S.P. or A.C.S. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES.</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>



<p>COMPONENTS:</p> <p>(1) Pyridinium,1-[[2-carboxy-8-oxo-7-[2-thienyl-acetyl]amino-5-Thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]methyl]-hydroxide, inner salt, (6R-trans) Cephaloridine; <math>C_{19}H_{17}N_3O_4S_2</math>; [50-59-9]</p> <p>(2) 1-Butanol,3-methyl- (isoamyl alcohol); <math>C_5H_{12}O</math>; [123-51-3]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephaloridine in isoamyl alcohol at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.322 \text{ mg cm}^{-3}</math>. (<math>7.750 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephaloridine sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Isoamyl alcohol was probably of A.C.S. or U.S.P. grade (1).</p>
	<p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>

<b>COMPONENTS:</b> (1) Pyridinium,1-[[2-carboxy-8-oxo-7-[2-thienyl-acetyl]amino-5-Thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]methyl]-hydroxide, inner salt, (6R-trans) Cephaloridine; $C_{19}H_{17}N_3O_4S_2$ ; [50-59-9] (2) Cyclohexane; $C_6H_{12}$ ; [110-82-7]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b> One temperature: 21°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of cephaloridine in cyclohexane at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.060 \text{ mg cm}^{-3}</math>. (<math>1.444 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Cephaloridine sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Cyclohexane was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>





<p>COMPONENTS:</p> <p>(1) Pyridinium,1-[[2-carboxy-8-oxo-7-[2-thienyl-acetyl]amino-5-Thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]methyl]-hydroxide, inner salt, (6R-trans) Cephaloridine; <math>C_{19}H_{17}N_3O_4S_2</math>; [50-59-9]</p> <p>(2) Pentane,2,2,4-trimethyl- (isooctane); <math>C_8H_{18}</math>; [540-84-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1967</u>, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephaloridine in isooctane at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.050 \text{ cm}^{-3}</math>. (<math>1.203 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephaloridine sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Isooctane was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <b>Antibiotics and Chemotherapy</b> <u>1957</u>, 7, 374-7.</p>

<b>COMPONENTS:</b> (1) Pyridinium,1-[[2-carboxy-8-oxo-7-[2-thienyl-acetyl]amino-5-Thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]methyl]-hydroxide, inner salt, (6R-trans) Cephaloridine; $C_{19}H_{17}N_3O_4S_2$ ; [50-59-9] (2) Methane, tetrachloro- (carbon tetrachloride); $CCl_4$ ; [56-23-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u> , <b>50</b> , 457-62.
<b>VARIABLES:</b>  One temperature: 21°C	<b>PREPARED BY:</b>  A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of cephaloridine in carbon tetrachloride at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.052 \text{ mg cm}^{-3}</math>. (<math>1.251 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Cephaloridine sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Carbon tetrachloride was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b>  <p>Solubility precision: none specified          Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>







<p>COMPONENTS:</p> <p>(1) Pyridinium,1-[[2-carboxy-8-oxo-7-[2-thienyl-acetyl]amino-5-Thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]methyl]-hydroxide, inner salt, (6R-trans) Cephaloridine; <math>C_{19}H_{17}N_3O_4S_2</math>; [50-59-9]</p> <p>(2) 2-Butanone (methyl ethyl ketone); <math>C_4H_8O</math>; [78-93-3]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <i>50</i>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephaloridine in methyl ethyl ketone at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.110 \text{ mg cm}^{-3}</math>. (<math>2.647 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephaloridine sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Methyl ethyl ketone was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <i>7</i>, 374-7.</p>



<p>COMPONENTS:</p> <p>(1) Pyridinium,1-[[2-carboxy-8-oxo-7-[2-thienyl-acetyl]amino-5-Thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]methyl]-hydroxide, inner salt, (6R-trans) Cephaloridine; <math>C_{19}H_{17}N_3O_4S_2</math>; [50-59-9]</p> <p>(2) Ethane,dichloro- (ethylene chloride); <math>C_2H_4Cl_2</math>; [1300-21-6]</p>	<p>ORIGINAL MEASUREMENTS: Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephaloridine in ethylene chloride at <math>21 \pm 1^\circ\text{C}</math> was reported as: <math>0.120 \text{ mg cm}^{-3}</math>. (<math>2.888 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephaloridine sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Ethylene chloride was probably of A.C.S. or U.S.P. grade (1).</p>
	<p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p>
	<p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>





<p>COMPONENTS:</p> <p>(1) Pyridinium,1-[[2-carboxy-8-oxo-7-[2-thienyl-acetyl]amino-5-Thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]methyl]-hydroxide, inner salt, (6R-trans) Cephaloridine; C<sub>19</sub>H<sub>17</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub>; [50-59-9]</p> <p>(2) Carbon disulfide; CS<sub>2</sub>; [75-15-0]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <u>50</u>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephaloridine in carbon disulfide at 21 ± 1°C was reported as:  0.020 mg cm<sup>-3</sup>. (4.813 x 10<sup>-5</sup> mol dm<sup>-3</sup> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten cm<sup>3</sup> of solvent were added to about 200 mg of the antibiotic in a 15 cm<sup>3</sup> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (21 ± 1°C). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 cm<sup>3</sup> of the clear filtrate were added to a tared (± 0.1 mg) weighing bottle and evaporated at 100°C. The residue was further dried for 3 hr at 60°C in a vacuum oven. After cooling, the residue was reweighed (± 0.1 mg). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (± 0.01 mg) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (± 0.01 mg) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephaloridine sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Carbon disulfide was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: ± 1°C (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <u>7</u>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) Pyridinium,1-[[2-carboxy-8-oxo-7-[2-thienyl-acetyl]amino-5-Thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]methyl]-hydroxide, inner salt, (6R-trans) Cephaloridine; <math>C_{19}H_{17}N_3O_4S_2</math>; [50-59-9]</p> <p>(2) Pyridine; <math>C_6H_5N</math>; [110-86-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1967</u>, <b>50</b>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephaloridine in pyridine at <math>21 \pm 1^\circ\text{C}</math> was reported as:  <math>0.740 \text{ mg cm}^{-3}</math>. (<math>1.781 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>21 \pm 1^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephaloridine sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Pyridine was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>





<p>COMPONENTS:</p> <p>(1) Pyridinium,1-[[2-carboxy-8-oxo-7-[2-thienyl-acetyl]amino-5-Thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]methyl]-hydroxide, inner salt, (6R-trans) Cephaloridine; <math>C_{19}H_{17}N_3O_4S_2</math>; [50-59-9]</p> <p>(2) 1,2-Propanediol (propylene glycol); <math>C_3H_8O_2</math>; [57-55-6]</p>	<p>ORIGINAL MEASUREMENTS: Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. 1967, 50, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY: A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephaloridine in propylene glycol at <math>21 \pm 1^\circ\text{C}</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.8 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ\text{C}</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephaloridine sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Propylene glycol was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p>

<p>COMPONENTS:</p> <p>(1) Pyridinium,1-[[2-carboxy-8-oxo-7-[2-thienyl-acetyl]amino-5-Thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]methyl]-hydroxide, inner salt, (6R-trans) Cephaloridine; <math>C_{19}H_{17}N_3O_4S_2</math>; [50-59-9]</p> <p>(2) Methane,sulfinylbis- (dimethyl sulfoxide); <math>C_2H_6OS</math>; [67-68-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1967</b>, <i>50</i>, 457-62.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cephaloridine in dimethyl sulfoxide at <math>21 \pm 1^\circ\text{C}</math> was reported as greater than: <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>4.8 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>21 \pm 1^\circ\text{C}</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cephaloridine sodium was provided by Eli Lilly and Co.; its purity was not specified.</p> <p>Dimethyl sulfoxide was probably of A.C.S. or U.S.P. grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: <math>\pm 1^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p>

<b>COMPONENTS:</b> (1) Pyridinium,4-(aminocarbonyl)-1[[2-carboxy-8-oxo-7-[phenylsulfoacetyl]amino]-5-Thia-1-aza-bicyclo[4,2,0]oct-2-en-3-yl]-methyl]-hydroxide, inner salt, monosodium salt (cefsulodin sodium); $C_{22}H_{19}N_4O_8S_2Na$ ; [52152-93-9] (2) All solvents	<b>EVALUATOR:</b> Eric Tomlinson. Department of Pharmacy, University of Amsterdam, The Netherlands. December 1983.
<b>CRITICAL EVALUATION:</b>  Aoki et al (1) have studied the solubility of cefsulodin sodium in buffered aqueous solutions as well as in various non aqueous solvents at 294 K (units - evaluator). The sample studied was of known purity as determined by a microbiological method. The procedure for determining the solubilities was not described, though the assay procedure was given as a microbiological one. The reported aqueous solubilities at three pHs can be obtained from the appropriate compilation sheets. These values are regarded as being <b>doubtful</b> , due to the lack of a described procedure and values from other studies.  A similar designation can be given to the similarly reported value for the solubility in methanol ( $4.0 \times 10^{-3}$ mol dm <sup>-3</sup> ). However, the value of greater than $1.8 \times 10^{-2}$ mol dm <sup>-3</sup> which Aoki et al report for solubility in either acetone, ethyl acetate, chloroform, or hexane, must be regarded as being <b>highly doubtful</b> .  <b>REFERENCE</b>  (1) Aoki, I.; Konishi, E.; Kuwayama, N. <i>Iyakuin Kenkyu</i> <u>1978</u> , <b>9</b> , 1022.	

<p>COMPONENTS:</p> <p>(1) Pyridinium,4-(aminocarbonyl)-1[[[2-carboxy-8-oxo-7-[(phenylsulfoacetyl)amino]-5-Thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-methyl]-hydroxide, inner salt, monosodium salt (Cefsulodin sodium); <math>C_{22}H_{19}N_4O_8S_2Na</math>; [52152-93-9]</p> <p>(2) 1,2,3-Propanetricarboxylic acid, 2-hydroxy (citric acid); <math>C_6H_8O_7</math>; [77-92-9]</p> <p>(3) Phosphoric acid, disodium salt; <math>HNa_2O_4P</math>; [7558-79-4]</p> <p>(4) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Aoki, I.; Konishi, E.; Kuwayama, N. <i>Iyakuhin Kenkyu</i> <u>1978</u>, <b>9</b>, 1022-30.</p>																
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>																
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of Cefsulodin sodium in buffered aqueous solutions at 21°C was reported as:</p> <table border="1" data-bbox="206 629 1079 799"> <thead> <tr> <th>pH</th> <th>Solvent <math>cm^3</math>/solute 1 g</th> <th><math>10^1</math> mol <math>dm^{-3}</math><sup>a</sup></th> <th>mg <math>cm^{-3}</math><sup>a</sup></th> </tr> </thead> <tbody> <tr> <td>2.2</td> <td>70</td> <td>0.26</td> <td>14.3</td> </tr> <tr> <td>4.2</td> <td>2.5</td> <td>7.21</td> <td>400.0</td> </tr> <tr> <td>6.4</td> <td>2.2</td> <td>8.20</td> <td>454.5</td> </tr> </tbody> </table> <p><sup>a</sup> Calculated by compiler</p>		pH	Solvent $cm^3$ /solute 1 g	$10^1$ mol $dm^{-3}$ <sup>a</sup>	mg $cm^{-3}$ <sup>a</sup>	2.2	70	0.26	14.3	4.2	2.5	7.21	400.0	6.4	2.2	8.20	454.5
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2.2	70	0.26	14.3														
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<p>AUXILIARY INFORMATION</p>																	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Procedure was not described. McIlvaine buffer solutions were used for solubility test (0.1 mol <math>dm^{-3}</math> citric acid and 0.2 mol <math>dm^{-3}</math> <math>Na_2HPO_4</math> was mixed and adjusted to pH 2.2, 4.2, and 6.4). The amount of the dissolved antibiotic was determined microbiologically.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cefsulodin sodium was synthesized in the Central Research Division of Takeda Chemical Industries, Ltd. Osaka, Japan. Its potency was determined by a plate cylinder method to be 933 <math>\mu g</math> <math>mg^{-1}</math>. The moisture content was 6.5% determined by Karl-Fischer method.</p> <p>All chemicals used were of analytical grade.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: probably <math>\pm 1^\circ C</math> (compiler)</p> <p>REFERENCES:</p>																

