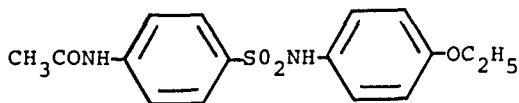
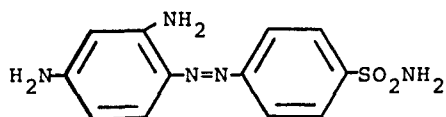


PREFACE

With few exceptions, these volumes of the solubility data series deal with solubilities of the derivatives of 4-aminobenzenesulfonamide, usually referred to as "sulfanilamide" (sulfanilic acid