<p>COMPONENTS:</p> <p>(1) Pyridinium,4-(aminocarbonyl)-1[[[2-carboxy-8-oxo-7-[(phenylsulfoacetyl)amino]-5-Thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-methyl]-hydroxide, inner salt, monosodium salt (Cefsulodin sodium); <math>C_{22}H_{19}N_4O_8S_2Na</math>; [52152-93-9]</p> <p>(2) Methanol; <math>CH_4O</math>; [67-56-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Aoki, I.; Konishi, E.; Kuwayama, N. <i>Iyakuhin Kenkyu</i> <u>1978</u>, <b>9</b>, 1022-30.</p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of Cefsulodin sodium in methanol at 21°C was reported as:  <math>450 \text{ cm}^3 \cdot \text{g}^{-1}</math>. (<math>2.2 \text{ mg cm}^{-3}</math>; <math>4.0 \times 10^{-3} \text{ mol dm}^{-3}</math> - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Nothing specified. The amount of the dissolved solute was determined microbiologically.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cefsulodin sodium was synthesized in the Central Research Division of Takeda Chemical Industries, Ltd. Osaka, Japan. Its potency was determined by a plate cylinder method to be <math>933 \mu\text{g mg}^{-1}</math>. The moisture content was 6.5% determined by Karl-Fischer method.</p> <p>Methanol was of special grade (Wako Pure Chemical Industries, Ltd, Japan).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: probably <math>\pm 1^\circ\text{C}</math> (compiler)</p> <p>REFERENCES:</p>







<p>COMPONENTS:</p> <p>(1) Pyridinium,4-(aminocarbonyl)-1[[[2-carboxy-8-oxo-7-[(phenylsulfoacetyl)amino]-5-Thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-methyl]-hydroxide, inner salt, monosodium salt (Cefsulodin sodium); <math>C_{22}H_{19}N_4O_8S_2Na</math>; [52152-93-9]</p> <p>(2) Hexane; <math>C_6H_{14}</math>; [110-54-3]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Aeki, I.; Konishi, E.; Kuwayama, N. <i>Iyakuin Kenkyu</i> <u>1978, 9, 1022-30.</u></p>
<p>VARIABLES:</p> <p>One temperature: 21°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of Cefsulodin sodium in hexane at 21°C was reported as greater than:  <math>100 \text{ cm}^3 \cdot \text{g}^{-1}</math>. (<math>&lt;10 \text{ mg cm}^{-3}</math>; <math>&lt;1.8 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Nothing specified. The amount of the dissolved antibiotic was determined microbiologically.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cefsulodin sodium was synthesized in the Central Research Division of Takeda Chemical Industries, Ltd. Osaka, Japan. Its potency was determined by a plate cylinder method to be <math>933 \mu\text{g mg}^{-1}</math>. The moisture content was 6.5% determined by Karl-Fischer method.</p> <p>Hexane was of special grade (Wako Pure Chemical Industries, Ltd. Japan).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: probably <math>\pm 1^\circ\text{C}</math> (compiler)</p> <p>REFERENCES:</p>

## COMPONENTS:

- (1) 3-Isoxazolidinone,4-amino- (cycloserine);  
 $C_3H_6N_2O_2$ ; [68-41-7]  
 (2) All solvents

## EVALUATOR:

Eric Tomlinson,  
 Department of Pharmacy,  
 University of Amsterdam,  
 The Netherlands.  
 December 1983.

## CRITICAL EVALUATION:

Marsh and Weiss have determined the solubilities of cycloserine in 24 different solvents at  $301 \pm 4$  K (1). These workers studied a sample provided by Commercial Solvents Corp., its purity and optical rotation were not specified. The amount of cycloserine dissolved was estimated by either drying a solution to constant weight, or, with some solvents, by visual examination, such that no evidence of undissolved solute indicated a solubility of greater than  $20 \text{ mg cm}^{-3}$ . All values reported were uncorrected for solvent blank, which was generally less than  $0.05 \text{ mg total}$ . All data according to Marsh and Weiss have been recalculated to SI units (evaluator). Solubilities are given in the Table.

Solvent <sup>a</sup>	Solubility (at $301 \pm 4$ K), ( $\text{mol dm}^{-3}$ ) <sup>b</sup>
water	<sup>c</sup>
methanol	$1.91 \times 10^{-2}$
ethanol	$4.41 \times 10^{-3}$
isopropanol	$4.90 \times 10^{-3}$
isoamyl alcohol	$3.04 \times 10^{-4}$
cyclohexane	$2.64 \times 10^{-4}$
benzene	$4.60 \times 10^{-4}$
toluene	$2.94 \times 10^{-4}$
ligroin	$1.95 \times 10^{-4}$
isooctane	0
carbon tetrachloride	$2.0 \times 10^{-5}$
ethyl acetate	$3.43 \times 10^{-3}$
isoamyl acetate	$6.85 \times 10^{-4}$
acetone	$8.33 \times 10^{-3}$
methyl ethyl ketone	$4.41 \times 10^{-3}$
diethylether	$4.47 \times 10^{-3}$
ethylene chloride	$5.87 \times 10^{-4}$
1,4-dioxane	$4.41 \times 10^{-3}$
chloroform	$6.56 \times 10^{-4}$
carbon disulfide	0
pyridine	$8.82 \times 10^{-3}$
formamide	$1.57 \times 10^{-2}$
ethylene glycol	$1.47 \times 10^{-2}$
benzyl alcohol	$9.79 \times 10^{-3}$

(<sup>a</sup> All solvents are probably of U.S.P. or A.C.S. grade as previous (2); <sup>b</sup> units calculated by evaluator; <sup>c</sup> solubility greater than  $1.9 \times 10^{-1} \text{ mol dm}^{-3}$ ).

All these values for solubility in both aqueous and non aqueous solvents have an estimated precision of  $\pm 5\%$  (evaluator). Because of the unstated purity of the sample, and since the values reported are unconfirmed, these solubilities are designated as being highly **tentative**, except for where the solubility is reported as being greater than  $1.9 \times 10^{-1} \text{ mol dm}^{-3}$ , (which are regarded as being **doubtful**). The value reported as being  $0 \text{ mol dm}^{-3}$  is **rejected** since the sensitivity of the assay used is not sufficient for this value to be viewed with any certainty.

One other study on the solubility of cycloserine has been reported. Yakhontova et al (3) examined the solubility of D-cycloserine of known purity, and reported values at  $298.2 \pm 0.2$  K (units and precision - evaluator) for solubility in ethanol ( $4.90 \times 10^{-3} \text{ mol dm}^{-3}$  - units, evaluator), and in water-ethanol-isopropanol mixtures at  $253.2 \pm 0.2$ ,  $273.2 \pm 0.2$ , and  $298.2 \pm 0.2$  K. The value reported in ethanol alone is estimated as having a precision of  $\pm 5$  percent and is designated as **tentative**. Values for the water-ethanol-isopropanol mixture were reported only graphically, and are difficult to estimate from the original publication.

## REFERENCES

- (1) Marsh, J.R.; Weiss, P.J. *J. Ass. Offic. Anal. Chem.* **1959**, *9*, 277.
- (2) Weiss, P.J.; Andrew, M.L.; Wright, W.W. *Antibiotics and Chemotherapy* **1957**, *7*, 374.
- (3) Yakhontova, L.F.; Bruns, B.P.; Kartseva, V.D.; Kobzova, S.N.; Perevozskaya, N.A. *Antibiotiki, (Moscow)* **1969**, *14*, 205.

<p>COMPONENTS:</p> <p>(1) 3-Isoxazolidinone,4-amino- (cycloserine);  <math>C_3H_6N_2O_2</math>; [68-41-7]</p> <p>(2) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1959</u>, <b>9</b>, 277-9.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cycloserine in water at <math>28 \pm 4^\circ C</math> was reported as greater than:  <math>20 \text{ mg cm}^{-3}</math>. (Greater than <math>1.9 \times 10^{-1} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temperature (<math>28 \pm 4^\circ C</math>). If all of the material appeared to be in solution, the solubility was considered to be greater than <math>20 \text{ mg cm}^{-3}</math>.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>Water was probably of U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 3-Isoxazolidinone,4-amino- (cycloserine);  <math>C_3H_6N_2O_2</math>; [68-41-7]</p> <p>(2) Methanol; <math>CH_4O</math>; [67-56-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1959</u>, <b>9</b>, 277-9.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cycloserine in methanol at <math>28 \pm 4^\circ C</math> was reported as:  <math>1.95 \text{ mg cm}^{-3}</math>. (<math>1.91 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>Methanol was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 3-Isoxazolidinone,4-amino- (cycloserine); C<sub>3</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub>; [68-41-7]</p> <p>(2) Ethanol; C<sub>2</sub>H<sub>6</sub>O; [64-17-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1959</b>, <i>9</i>, 277-9.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cycloserine in ethanol at 28 ± 4°C was reported as: 0.45 mg cm<sup>-3</sup>. (4.41 × 10<sup>-3</sup> mol dm<sup>-3</sup> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten cm<sup>3</sup> of solvent were added to about 200 mg of the antibiotic in a 15 cm<sup>3</sup> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (28 ± 4°C). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 cm<sup>3</sup> of the clear filtrate were added to a tared (± 0.1 mg) weighing bottle and evaporated at 100°C. The residue was further dried for 3 hr at 60°C in a vacuum oven. After cooling, the residue was reweighed (± 0.1 mg). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (± 0.01 mg) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (± 0.01 mg) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>Ethanol was probably of U.S.P. or A.C.S. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: ± 4°C (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <b>1957</b>, <i>7</i>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 3-Isoxazolidinone,4-amino- (cycloserine);  <math>C_3H_6N_2O_2</math>; [68-41-7]</p> <p>(2) 2-propanol (isopropanol); <math>C_3H_8O</math>; [67-63-0]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1959</u>, <b>9</b>, 277-9.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cycloserine in isopropanol at <math>28 \pm 4^\circ C</math> was reported as:  <math>0.50 \text{ mg cm}^{-3}</math>. (<math>4.90 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>Isopropanol was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 3-Isloxazolidinone,4-amino- (cycloserine);  <math>C_3H_6N_2O_2</math>; [68-41-7]</p> <p>(2) 1-Butanol, 3-methyl- (isoamyl alcohol);  <math>C_5H_{12}O</math>; [123-51-3]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1959</u>, 9, 277-9.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cycloserine in isoamyl alcohol at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.31 \text{ mg cm}^{-3}</math>. (<math>3.04 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>Isoamyl alcohol was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <b>Antibiotics and Chemotherapy</b> <u>1957</u>, 7, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 3-Isoxazolidinone,4-amino- (cycloserine); C<sub>3</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub>; [68-41-7]</p> <p>(2) Cyclohexane; C<sub>6</sub>H<sub>12</sub>; [110-82-7]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1959</u>, 9, 277-9.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cycloserine in cyclohexane at 28 ± 4°C was reported as: 0.027 mg cm<sup>-3</sup>. (2.64 x 10<sup>-4</sup> mol dm<sup>-3</sup> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten cm<sup>3</sup> of solvent were added to about 200 mg of the antibiotic in a 15 cm<sup>3</sup> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (28 ± 4°C). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 cm<sup>3</sup> of the clear filtrate were added to a tared (± 0.1 mg) weighing bottle and evaporated at 100°C. The residue was further dried for 3 hr at 60°C in a vacuum oven. After cooling, the residue was reweighed (± 0.1 mg). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (± 0.01 mg) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (± 0.01 mg) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>Cyclohexane was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: ± 4°C (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <u>Antibiotics and Chemotherapy</u> <u>1957</u>, 7, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 3-Isoxazolidinone,4-amino- (cycloserine);  <math>C_3H_6N_2O_2</math>; [68-41-7]</p> <p>(2) Benzene; <math>C_6H_6</math>; [71-43-2]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1959</u>, 9, 277-9.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cycloserine in benzene at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.047 \text{ mg cm}^{-3}</math>. (<math>4.60 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>Benzene was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <u>Antibiotics and Chemotherapy</u> <u>1957</u>, 7, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 3-Isoxazolidinone,4-amino- (cycloserine); C<sub>3</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub>; [68-41-7]</p> <p>(2) Benzene, methyl- (toluene); C<sub>7</sub>H<sub>8</sub>; [108-88-3]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1959</u>, 9, 277-9.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cycloserine in toluene at 28 ± 4°C was reported as: 0.030 mg cm<sup>-3</sup>. (2.94 × 10<sup>-4</sup> mol dm<sup>-3</sup> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten cm<sup>3</sup> of solvent were added to about 200 mg of the antibiotic in a 15 cm<sup>3</sup> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (28 ± 4°C). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 cm<sup>3</sup> of the clear filtrate were added to a tared (± 0.1 mg) weighing bottle and evaporated at 100°C. The residue was further dried for 3 hr at 60°C in a vacuum oven. After cooling, the residue was reweighed (± 0.1 mg). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (± 0.01 mg) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (± 0.01 mg) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>Toluene was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: ± 4°C (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 3-Isoxazolidinone,4-amino- (cycloserine);  <math>C_3H_6N_2O_2</math>; [68-41-7]  (2) Petroleum ether (ligroin)</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1959</u>, <b>9</b>, 277-9.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cycloserine in ligroin at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.020 \text{ mg cm}^{-3}</math>. (<math>1.95 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>Ligroin was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>



<b>COMPONENTS:</b> (1) 3-Isoxazolidinone,4-amino- (cycloserine); $C_3H_6N_2O_2$ ; [68-41-7] (2) Methane, tetrachloro- (carbon tetrachloride); $CCl_4$ ; [56-23-5]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1959</u> , 9, 277-9.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of cycloserine in carbon tetrachloride at <math>28 \pm 4^\circ C</math> was reported as:  <math>0.002 \text{ mg cm}^{-3}</math>. (<math>1.95 \times 10^{-5} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>Carbon tetrachloride was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <b>REFERENCES.</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 3-Isoxazolidinone,4-amino- (cycloserine); C<sub>3</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub>; [68-41-7]</p> <p>(2) Acetic acid,ethyl ester (ethyl acetate); C<sub>4</sub>H<sub>8</sub>O<sub>2</sub>; [141-78-6]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1959</u>, 9, 277-9.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cycloserine in ethyl acetate at 28 ± 4°C was reported as: 0.35 mg cm<sup>-3</sup>. (3.43 x 10<sup>-3</sup> mol dm<sup>-3</sup> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten cm<sup>3</sup> of solvent were added to about 200 mg of the antibiotic in a 15 cm<sup>3</sup> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (28 ± 4°C). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 cm<sup>3</sup> of the clear filtrate were added to a tared (± 0.1 mg) weighing bottle and evaporated at 100°C. The residue was further dried for 3 hr at 60°C in a vacuum oven. After cooling, the residue was reweighed (± 0.1 mg). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (± 0.01 mg) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (± 0.01 mg) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: ± 4°C (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <b>Antibiotics and Chemotherapy</b> <u>1957</u>, 7, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 3-Isoxazolidinone,4-amino- (cycloserine); <math>C_3H_6N_2O_2</math>; [68-41-7]</p> <p>(2) 1-Butanol, 3-methyl acetate (isoamyl acetate); <math>C_7H_{14}O_2</math>; [123-92-2]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1959</u>, <b>9</b>, 277-9.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cycloserine in isoamyl acetate at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.070 \text{ mg cm}^{-3}</math>. (<math>6.85 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>Isoamyl acetate was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 3-Isoxazolidinone,4-amino- (cycloserine); <math>C_3H_6N_2O_2</math>; [68-41-7]</p> <p>(2) 2-Propanone (acetone); <math>C_3H_6O</math>; [67-64-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1959</u>, <b>9</b>, 277-9.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cycloserine in acetone at <math>28 \pm 4^\circ\text{C}</math> was reported as:  <math>0.85 \text{ mg cm}^{-3}</math>. (<math>8.33 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ\text{C}</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ\text{C}</math>. The residue was further dried for 3 hr at <math>60^\circ\text{C}</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>Acetone was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 4^\circ\text{C}</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<b>COMPONENTS:</b> (1) 3-Isloxazolidinone,4-amino- (cycloserine); $C_3H_6N_2O_2$ ; [68-41-7] (2) 2-Butanone (methyl ethyl ketone); $C_4H_8O$ ; [78-53-3]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1959</u> , <b>9</b> , 277-9.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of cycloserine in methyl ethyl ketone at $28 \pm 4^\circ C$ was reported as: $0.45 \text{ mg cm}^{-3}$ . ( $4.41 \times 10^{-3} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>Methyl ethyl ketone was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>

<b>COMPONENTS:</b> (1) 3-Isoxazolidinone,4-amino- (cycloserine); $C_3H_6N_2O_2$ ; [68-41-7] (2) Ethane,1,1'-oxybis- (diethyl ether); $C_4H_{10}O$ ; [60-29-7]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1959</u> , 9, 277-9.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of cycloserine in diethyl ether at <math>28 \pm 4^\circ C</math> was reported as:  <math>0.457 \text{ mg cm}^{-3}</math>. (<math>4.47 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>Diethyl ether was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 4^\circ C</math> (authors).</p>
	<b>REFERENCES:</b> (1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <u>Antibiotics and Chemotherapy</u> <u>1957</u> , 7, 374-7.

<b>COMPONENTS:</b> (1) 3-Isoxazolidinone,4-amino- (cycloserine); $C_3H_6N_2O_2$ ; [68-41-7] (2) Ethane,dichloro- (ethylene chloride); $C_2H_4Cl_2$ ; [1300-21-6]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1959</u> , 9, 277-9.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of cycloserine in ethylene chloride at <math>28 \pm 4^\circ C</math> was reported as:  <math>0.060 \text{ mg cm}^{-3}</math>. (<math>5.87 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b>  <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b>  <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>Ethylene chloride was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 3-Isoxazolidinone,4-amino- (cycloserine);  <math>C_3H_6N_2O_2</math>; [68-41-7]</p> <p>(2) 1,4-Dioxane; <math>C_4H_8O_2</math>; [123-91-1]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1959</u>, 9, 277-9.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cycloserine in 1,4-dioxane at 28 ± 4°C was reported as:  <math>0.45 \text{ mg cm}^{-3}</math>. (<math>4.41 \times 10^{-3} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (28 ± 4°C). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 <math>\text{cm}^3</math> of the clear filtrate were added to a tared (± 0.1 mg) weighing bottle and evaporated at 100°C. The residue was further dried for 3 hr at 60°C in a vacuum oven. After cooling, the residue was reweighed (± 0.1 mg). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (± 0.01 mg) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (± 0.01 mg) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>1,4-Dioxane was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: ± 4°C (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, 7, 374-7.</p>

<b>COMPONENTS:</b> (1) 3-Isoxazolidinone,4-amino- (cycloserine); $C_3H_6N_2O_2$ ; [68-41-7] (2) Methane, trichloro- (chloroform); $CHCl_3$ ; [67-66-3]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <b>1959</b> , <i>9</i> , 277-9.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  <p>Solubility of cycloserine in chloroform at <math>28 \pm 4^\circ C</math> was reported as:  <math>0.067 \text{ mg cm}^{-3}</math>. (<math>6.56 \times 10^{-4} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>Chloroform was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <b>1957</b>, <i>7</i>, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 3-Isoxazolidinone,4-amino- (cycloserine);  <math>C_3H_6N_2O_2</math>; [68-41-7]</p> <p>(2) Carbon disulfide; <math>CS_2</math>; [75-15-0]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1959</u>, <b>9</b>, 277-9.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cycloserine in carbon disulfide at <math>28 \pm 4^\circ C</math> was reported as:  <math>0 \text{ mg cm}^{-3}</math>. (<math>0 \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>Carbon disulfide was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>



<p>COMPONENTS:</p> <p>(1) 3-Isoxazolidinone,4-amino- (cycloserine);  <math>C_3H_6N_2O_2</math>; [68-41-7]</p> <p>(2) Formamide; <math>CH_3NO</math>; [75-12-7]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1959</u>, 9, 277-9.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cycloserine in formamide at <math>28 \pm 4^\circ C</math> was reported as:  <math>1.60 \text{ mg cm}^{-3}</math>. (<math>1.57 \times 10^{-2} \text{ mol dm}^{-3}</math> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a <math>15 \text{ cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and <math>2 \text{ cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>Formamide was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified  Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <u>Antibiotics and Chemotherapy</u> <u>1957</u>, 7, 374-7.</p>

<b>COMPONENTS:</b> (1) 3-Isoxazolidinone,4-amino- (cycloserine); $C_3H_6N_2O_2$ ; [68-41-7] (2) Ethanol, 2-methoxy- (ethylene glycol monomethyl ether); $C_3H_8O_2$ ; [109-86-4]	<b>ORIGINAL MEASUREMENTS:</b> Marsh, J.R.; Weiss, P.J. J. Ass. Offic. Anal. Chem. <u>1959</u> , 9, 277-9.
<b>VARIABLES:</b> One temperature: 28°C	<b>PREPARED BY:</b> A. Regosz
<b>EXPERIMENTAL VALUES:</b>  Solubility of cycloserine in ethylene glycol monomethyl ether at $28 \pm 4^\circ C$ was reported as: $1.50 \text{ mg cm}^{-3}$ . ( $1.47 \times 10^{-2} \text{ mol dm}^{-3}$ solution - compiler).	
<b>AUXILIARY INFORMATION</b>	
<b>METHOD APPARATUS/PROCEDURE:</b> <p>Ten <math>\text{cm}^3</math> of solvent were added to about 200 mg of the antibiotic in a 15 <math>\text{cm}^3</math> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (<math>28 \pm 4^\circ C</math>). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 <math>\text{cm}^3</math> of the clear filtrate were added to a tared (<math>\pm 0.1 \text{ mg}</math>) weighing bottle and evaporated at <math>100^\circ C</math>. The residue was further dried for 3 hr at <math>60^\circ C</math> in a vacuum oven. After cooling, the residue was reweighed (<math>\pm 0.1 \text{ mg}</math>). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (<math>\pm 0.01 \text{ mg}</math>) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (<math>\pm 0.01 \text{ mg}</math>) was repeated.</p>	<b>SOURCE AND PURITY OF MATERIALS:</b> <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>Ethylene glycol monomethyl ether was probably of A.C.S. or U.S.P. grade (1).</p> <b>ESTIMATED ERROR:</b> <p>Solubility precision: none specified          Temperature precision: <math>\pm 4^\circ C</math> (authors).</p> <b>REFERENCES:</b> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <u>Antibiotics and Chemotherapy</u> <u>1957</u>, 7, 374-7.</p>

<p>COMPONENTS:</p> <p>(1) 3-Isoxazolidinone,4-amino- (cycloserine); C<sub>3</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub>; [68-41-7]</p> <p>(2) Benzenemethanol (benzyl alcohol); C<sub>7</sub>H<sub>8</sub>O; [100-51-6]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Marsh, J.R.; Weiss, P.J. <i>J. Ass. Offic. Anal. Chem.</i> <u>1959</u>, <b>9</b>, 277-9.</p>
<p>VARIABLES:</p> <p>One temperature: 28°C</p>	<p>PREPARED BY:</p> <p>A. Regosz</p>
<p>EXPERIMENTAL VALUES:</p> <p>Solubility of cycloserine in benzyl alcohol at 28 ± 4°C was reported as: 1.00 mg cm<sup>-3</sup>. (9.79 × 10<sup>-3</sup> mol dm<sup>-3</sup> solution - compiler).</p>	
<p>AUXILIARY INFORMATION</p>	
<p>METHOD APPARATUS/PROCEDURE:</p> <p>Ten cm<sup>3</sup> of solvent were added to about 200 mg of the antibiotic in a 15 cm<sup>3</sup> glass-stoppered test tube and shaken thoroughly by hand for about 2 min at room temp (28 ± 4°C). If there was any visible insoluble material the suspension was centrifuged within an hour. After centrifugation, the clear part of the soln was filtered under vacuum and 2 cm<sup>3</sup> of the clear filtrate were added to a tared (± 0.1 mg) weighing bottle and evaporated at 100°C. The residue was further dried for 3 hr at 60°C in a vacuum oven. After cooling, the residue was reweighed (± 0.1 mg). If the residue was 0.5 mg or less, a second aliquot of clear filtrate was placed in a tared (± 0.01 mg) weighing bottle, and the procedure of evaporation, drying, cooling and reweighing (± 0.01 mg) was repeated.</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Cycloserine was provided by Commercial Solvents Corp., its purity and optical rotation were not described.</p> <p>Benzyl alcohol was probably of A.C.S. or U.S.P. grade (1).</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: none specified Temperature precision: ± 4°C (authors).</p> <p>REFERENCES:</p> <p>(1) Weiss P.J.; Andrew, M.L.; Wright, W.W. <i>Antibiotics and Chemotherapy</i> <u>1957</u>, <b>7</b>, 374-7.</p>



<p>COMPONENTS:</p> <p>(1) 3-Isloxazolidinone,4-amino- (D-cycloserine); <math>C_3H_6N_2O_2</math>; [68-41-7]</p> <p>(2) 2-Propanol (isopropanol); <math>C_3H_8O</math>; [67-63-0]</p> <p>(3) Ethanol; <math>C_2H_6O</math>; [64-17-5]</p> <p>(4) Water; <math>H_2O</math>; [7732-18-5]</p>	<p>ORIGINAL MEASUREMENTS:</p> <p>Yakhontova, L.F.; Bruns, B.P.; Kartseva, V.D.; Kobzova, S.N.; Perevozskaya, N.A. <i>Antibiotiki, (Moscow) 1969, 14, 205-10.</i></p>																												
<p>VARIABLES:</p> <p>Temperatures: <math>-20^{\circ}C</math>, <math>0^{\circ}C</math> and <math>25^{\circ}C</math></p>	<p>PREPARED BY:</p> <p>A. Regosz</p>																												
<p>EXPERIMENTAL VALUES:</p> <p>Solubility<sup>a</sup> of D-cycloserine in ethanol-isopropanol solutions<sup>b</sup> containing increasing amounts of water (wt %).</p> <div style="text-align: center;"> <table border="1" style="margin: 10px auto;"> <caption>Estimated data from the solubility graph</caption> <thead> <tr> <th>Amount of water [weight percent]</th> <th>Solubility at <math>-20^{\circ}C</math> (Curve 1) [mg cm<sup>-3</sup>]</th> <th>Solubility at <math>0^{\circ}C</math> (Curve 2) [mg cm<sup>-3</sup>]</th> <th>Solubility at <math>25^{\circ}C</math> (Curve 3) [mg cm<sup>-3</sup>]</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>0.000</td> <td>0.000</td> <td>0.000</td> </tr> <tr> <td>5</td> <td>0.001</td> <td>0.002</td> <td>0.005</td> </tr> <tr> <td>10</td> <td>0.002</td> <td>0.005</td> <td>0.015</td> </tr> <tr> <td>15</td> <td>0.003</td> <td>0.010</td> <td>0.025</td> </tr> <tr> <td>20</td> <td>0.005</td> <td>0.015</td> <td>0.040</td> </tr> <tr> <td>25</td> <td>0.008</td> <td>0.025</td> <td>0.055</td> </tr> </tbody> </table> </div> <p>[Curves 1, 2 and 3 are for values determined at <math>-20^{\circ}C</math>, <math>0^{\circ}C</math> and <math>25^{\circ}C</math>, respectively].</p> <p><sup>a</sup> determined at pH = pI (5.85) (<math>pK_1 = 4.3</math> and <math>pK_2 = 7.4</math> were determined potentiometrically)</p> <p><sup>b</sup> ethanol and isopropanol were mixed in equal volumes</p> <p><sup>c</sup> calculated by the compiler</p>		Amount of water [weight percent]	Solubility at $-20^{\circ}C$ (Curve 1) [mg cm <sup>-3</sup> ]	Solubility at $0^{\circ}C$ (Curve 2) [mg cm <sup>-3</sup> ]	Solubility at $25^{\circ}C$ (Curve 3) [mg cm <sup>-3</sup> ]	0	0.000	0.000	0.000	5	0.001	0.002	0.005	10	0.002	0.005	0.015	15	0.003	0.010	0.025	20	0.005	0.015	0.040	25	0.008	0.025	0.055
Amount of water [weight percent]	Solubility at $-20^{\circ}C$ (Curve 1) [mg cm <sup>-3</sup> ]	Solubility at $0^{\circ}C$ (Curve 2) [mg cm <sup>-3</sup> ]	Solubility at $25^{\circ}C$ (Curve 3) [mg cm <sup>-3</sup> ]																										
0	0.000	0.000	0.000																										
5	0.001	0.002	0.005																										
10	0.002	0.005	0.015																										
15	0.003	0.010	0.025																										
20	0.005	0.015	0.040																										
25	0.008	0.025	0.055																										
<p>AUXILIARY INFORMATION</p>																													
<p>METHOD APPARATUS/PROCEDURE:</p> <p>An excess of D-cycloserine and a mixture of ethanol-isopropanol (1:1) containing an appropriate amount of water were placed in a solubility apparatus joined with a thermostat and <math>N_2</math> was bubbled through the suspension at given temperature. Aliquots of the saturated solutions were filtered and the concentration of the antibiotic was determined colorimetrically after reaction with sodium nitroprusside (1).</p>	<p>SOURCE AND PURITY OF MATERIALS:</p> <p>Purity of the D-cycloserine was 99%. Its source was not specified.</p> <p>The sources and purities of solvents used were not described.</p> <p>ESTIMATED ERROR:</p> <p>Solubility precision: <math>\pm 5\%</math> (compiler)</p> <p>Temperature precision: <math>\pm 0.2^{\circ}C</math> (compiler)</p> <p>REFERENCES:</p> <p>(1) Jones, L.R. <i>Anal. Chem.</i> <u>1956</u>, <b>28</b>, 39-41.</p>																												

## SYSTEM INDEX

Underlined page numbers refer to evaluation text and those not underlined to compiled tables. Compounds are listed as in Chemical Abstracts.

### A

- 7-Aminoacetoxycephalosporanic acid,  
see 5-thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid,  
7-amino-3-(hydroxymethyl)-8-oxo, acetate ester
- 7-Aminodeacetoxycephalosporanic acid,  
see 5-thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid,  
7-amino-3-methyl-8-oxo-
- 6-Aminopenicillanic acid,  
see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
6-amino-3,3-dimethyl-7-oxo-
- Ammonium penicillin G,  
see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
3,3-dimethyl-7-oxo-6-[(phenyl acetyl)amino],  
monoammonium salt
- Amoxillin trihydrate,  
see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
6-[(amino(4-hydroxyphenyl)acetyl)amino]-  
3,3-dimethyl-7-oxo, trihydrate
- Ampicillin anhydrate,  
see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
6-[(aminophenylacetyl)amino]-  
3,3-dimethyl-7-oxo-
- Ampicillin sodium,  
see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
6-[(aminophenylacetyl)amino]-  
3,3-dimethyl-7-oxo, monosodium salt
- Ampicillin trihydrate,  
see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
6-[(aminophenylacetyl)amino]-  
3,3-dimethyl-7-oxo, trihydrate
- Ampicillin,  
see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
6-[(aminophenylacetyl)amino]-  
3,3-dimethyl-7-oxo-
- Azidocillin,  
see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
6-[2-azido-2-phenyl-acetamido]-  
3,3-dimethyl-7-oxo-

### B

- Benethamine penicillin G,  
see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-  
complexed with *N*-(phenylmethyl)benzene ethanamine (1:1)
- Benethamine penicillin V,  
see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-  
complexed with *N*-(phenylmethyl)benzene ethanamine (1:1)
- Benzathine penicillin V,  
see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-  
complexed with *N,N'*-bis(phenylmethyl)-  
1,2-ethanediamine (2:1)
- Benzathine penicillin G,  
see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-  
complexed with *N,N'*-bis(phenylmethyl)-  
1,2-ethanediamine (2:1)
- Benzathine penicillin P,  
see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
3,3-dimethyl-7-oxo-6-[(4-methylphenoxyacetyl)amino]-  
complexed with *N,N'*-bis(phenylmethyl)-  
1,2-ethanediamine (2:1)

(cont.)

## C

- Calcium penicillin V,  
see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], calcium salt
- Cefsulodin sodium,  
see pyridinium,4-(aminocarbonyl)-1[[2-carboxy-8-oxo-7-[(phenyl-  
sulfoacetyl)-amino]-5-thia-1-azabicyclo[4,2,0]oct-2-  
en-3-yl]-methyl]-hydroxide, inner salt, monosodium salt
- Cephalexin monohydrate,  
see 5-thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid,  
7[(aminophenylacetyl)amino]-3-methyl-8-oxo, monohydrate
- Cephaloglycin dihydrate,  
see 5-thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid,  
3[(acetyloxy)methyl]-7[(aminophenylacetyl)amino]-8-oxo,  
dihydrate
- Cephalomothin sodium,  
see 5-thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid,  
3[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino],  
monosodium salt
- Cephaloridine,  
see pyridinium,1-[[2-carboxy-8-oxo-7-(2-thienylacetyl)amino-5-  
thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-methyl]-hydroxide,  
inner salt (6*R*-trans)
- Cephradine monohydrate,  
see 5-thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid,  
7[(amino-1,4-cyclohexadien-1-yl-acetyl)amino]-3-methyl-  
8-oxo, monohydrate
- Chloroprocaine penicillin O,  
see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
3,3-dimethyl-7-oxo-6-[2-allylthioacetamido]-  
complexed with 2-(diethylamino)ethyl-4-amino-2-  
chlorobenzoate (1:1)
- Cholic acid,  
see cholane-24-oic acid, 3,7,12-trihydroxy-
- Ciclacillin anhydrate,  
see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
6-[[[(1-aminocyclohexyl)carbonyl]amino]-3,3-dimethyl-  
7-oxo-
- Ciclacillin dihydrate,  
see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
[[[(1-aminocyclohexyl)carbonyl]amino]-3,3-dimethyl-  
7-oxo, dihydrate
- Citric acid,  
see 1,2,3-propanetricarboxylic acid, 2-hydroxy-
- Clemizole penicillin G,  
see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-  
complexed with 1-(*p*-chlorobenzyl)-2-(1-pyrrolidinyl-  
methyl)benzimidazole (1:1)
- Cloxacillin sodium monohydrate,  
see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]  
amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate
- CP-38,371,  
see 4-thia-1-azabicyclo[3,2,0]hept-2-yl-5-tetrazole,  
6-[D-2-amino-2-(4-aminophenyl)-acetamido]-3,3-dimethyl-  
7-oxo, trihydrate
- Cycloserine,  
see 3-isoxazolidinone, 4-amino-

## D

- Dicloxacillin sodium monohydrate,  
see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
6-[[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]  
amino]-3,3-dimethyl-7-oxo, monosodium salt, monohydrate

(cont.)

## E

- 1-Ephenamine penicillin G,  
 see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-  
 complexed with (-)-2-(methylamino)-1,2-diphenylethanol  
 (1:1)
- Epicillin anhydrate,  
 see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
 6-[(amino-1,4-cyclohexadien-1-ylacetyl)amino]-  
 3,3-dimethyl-7-oxo-

## H

- Hydrabamine penicillin G,  
 see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-  
 complexed with *N,N'*-bis[(1,2,3,4,4a,9,10,10a-octahydro-  
 1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenyl)methyl]-  
 1,2-ethanediamine (2:1)
- Hydrabamine penicillin V,  
 see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-  
 complexed with *N,N'*-bis[(1,2,3,4,4a,9,10,10a-octahydro-  
 1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenyl)methyl]-  
 1,2-ethanediamine (2:1)

## I

- 3-Isloxazolidinone, 4-amino-
- |                                 |               |
|---------------------------------|---------------|
| + acetic acid, ethyl ester      | 740, 752      |
| + benzene                       | 740, 747      |
| + benzene, methyl-              | 740, 748      |
| + benzenemethanol               | 740, 764      |
| + 1-butanol, 3-methyl-          | 740, 745      |
| + 1-butanol, 3-methyl-, acetate | 740, 753      |
| + 2-butanone                    | 740, 755      |
| + carbon disulfide              | 740, 760      |
| + cyclohexane                   | 740, 746      |
| + 1,4-dioxane                   | 740, 758      |
| + ethane, dichloro-             | 740, 757      |
| + ethane, 1,1'-oxybis-          | 740, 756      |
| + ethanol                       | 740, 743, 765 |
| + ethanol (quaternary)          | 740, 766      |
| + ethanol, 2-methoxy-           | 740, 763      |
| + formamide                     | 740, 762      |
| + methane, tetrachloro-         | 740, 751      |
| + methane, trichloro-           | 740, 759      |
| + methanol                      | 740, 742      |
| + pentane, 2,2,4-trimethyl-     | 740, 750      |
| + petroleum ether               | 740, 749      |
| + 2-propanol                    | 740, 744      |
| + 2-propanol (quaternary)       | 740, 766      |
| + 2-propanone                   | 740, 754      |
| + pyridine                      | 740, 761      |
| + water                         | 740, 741, 766 |

## M

- Methicillin sodium,  
 see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
 6-[(2,6-dimethoxybenzoyl)amino]-3,3-dimethyl-7-oxo,  
 monosodium salt

(cont.)

## N

Nafcillin sodium,  
 see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
 6-[[ (2-ethoxy-1-naphthalenyl) carbonyl] amino]-  
 3,3-dimethyl-7-oxo-, monosodium salt

## O

Oxacillin sodium,  
 see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
 3,3-dimethyl-6[[ (5-methyl-3-phenyl-4-isoxazolyl) carbonyl]  
 amino]-7-oxo-, monosodium salt

## P

Penicillin V,  
 see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl) amino]

Phenethicillin potassium,  
 see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl) amino],  
 monopotassium salt

Phenoxymethyl penicillin,  
 see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl) amino]

7-Phenylacetamidodeacetoxycephalosporanic acid,  
 see 5-thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid,  
 3-methyl-8-oxo-7-(2-phenylacetamido)-

Potassium penicillin G,  
 see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
 3,3-dimethyl-7-oxo-6-[(phenylacetyl) amino],  
 monopotassium salt

Potassium penicillin V,  
 see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl) amino],  
 monopotassium salt

Procaine hydrochloride,  
 see benzoic acid, 4-amino-2-(diethylamino), ethyl ester,  
 monohydrochloride (ternary)

Procaine penicillin G, monohydrate,  
 see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
 3,3-dimethyl-7-oxo-6-[(phenylacetyl) amino],  
 complexed with 2-(diethylamino)ethyl-4-aminobenzoate  
 (1:1) monohydrate

Procaine penicillin G,  
 see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
 3,3-dimethyl-7-oxo-6-[(phenylacetyl) amino]  
 complexed with 2-(diethylamino)ethyl-4-aminobenzoate  
 (1:1)

Propicillin potassium,  
 see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxybutyl) amino],  
 monopotassium salt

Pyridinium, 4-(aminocarbonyl)-1-[[[2-carboxy-8-oxo-7-(phenylsulfoacetyl)  
 amino]-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-methyl]-  
 hydroxide, inner salt, monosodium salt

+ acetic acid, ethyl ester	733, 737
+ hexane	733, 738
+ methane, trichloro-	733, 739
+ methanol	733, 735
+ phosphoric acid, disodium salt (multicomponent)	733, 734
+ 1,2,3-propanetricarboxylic acid, 2-hydroxy-,	733, 734
+ 2-propanone	733, 736
+ water	733, 734

(cont.)

Pyridinium, 1-[[2-carboxy-8-oxo-7-[2-thienylacetyl]amino-5-thia-1-azabicyclo[4,2,0]oct-2-en-3yl]methyl]-, hydroxide, inner salt, (6 <i>R</i> -trans)	
+ acetic acid, ethyl ester	706, 719
+ benzene	706, 715
+ 1-butanol, 3-methyl-	706, 713
+ 1-butanol, 3-methyl-, acetate	706, 720
+ 2-butanone	706, 722
+ carbon disulfide	706, 727
+ cyclohexane	706, 714
+ 1,4-dioxane	706, 725
+ ethane, dichloro-	706, 724
+ ethane, 1,1'-oxybis-	706, 723
+ 1,2-ethanediol	706, 730
+ ethanol	706, 711
+ formamide	706, 729
+ hydrochloric acid	706, 708
+ methane, sulfinylbis-	706, 732
+ methane, tetrachloro-	706, 718
+ methane, trichloro-	706, 726
+ methanol	706, 710
+ pentane, 2,2,4-trimethyl-	706, 717
+ petroleum ether	706, 716
+ 1,2-propanediol	706, 731
+ 2-propanol	706, 712
+ 2-propanone	706, 721
+ pyridine	706, 728
+ sodium hydroxide (aqueous)	706, 709
+ water	706, 707 - 709

## S

Sodium citrate,	
see 1,2,3-propanetricarboxylic acid, 2-hydroxy-,	
trisodium salt	
Sodium dodecyl sulfate,	
see sulfuric acid, monododecyl ester, sodium salt	
Sodium penicillin G,	
see 4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,	
3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino],	
monosodium salt	
Sodium tartarate,	
see butanedioic acid, 2,3-dihydroxy-, disodium salt	
Sucrose,	
see $\alpha$ -D-Glucopyranoside, $\beta$ -D-Fructofuranosyl-	

## T

Tartaric acid,	
see butanedioic acid, 2,3-dihydroxy-	
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,	
6-[[[(1-aminocyclohexyl)carbonyl]amino]-3,3-dimethyl-7-oxo-	
+ hydrochloric acid (multicomponent)	359, 360, 362
+ phosphoric acid, trisodium salt (multicomponent)	359, 362
+ potassium chloride (multicomponent)	359, 360
+ potassium hydroxide (multicomponent)	359, 360
+ sodium chloride (multicomponent)	359, 362
+ water	359, 360 - 362
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,	
6-amino-3,3-dimethyl-7-oxo-	
+ acetic acid	1, 4
+ acetic acid (quaternary)	1, 5
+ acetic acid, sodium salt (quaternary)	1, 5
+ ammonium chloride (aqueous)	1, 7
+ ammonium chloride (multicomponent)	1, 8
+ benzeneacetic acid (multicomponent)	1, 8
+ ethanol	1, 6
+ hydrochloric acid (multicomponent)	1, 3, 8, 9
+ sodium chloride (multicomponent)	1, 8, 9
+ water	1, 2 - 9

(cont.)

4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(amino-1,4-cyclohexadien-1-ylacetyl)amino]-3,3-dimethyl- 7-oxo	
+ hydrochloric acid (multicomponent)	<u>487</u> , 488, 489
+ potassium chloride (multicomponent)	<u>487</u> , 488, 489
+ potassium hydroxide (multicomponent)	<u>487</u> , 488, 489
+ water	<u>487</u> , 488, 489
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(amino(4-hydroxyphenyl)acetyl)amino]-3,3-dimethyl- 7-oxo, trihydrate	
+ hydrochloric acid (multicomponent)	<u>479</u> , 480, 481
+ potassium chloride (multicomponent)	<u>479</u> , 480, 481
+ potassium hydroxide (multicomponent)	<u>479</u> , 480, 481
+ water	<u>479</u> , 480, 481
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo	
+ acetic acid, ethyl ester	<u>410</u> , 424
+ benzene	<u>410</u> , 420
+ 1-butanol, 3-methyl-	<u>410</u> , 418
+ 1-butanol, 3-methyl-, acetate	<u>410</u> , 425
+ 2-butanone	<u>410</u> , 428
+ carbon disulfide	<u>410</u> , 434
+ cholan-24-oic acid, 3,7,12-trihydroxy- (aqueous)	<u>394</u> , 408
+ cyclohexane	<u>410</u> , 419
+ 1,4-dioxane	<u>410</u> , 431
+ 1,4-dioxane (quaternary)	<u>410</u> , 432
+ ethane, dichloro-	<u>410</u> , 430
+ ethane, 1,1'-oxybis-	<u>410</u> , 429
+ 1,2-ethanediol	<u>410</u> , 437
+ ethanol	<u>410</u> , 413
+ ethanol (quaternary)	<u>410</u> , 414
+ formamide	<u>410</u> , 436
+ furan, tetrahydro- (quaternary)	<u>410</u> , 441
+ hydrochloric acid (multicomponent)	<u>394</u> , 402,
	403, 405, 406
+ methane, sulfinylbis-	<u>410</u> , 439
+ methane, sulfinylbis- (quaternary)	<u>410</u> , 440
+ methane, tetrachloro-	<u>410</u> , 423
+ methane, trichloro-	<u>410</u> , 433
+ methanol	<u>410</u> , 411
+ methanol (quaternary)	<u>410</u> , 412
+ pentane, 2,2,4-trimethyl-	<u>410</u> , 422
+ petroleum ether	<u>410</u> , 421
+ potassium chloride (multicomponent)	<u>394</u> , 400 - 403
+ potassium chloride (quaternary)	<u>410</u> , 412, 414,
	<u>416</u> , 417, 427,
	432, 440, 441
+ potassium hydroxide (multicomponent)	<u>394</u> , 402, 403
+ 1,2-propanediol	<u>410</u> , 438
+ 1-propanol (quaternary)	<u>410</u> , 417
+ 2-propanol	<u>410</u> , 415
+ 2-propanol (quaternary)	<u>410</u> , 416
+ 2-propanone	<u>410</u> , 426
+ 2-propanone (quaternary)	<u>410</u> , 427
+ pyridine	<u>410</u> , 435
+ sodium hydroxide (aqueous)	<u>394</u> , 404
+ sulfuric acid, monododecyl ester, sodium salt, (aqueous)	<u>394</u> , 407
+ water	<u>394</u> , <u>395</u> - 409,
	<u>410</u> , 412, 414,
	<u>416</u> , 417, 427,
	432, 440, 441
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo, trihydrate	
+ acetic acid, ethyl ester	<u>457</u> , 465
+ benzene	<u>457</u> , 461

(cont.)

4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo, trihydrate		
+ 1-butanol, 3-methyl-, acetate	<u>457</u> ,	466
+ 2-butanone	<u>457</u> ,	468
+ carbon disulfide	<u>457</u> ,	473
+ cholan-24-oic acid, 3,7,12-trihydroxy-	<u>442</u> ,	454
+ cyclohexane	<u>457</u> ,	470
+ 1,4-dioxane	<u>457</u> ,	471
+ ethane, dichloro-	<u>457</u> ,	470
+ ethane, 1,1'-oxybis-	<u>457</u> ,	469
+ 1,2-ethanediol	<u>457</u> ,	476
+ ethanol	<u>457</u> ,	459
+ formamide	<u>457</u> ,	475
+ hydrochloric acid (multicomponent)	<u>442</u> ,	<u>448</u> - 450,
		452, 455
+ methane, sulfinylbis-	<u>457</u> ,	478
+ methane, trichloro-	<u>457</u> ,	472
+ methane, tetrachloro-	<u>457</u> ,	464
+ methanol	<u>457</u> ,	458
+ pentane, 2,2,4-trimethyl-	<u>457</u> ,	463
+ petroleum ether	<u>457</u> ,	462
+ phosphoric acid, trisodium salt (multicomponent)	<u>442</u> ,	455
+ potassium chloride (multicomponent)	<u>442</u> ,	<u>448</u> , 449
+ potassium hydroxide (multicomponent)	<u>442</u> ,	<u>448</u> , 449
+ 1,2-propanediol	<u>457</u> ,	477
+ 2-propanone	<u>457</u> ,	467
+ pyridine	<u>457</u> ,	474
+ sodium chloride (multicomponent)	<u>442</u> ,	455
+ sodium hydroxide (aqueous)	<u>442</u> ,	451
+ sulfuric acid, monododecyl ester, sodium salt (aqueous)		<u>442</u> , 453
+ water	<u>442</u> ,	<u>443</u> - 456
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo, monosodium salt		
+ acetic acid, ethyl ester	<u>367</u> ,	380
+ benzene	<u>367</u> ,	376
+ 1-butanol, 3-methyl-	<u>367</u> ,	374
+ 1-butanol, 3-methyl-, acetate	<u>367</u> ,	381
+ 2-butanone	<u>367</u> ,	383
+ carbon disulfide	<u>367</u> ,	388
+ cyclohexane	<u>367</u> ,	375
+ 1,4-dioxane	<u>367</u> ,	386
+ ethane, dichloro-	<u>367</u> ,	385
+ ethane, 1,1'-oxybis-	<u>367</u> ,	384
+ 1,2-ethanediol	<u>367</u> ,	391
+ ethanol	<u>367</u> ,	372
+ formamide	<u>367</u> ,	390
+ hydrochloric acid	<u>367</u> ,	369
+ methane, sulfinylbis-	<u>367</u> ,	393
+ methane, tetrachloro-	<u>367</u> ,	379
+ methane, trichloro-	<u>367</u> ,	387
+ methanol	<u>367</u> ,	371
+ pentane, 2,2,4-trimethyl-	<u>367</u> ,	378
+ petroleum ether	<u>367</u> ,	377
+ 1,2-propanediol	<u>367</u> ,	392
+ 2-propanol	<u>367</u> ,	373
+ 2-propanone	<u>367</u> ,	382
+ pyridine	<u>367</u> ,	389
+ sodium hydroxide (aqueous)	<u>367</u> ,	370
+ water	<u>367</u> ,	<u>368</u> - 370
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[2-azido-2-phenyl-acetamido]-3,3-dimethyl-7-oxo,		
+ hydrochloric acid (multicomponent)	<u>367</u> ,	368
+ phosphoric acid, trisodium salt (multicomponent)	<u>367</u> ,	368
+ sodium chloride (multicomponent)	<u>367</u> ,	368
+ water	<u>367</u> ,	368

(cont.)

- 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-  
3,3-dimethyl-7-oxo, monosodium salt, monohydrate
- + acetic acid, ethyl ester 576, 587
  - + benzene 576, 583
  - + 1-butanol, 3-methyl- 576, 602
  - + 1-butanol, 3-methyl-, acetate 576, 588
  - + 2-butanone 576, 590
  - + carbon disulfide 576, 595
  - + cyclohexane 576, 582
  - + 1,4-dioxane 576, 593
  - + ethane, dichloro- 576, 592
  - + ethane, 1,1'-oxybis- 576, 591
  - + 1,2-ethanediol 576, 598
  - + ethanol 576, 581
  - + formamide 576, 597
  - + hydrochloric acid 576, 578
  - + methane, sulfinylbis- 576, 594
  - + methane, tetrachloro- 576, 600
  - + methane, trichloro- 576, 594
  - + methanol 576, 580
  - + pentane, 2,2,4-trimethyl- 576, 585
  - + petroleum ether 576, 584
  - + 1,2-propanediol 576, 599
  - + 2-propanol 576, 601
  - + 2-propanone 576, 589
  - + pyridine 576, 596
  - + sodium hydroxide (aqueous) 576, 579
  - + water 576, 577 - 596
- 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
6-[[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-  
3,3-dimethyl-7-oxo, monosodium salt, monohydrate
- + acetic acid, ethyl ester 548, 560
  - + benzene 548, 556
  - + 1-butanol, 3-methyl- 548, 575
  - + 1-butanol, 3-methyl-, acetate 548, 561
  - + 2-butanone 548, 563
  - + carbon disulfide 548, 568
  - + cyclohexane 548, 555
  - + 1,4-dioxane 548, 566
  - + ethane, dichloro- 548, 565
  - + ethane, 1,1'-oxybis- 548, 564
  - + 1,2-ethanediol 548, 571
  - + ethanol 548, 554
  - + formamide 548, 570
  - + hydrochloric acid 548, 551
  - + methane, sulfinylbis- 548, 573
  - + methane, tetrachloro- 548, 559
  - + methane, trichloro- 548, 567
  - + methanol 548, 553
  - + pentane, 2,2,4-trimethyl- 548, 568
  - + petroleum ether 548, 557
  - + 1,2-propanediol 548, 572
  - + 2-propanol 548, 574
  - + 2-propanone 548, 562
  - + pyridine 548, 569
  - + sodium hydroxide (aqueous) 548, 552
  - + water 548, 549 - 552
- 4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid,  
6-[(2,6-dimethoxybenzoyl)amino]-3,3-dimethyl-7-oxo,  
monosodium salt
- + acetic acid, ethyl ester 518, 529
  - + benzene 518, 525
  - + 1-butanol, 3-methyl- 518, 544
  - + 1-butanol, 3-methyl-, acetate 518, 530
  - + 2-butanone 518, 532
  - + carbon disulfide 518, 537
  - + cyclohexane 518, 524
  - + 1,4-dioxane 518, 535

(cont.)

4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[(2,6-dimethoxybenzoyl)amino]-3,3-dimethyl-7-oxo, monosodium salt	
+ ethane, dichloro-	518, 534
+ ethane, 1,1'-oxybis	518, 533
+ 1,2-ethanediol	518, 540
+ ethanol	518, 523
+ formamide	518, 539
+ hydrochloric acid	518, 520
+ methane, sulfinylbis-	518, 542
+ methane, tetrachloro-	518, 528
+ methane, trichloro-	518, 536
+ methanol	518, 522
+ pentane, 2,2,4-trimethyl-	518, 527
+ petroleum ether	518, 526
+ 1,2-propanediol	518, 541
+ 2-propanol	518, 543
+ 2-propanone	518, 531
+ pyridine	518, 538
+ sodium hydroxide (aqueous)	518, 521
+ water	518, 519 - 521
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-6-[(5-methyl-3-phenyl-4-isoxazolyl)carbonyl]amino]- 7-oxo, monosodium salt	
+ acetic acid, ethyl ester	603, 614
+ benzene	603, 610
+ 1-butanol, 3-methyl-	603, 629
+ 1-butanol, 3-methyl-, acetate	603, 615
+ 2-butanone	603, 617
+ carbon disulfide	603, 622
+ cyclohexane	603, 609
+ 1,4-dioxane	603, 620
+ ethane, dichloro-	603, 619
+ ethane, 1,1'-oxybis	603, 618
+ 1,2-ethanediol	603, 625
+ ethanol	603, 608
+ formamide	603, 624
+ hydrochloric acid	603, 605
+ methane, sulfinylbis-	603, 627
+ methane, tetrachloro-	603, 613
+ methane, trichloro-	603, 621
+ methanol	603, 607
+ pentane, 2,2,4-trimethyl-	603, 612
+ petroleum ether	603, 611
+ 1,2-propanediol	603, 626
+ 2-propanol	603, 628
+ 2-propanone	603, 616
+ pyridine	603, 623
+ sodium hydroxide (aqueous)	603, 606
+ water	603, 604 - 606
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[2-(allylthio)-amino]-ethyl- 4-amino-2-chlorobenzoate (1:1)	
+ acetic acid, ethyl ester	334, 346
+ benzene	334, 341
+ benzene, methyl-	334, 342
+ benzenemethanol	334, 358
+ 1-butanol, 3-methyl-	334, 339
+ 1-butanol, 3-methyl-, acetate	334, 347
+ 2-butanone	334, 349
+ carbon disulfide	334, 354
+ cyclohexane	334, 340
+ 1,4-dioxane	334, 352
+ ethane, dichloro-	334, 351
+ ethane, 1,1'-oxybis-	334, 350
+ 1,2-ethanediol	334, 357
+ ethanol	334, 337
+ formamide	334, 356
+ methane, tetrachloro-	334, 345

(cont.)

4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[2-(allylthio)-amino]-ethyl- 4-amino-2-chlorobenzoate (1:1)		
+ methane, trichloro-	<u>334</u> ,	353
+ methanol	<u>334</u> ,	336
+ pentane, 2,2,4-trimethyl-	<u>334</u> ,	344
+ petroleum ether	<u>334</u> ,	343
+ 2-propanol	<u>334</u> ,	338
+ 2-propanone	<u>334</u> ,	348
+ pyridine	<u>334</u> ,	355
+ water	<u>334</u> ,	335
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[[1-(aminocyclohexyl)carbonyl]amino]- dihydrate		
+ water	<u>363</u> ,	364
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino] complexed with 2-(diethylamino)-ethyl-4-aminobenzoate (1:1)		
+ butanedioic acid, 2,3-dihydroxy-, disodium salt	<u>175</u> ,	186,
	<u>187</u> ,	189,
	<u>190</u> ,	196
+ butanedioic acid, 2,3-dihydroxy- (multicomponent)	<u>175</u> ,	186,
	<u>187</u> ,	190
+ D-gluconic acid (multicomponent)	<u>175</u> ,	188
+ D-gluconic acid, monosodium salt (multicomponent)	<u>175</u> ,	188,
	<u>190</u> ,	197
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(4-methylphenoxyacetyl)amino]- complexed with <i>N,N'</i> -bis(phenylmethyl)-1,2-ethane diamine (2:1)		
+ hydrochloric acid	<u>330</u> ,	332
+ sodium hydroxide (aqueous)	<u>330</u> ,	333
+ water	<u>330</u> ,	331 - 333
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-		
+ acetic acid, ethyl ester	<u>10</u> ,	26
+ benzene	<u>10</u> ,	21
+ benzene, methyl-	<u>10</u> ,	22
+ benzenemethanol	<u>10</u> ,	38
+ 1-butanol, 3-methyl-	<u>10</u> ,	19
+ 1-butanol, 3-methyl-, acetate	<u>10</u> ,	27
+ 2-butanone	<u>10</u> ,	29
+ carbon disulfide	<u>10</u> ,	34
+ cyclohexane	<u>10</u> ,	20
+ 1,4-dioxane	<u>10</u> ,	32
+ ethane, dichloro-	<u>10</u> ,	31
+ ethane, 1,1'-oxybis-	<u>10</u> ,	30
+ 1,2-ethanediol	<u>10</u> ,	37
+ ethanol	<u>10</u> ,	17
+ formamide	<u>10</u> ,	36
+ hydrochloric acid (multicomponent)	<u>10</u> ,	12
+ hydrochloric acid (quaternary)	<u>10</u> ,	14
+ methane, tetrachloro-	<u>10</u> ,	25
+ methane, trichloro-	<u>10</u> ,	33
+ methanol	<u>10</u> ,	16
+ pentane, 2,2,4-trimethyl-	<u>10</u> ,	24
+ petroleum ether	<u>10</u> ,	23
+ phosphoric acid (multicomponent)	<u>10</u> ,	15
+ phosphoric acid, disodium salt (multicomponent)	<u>10</u> ,	15
+ phosphoric acid, trisodium salt (multicomponent)	<u>10</u> ,	12
+ 2-propanol	<u>10</u> ,	18
+ 2-propanone	<u>10</u> ,	28
+ pyridine	<u>10</u> ,	35
+ sodium chloride (multicomponent)	<u>10</u> ,	12
+ sorbitan monooleate, polyoxyethylene derivatives (multicomponent)	<u>10</u> ,	15
+ sorbitan monooleate, polyoxyethylene derivatives (quaternary)	<u>10</u> ,	14
+ water	<u>10</u> ,	11 - 15

(cont.)

4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]- complexed with <i>N,N'</i> -bis[(1,2,3,4,4a,9,10,10a-octahydro- 1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenyl)methyl]- 1,2-ethanediamine (2:1)		
+ acetic acid, ethyl ester	102,	114
+ benzene	102,	109
+ benzene, methyl-	102,	110
+ benzenemethanol	102,	126
+ 1-butanol, 3-methyl-	102,	107
+ 1-butanol, 3-methyl-, acetate	102,	115, 118
+ 2-butanone	102,	117
+ carbon disulfide	102,	122
+ cyclohexane	102,	108
+ 1,4-dioxane	102,	120
+ ethane, dichloro-	102,	119
+ 1,2-ethanediol	102,	125
+ ethanol	102,	105
+ formamide	102,	124
+ methane, tetrachloro-	102,	113
+ methane, trichloro-	102,	121
+ methanol	102,	104
+ pentane, 2,2,4-trimethyl-	102,	112
+ petroleum ether	102,	111
+ 2-propanol	102,	106
+ 2-propanone	102,	116
+ pyridine	102,	123
+ water	102,	103
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]- complexed with <i>N,N'</i> -bis(phenylmethyl)-1,2-ethanediamine (2:1)		
+ acetic acid, ethyl ester	78,	89
+ benzene	78,	84
+ benzene, methyl-	78,	85
+ benzenemethanol	78,	101
+ 1-butanol, 3-methyl-	78,	82
+ 1-butanol, 3-methyl-, acetate	78,	90
+ 2-butanone	78,	92
+ carbon disulfide	78,	97
+ cyclohexane	78,	83
+ 1,4-dioxane	78,	95
+ ethane, dichloro-	78,	94
+ ethane, 1,1'-oxybis-	78,	93
+ 1,2-ethanediol	78,	100
+ ethanol	78,	80
+ formamide	78,	99
+ hydrochloric acid	72,	75
+ methane, tetrachloro-	78,	88
+ methane, trichloro-	78,	96
+ methanol	78,	79
+ pentane, 2,2,4-trimethyl-	78,	87
+ petroleum ether	78,	86
+ 2-propanol	79,	81
+ 2-propanone	78,	91
+ pyridine	78,	98
+ sodium hydroxide (aqueous)	72,	76
+ water	72,	73 - 77
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]- complexed with <i>N</i> -(phenylmethyl)benzene ethanamine (1:1)		
+ hydrochloric acid	68,	70
+ sodium hydroxide (aqueous)	68,	71
+ water	68,	69 - 71
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino], calcium salt (2:1)		
+ water	66,	67

(cont.)

4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl) amino], monopotassium salt		
+ acetic acid, ethyl ester	<u>39</u> ,	53
+ benzene	<u>39</u> ,	48
+ benzene, methyl-	<u>39</u> ,	49
+ benzenemethanol	<u>39</u> ,	65
+ 1-butanol, 3-methyl-	<u>39</u> ,	46
+ 1 butanol, 3-methyl-, acetate	<u>39</u> ,	54
+ 2-butanone	<u>39</u> ,	56
+ carbon disulfide	<u>39</u> ,	61
+ cyclohexane	<u>39</u> ,	47
+ 1,4-dioxane	<u>39</u> ,	59
+ ethane, dichloro-	<u>39</u> ,	58
+ ethane, 1,1'-oxybis-	<u>39</u> ,	57
+ ethanol	<u>39</u> ,	44
+ ethanol, 2-methoxy-	<u>39</u> ,	64
+ formamide	<u>39</u> ,	63
+ methane, tetrachloro-	<u>39</u> ,	52
+ methane, trichloro-	<u>39</u> ,	60
+ methanol	<u>39</u> ,	43
+ pentane, 2,2,4-trimethyl-	<u>39</u> ,	51
+ petroleum ether	<u>39</u> ,	50
+ phosphoric acid (multicomponent)	<u>39</u> ,	41
+ phosphoric acid, disodium salt (multicomponent)	<u>39</u> ,	41
+ 2-propanol	<u>39</u> ,	45
+ 2-propanone	<u>39</u> ,	55
+ pyridine	<u>39</u> ,	62
+ sorbitan monooleate, polyoxyethylene derivatives (multicomponent)	<u>39</u> ,	41
+ water	<u>39</u> ,	40 - 42
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxybutyl) amino], monopotassium salt		
+ hydrochloric acid (multicomponent)	<u>545</u> ,	546, 547
+ polyoxyethylene-23-lauryl ether (multicomponent)	<u>545</u> ,	546, 547
+ potassium chloride (multicomponent)	<u>545</u> ,	546, 547
+ water	<u>545</u> ,	546, 547
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl) amino], monopotassium salt		
+ acetic acid, ethyl ester	<u>491</u> ,	502
+ benzene	<u>491</u> ,	498
+ 1-butanol, 3-methyl-	<u>491</u> ,	517
+ 1-butanol, 3-methyl-, acetate	<u>491</u> ,	503
+ 2-butanone	<u>491</u> ,	505
+ carbon disulfide	<u>491</u> ,	510
+ cyclohexane	<u>491</u> ,	507
+ 1,4-dioxane	<u>491</u> ,	508
+ ethane, dichloro-	<u>491</u> ,	507
+ ethane, 1,1'-oxybis-	<u>491</u> ,	506
+ 1,2-ethanediol	<u>491</u> ,	513
+ ethanol	<u>491</u> ,	496
+ formamide	<u>491</u> ,	512
+ hydrochloric acid	<u>491</u> ,	493
+ methane, sulfinylbis-	<u>491</u> ,	515
+ methane, tetrachloro-	<u>491</u> ,	501
+ methane, trichloro-	<u>491</u> ,	509
+ methanol	<u>491</u> ,	495
+ pentane, 2,2,4-trimethyl-	<u>491</u> ,	500
+ petroleum ether	<u>491</u> ,	499
+ 1,2-propanediol	<u>491</u> ,	514
+ 2-propanol	<u>491</u> ,	516
+ 2-propanone	<u>491</u> ,	504
+ pyridine	<u>491</u> ,	511
+ sodium hydroxide (aqueous)	<u>491</u> ,	494
+ water	<u>491</u> ,	492 - 494

(cont.)

4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)- complexed with 1-( <i>p</i> -chlorobenzyl)-2-(1-pyrrolidinylmethyl)- benzimidazole (1:1)	
+ acetic acid, ethyl ester	<u>249</u> , 262
+ benzene	<u>249</u> , 258
+ 1-butanol, 3-methyl-	<u>249</u> , 256
+ 1-butanol, 3-methyl-, acetate	<u>249</u> , 263
+ 2-butanone	<u>249</u> , 265
+ carbon disulfide	<u>249</u> , 270
+ cyclohexane	<u>249</u> , 257
+ 1,4-dioxane	<u>249</u> , 268
+ ethane, dichloro-	<u>249</u> , 267
+ ethane, 1,1'-oxybis-	<u>249</u> , 266
+ 1,2-ethanediol	<u>249</u> , 273
+ ethanol	<u>249</u> , 254
+ formamide	<u>249</u> , 272
+ hydrochloric acid	<u>249</u> , 251
+ methane, sulfinylbis-	<u>249</u> , 275
+ methane, tetrachloro-	<u>249</u> , 261
+ methane, trichloro-	<u>249</u> , 269
+ methanol	<u>249</u> , 253
+ pentane, 2,2,4-trimethyl-	<u>249</u> , 260
+ petroleum ether	<u>249</u> , 259
+ 1,2-propanediol	<u>249</u> , 274
+ 2-propanol	<u>249</u> , 255
+ 2 propanone	<u>249</u> , 264
+ pyridine	<u>249</u> , 271
+ sodium hydroxide (aqueous)	<u>249</u> , 252
+ water	<u>249</u> , 250 - 252
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)- complexed with (-)-2-(methylamino)-1,2-diphenylethanol (1:1)	
+ acetic acid, ethyl ester	<u>224</u> , 236
+ benzene	<u>224</u> , 231
+ benzene, methyl-	<u>224</u> , 232
+ benzenemethanol	<u>224</u> , 248
+ 1-butanol, 3-methyl-	<u>224</u> , 229
+ 1-butanol, 3-methyl-, acetate	<u>224</u> , 237
+ 2-butanone	<u>224</u> , 239
+ carbon disulfide	<u>224</u> , 244
+ cyclohexane	<u>224</u> , 230
+ 1,4-dioxane	<u>224</u> , 242
+ ethane, dichloro-	<u>224</u> , 241
+ ethane, 1,1'-oxybis-	<u>224</u> , 240
+ ethanediol	<u>224</u> , 247
+ ethanol	<u>224</u> , 227
+ formamide	<u>224</u> , 246
+ methane, tetrachloro-	<u>224</u> , 235
+ methane, trichloro-	<u>224</u> , 243
+ methanol	<u>224</u> , 226
+ pentane, 2,2,4-trimethyl-	<u>224</u> , 234
+ petroleum ether	<u>224</u> , 233
+ 2-propanol	<u>224</u> , 228
+ 2-propanone	<u>224</u> , 238
+ pyridine	<u>224</u> , 245
+ water	<u>224</u> , 225
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]- complexed with <i>N,N'</i> -bis[(1,2,3,4,4a,9,10,10a-octahydro- 1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenyl)methyl]- 1,2-ethanediamine (2:1)	
+ acetic acid, ethyl ester	<u>276</u> , 288
+ benzene	<u>276</u> , 283
+ benzene, methyl-	<u>276</u> , 284
+ benzenemethanol	<u>276</u> , 300
+ 1-butanol, 3-methyl-	<u>276</u> , 281
+ 1-butanol, 3-methyl-, acetate	<u>276</u> , 289

(cont.)

4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]- complexed with <i>N,N'</i> -bis[(1,2,3,4,4a,9,10,10a-octahydro- 1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenyl)methyl]- 1,2-ethanediamine (2:1)			
+ 2-butanone		<u>276</u> ,	291
+ carbon disulfide		<u>276</u> ,	296
+ cyclohexane		<u>276</u> ,	282
+ 1,4-dioxane		<u>276</u> ,	294
+ ethane, dichloro-		<u>276</u> ,	293
+ ethane, 1,1'-oxybis-		<u>276</u> ,	292
+ 1,2-ethanediol		<u>276</u> ,	299
+ ethanol		<u>276</u> ,	279
+ formamide		<u>276</u> ,	298
+ methane, tetrachloro-		<u>276</u> ,	287
+ methane, trichloro-		<u>276</u> ,	295
+ methanol		<u>276</u> ,	278
+ pentane, 2,2,4-trimethyl-		<u>276</u> ,	286
+ petroleum ether		<u>276</u> ,	285
+ 2-propanol		<u>276</u> ,	280
+ 2-propanone		<u>276</u> ,	290
+ pyridine		<u>276</u> ,	297
+ water		<u>276</u> ,	277
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]- complexed with <i>N,N'</i> -bis(phenylmethyl)-1,2-ethanediamine (2:1)			
+ acetic acid, ethyl ester		<u>306</u> ,	317
+ benzene		<u>306</u> ,	312
+ benzene, methyl-		<u>306</u> ,	313
+ benzenemethanol		<u>306</u> ,	329
+ 1-butanol, 3-methyl-		<u>306</u> ,	310
+ 1-butanol, 3-methyl-, acetate		<u>306</u> ,	318
+ 2-butanone		<u>306</u> ,	320
+ carbon disulfide		<u>306</u> ,	325
+ cyclohexane		<u>306</u> ,	311
+ 1,4-dioxane		<u>306</u> ,	323
+ ethane, dichloro-		<u>306</u> ,	322
+ ethane, 1,1'-oxybis-		<u>306</u> ,	321
+ 1,2-ethanediol		<u>306</u> ,	328
+ ethanol		<u>306</u> ,	308
+ formamide		<u>306</u> ,	327
+ hydrochloric acid		<u>301</u> ,	303
+ methane, tetrachloro-		<u>306</u> ,	316
+ methane, trichloro-		<u>306</u> ,	324
+ methanol		<u>306</u> ,	307
+ pentane, 2,2,4-trimethyl-		<u>306</u> ,	315
+ petroleum ether		<u>306</u> ,	314
+ 2-propanol		<u>306</u> ,	309
+ 2-propanone		<u>306</u> ,	319
+ pyridine		<u>306</u> ,	326
+ sodium hydroxide (aqueous)		<u>301</u> ,	304
+ water		<u>301</u> ,	<u>302</u> - 305
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]- complexed with 2-(diethylamino)ethyl-4-aminobenzoate (1:1)			
+ acetic acid, ethyl ester		<u>200</u> ,	211
+ benzene		<u>200</u> ,	206
+ benzene, methyl-		<u>200</u> ,	207
+ benzenemethanol		<u>200</u> ,	223
+ benzoic acid, 4-amino-2-(diethylamino), ethyl ester, monohydrochloride		<u>175</u> ,	<u>177</u> , <u>179</u> ,
		<u>191</u> ,	<u>192</u> , <u>194</u> ,
		<u>195</u> ,	<u>197</u> , <u>198</u> ,
+ 1-butanol, 3-methyl-		<u>200</u> ,	<u>204</u>
+ 1-butanol, 3-methyl-, acetate		<u>200</u> ,	<u>212</u>
+ 2-butanone		<u>200</u> ,	<u>214</u>
+ carbon disulfide		<u>200</u> ,	<u>219</u>
+ cyclohexane		<u>200</u> ,	<u>205</u>

(cont.)

4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]- complexed with 2-(diethylamino)-ethyl-4-aminobenzoate (1:1)	
+ 1,4-dioxane	<u>200</u> , 217
+ ethane, dichloro-	<u>200</u> , 216
+ ethane, 1,1'-oxybis-	<u>200</u> , 215
+ 1,2-ethanediol	<u>200</u> , 222
+ ethanol	<u>200</u> , 202
+ formamide	<u>200</u> , 221
+ $\alpha$ -D-glycopyranoside, $\beta$ -D-fructofuranosyl (multicomponent)	175, 183, 184, 189, 190, 192 - 196, 198
+ D-glucose	175, 185
+ D-gluctol (multicomponent)	<u>175</u> , 182, 184, 198, 190, 193 - 198
+ methane, tetrachloro-	<u>200</u> , 210
+ methane, trichloro-	<u>200</u> , 218
+ methanol	<u>200</u> , 201
+ pentane, 2,2,4-trimethyl-	<u>200</u> , 209
+ petroleum ether	<u>200</u> , 208
+ phosphoric acid, disodium salt (multicomponent)	<u>175</u> , 178, 179
+ phosphoric acid, monosodium salt (multicomponent)	<u>175</u> , 178, 179
+ 1,2,3-propanetricarboxylic acid, 2-hydroxy-	175, 180, 189, 190, 193, 195 - 198
+ 1,2,3-propanetricarboxylic acid, 2-hydroxy-, trisodium salt	<u>175</u> , 180 - 185, 191 - 198
+ 2-propanol	<u>200</u> , 203
+ 2-propanone	<u>200</u> , 213
+ pyridine	<u>200</u> , 220
+ water	<u>175</u> , <u>176</u> - 199
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]- complexed with 2-(diethylamino)-ethyl-4-aminobenzoate (1:1) monohydrate	
+ hydrochloric acid	171, 173
+ sodium hydroxide (aqueous)	<u>171</u> , 174
+ water	<u>171</u> , 172 - 174
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]- complexed with <i>N</i> -(phenylmethyl)benzene ethanamine (1:1)	
+ hydrochloric acid	167, 169
+ sodium hydroxide (aqueous)	<u>167</u> , 170
+ water	<u>167</u> , 168 - 170
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, monoammonium salt	
+ 2-propanone (ternary)	165, 166
+ water	<u>165</u> , 166
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, monopotassium salt	
+ acetic acid, butyl ester (quaternary)	127, 128, 134
+ acetic acid, butyl ester (ternary)	<u>127</u> , <u>128</u> , 133
+ 1-butanol	<u>127</u> , 128, 130
+ 1-butanol (quaternary)	<u>127</u> , <u>128</u> , 134
+ 1-butanol (ternary)	<u>127</u> , <u>128</u> , 131 - 133
+ hydrochloric acid (multicomponent)	1, 8, 9
+ 2-propanone (ternary)	<u>127</u> , 128, 129
+ water	<u>127</u> , <u>128</u> , 129, 131, 132, 134

(cont.)

4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, monosodium salt			
+ acetic acid, ethyl ester	<u>135</u> , <u>136</u>		152
+ benzene	<u>135</u> , <u>136</u>		147
+ benzene, methyl-	<u>135</u> , <u>136</u>		148
+ benzenemethanol	<u>135</u> , <u>136</u>		164
+ 1-butanol	<u>135</u> , <u>136</u>		138
+ 1-butanol (ternary)	<u>135</u> , <u>136</u>		139, 140
+ 1-butanol, 3-methyl-	<u>135</u> , <u>136</u>		145
+ 1-butanol, 3-methyl-, acetate	<u>135</u> , <u>136</u>		153
+ 2-butanone	<u>135</u> , <u>136</u>		155
+ carbon disulfide	<u>135</u> , <u>136</u>		160
+ cyclohexane	<u>135</u> , <u>136</u>		146
+ 1,4-dioxane	<u>135</u> , <u>136</u>		158
+ ethane, dichloro-	<u>135</u> , <u>136</u>		157
+ ethane, 1,1'-oxybis-	<u>135</u> , <u>136</u>		156
+ 1,2-ethanediol	<u>135</u> , <u>136</u>		163
+ ethanol	<u>135</u> , <u>136</u>		143
+ formamide	<u>135</u> , <u>136</u>		162
+ methane, tetrachloro-	<u>135</u> , <u>136</u>		151
+ methane, trichloro-	<u>135</u> , <u>136</u>		159
+ methanol	<u>135</u> , <u>136</u>		142
+ pentane, 2,2,4-trimethyl-	<u>135</u> , <u>136</u>		150
+ petroleum ether	<u>135</u> , <u>136</u>		149
+ 2-propanol	<u>135</u> , <u>136</u>		144
+ 2-propanone	<u>135</u> , <u>136</u>		154
+ 2-propanone (ternary)	<u>135</u> , <u>136</u>		137
+ pyridine	<u>135</u> , <u>136</u>		161
+ water	<u>135</u> , <u>136</u>		137, 139 - 141
4-Thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[ (2-ethoxy-1-naphthalenyl)carbonyl]amino]- 3,3-dimethyl-7-oxo-, monosodium salt			
+ acetic acid, ethyl ester	<u>630</u>		641
+ benzene	<u>630</u>		637
+ 1-butanol, 3-methyl-	<u>630</u>		656
+ 1-butanol, 3-methyl-, acetate	<u>630</u>		642
+ 2-butanone	<u>630</u>		644
+ carbon disulfide	<u>630</u>		649
+ cyclohexane	<u>630</u>		636
+ 1,4-dioxane	<u>630</u>		647
+ ethane, dichloro-	<u>630</u>		646
+ ethane, 1,1'-oxybis-	<u>630</u>		645
+ 1,2-ethanediol	<u>630</u>		652
+ ethanol	<u>630</u>		635
+ formamide	<u>630</u>		651
+ hydrochloric acid	<u>630</u>		632
+ methane, sulfinylbis-	<u>630</u>		654
+ methane, tetrachloro-	<u>630</u>		640
+ methane, trichloro-	<u>630</u>		648
+ methanol	<u>630</u>		634
+ pentane, 2,2,4-trimethyl-	<u>630</u>		639
+ petroleum ether	<u>630</u>		638
+ 1,2-propanediol	<u>630</u>		653
+ 2-propanol	<u>630</u>		655
+ 2-propanone	<u>630</u>		643
+ pyridine	<u>630</u>		650
+ sodium hydroxide (aqueous)	<u>630</u>		633
+ water	<u>630</u> , <u>631</u>		633
4-Thia-1-azabicyclo[3,2,0]hept-2-yl-5-tetrazole, 6-[D-2-amino-2-(4-aminophenyl)-acetamido]- 3,3-dimethyl-7-oxo-, trihydrate			
+ hydrochloric acid (multicomponent)	<u>484</u> , <u>485</u>		486
+ sodium hydroxide (multicomponent)	<u>484</u> , <u>485</u>		486
+ water	<u>484</u> , <u>485</u>		486

(cont.)

5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid- 3-[(acetyloxy)methyl]-7-[(aminophenylacetyl)amino]- 8-oxo-, dihydrate	
+ hydrochloric acid (multicomponent)	<u>702</u> , 703, 704
+ potassium chloride (multicomponent)	<u>702</u> , 703 - 705
+ potassium hydroxide (multicomponent)	<u>702</u> , 703, 704
+ water	<u>702</u> , 703 - 705
5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid- 3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino]-, monosodium salt	
+ acetic acid, ethyl ester	<u>667</u> , 680
+ benzene	<u>667</u> , 676
+ 1-butanol, 3-methyl-	<u>667</u> , 674
+ 1-butanol, 3-methyl-, acetate	<u>667</u> , 681
+ 2-butanone	<u>667</u> , 683
+ carbon disulfide	<u>667</u> , 688
+ cyclohexane	<u>667</u> , 675
+ 1,4-dioxane	<u>667</u> , 686
+ ethane, dichloro-	<u>667</u> , 685
+ ethane, 1,1'-oxybis-	<u>667</u> , 684
+ 1,2-ethanediol	<u>667</u> , 691
+ ethanol	<u>667</u> , 672
+ formamide	<u>667</u> , 690
+ hydrochloric acid	<u>667</u> , 669
+ methane, sulfinylbis-	<u>667</u> , 693
+ methane tetrachloro-	<u>667</u> , 679
+ methane, trichloro-	<u>667</u> , 687
+ methanol	<u>667</u> , 671
+ pentane, 2,2,4-trimethyl-	<u>667</u> , 678
+ petroleum ether	<u>667</u> , 677
+ 1,2-propanediol	<u>667</u> , 692
+ 2-propanol	<u>667</u> , 673
+ 2-propanone	<u>667</u> , 682
+ pyridine	<u>667</u> , 689
+ sodium hydroxide (aqueous)	<u>667</u> , 670
+ water	<u>667</u> , 668 - 670
5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid, 7-[(amino-1,4-cyclohexadien-1-ylacetyl)amino]- 3-methyl-8-oxo-, monohydrate	
+ hydrochloric acid (multicomponent)	<u>698</u> , 699, 700
+ potassium chloride (multicomponent)	<u>698</u> , 699 - 701
+ potassium hydroxide (multicomponent)	<u>698</u> , 699, 700
+ water	<u>698</u> , 699 - 701
5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid, 7-amino-3-(hydroxymethyl)-8-oxo-, acetate ester	
+ sodium chloride (aqueous)	<u>662</u> , 663
+ water	<u>662</u> , 663
5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid, 7-amino-3-methyl-8-oxo-	
+ ammonium chloride (aqueous)	<u>657</u> , 659
+ ammonium chloride (multicomponent)	<u>657</u> , 660
+ benzenoacetic acid (multicomponent)	<u>657</u> , 660
+ hydrochloric acid (multicomponent)	<u>657</u> , 660, 661
+ potassium chloride (aqueous)	<u>657</u> , 658
+ sodium chloride (multicomponent)	<u>657</u> , 660
+ sodium hydroxide (multicomponent)	<u>657</u> , 661
+ water	<u>657</u> , 660, 661
5-Thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid- 7-[(aminophenylacetyl)amino]-3-methyl-8-oxo-, monohydrate	
+ hydrochloric acid (multicomponent)	<u>694</u> , 695, 696
+ potassium chloride (multicomponent)	<u>694</u> , 695 - 697
+ potassium hydroxide (multicomponent)	<u>694</u> , 695, 696
+ water	<u>694</u> , 695 - 697
5-Thia-1-azabicyclo[4,2,0]oct-2-ene-carboxylic acid, 3-methyl-8-oxo-7-(2-phenylacetamido)-	
+ ammonium chloride (aqueous)	<u>664</u> , 666
+ potassium chloride (aqueous)	<u>664</u> , 665
+ water	<u>664</u> , 665, 666

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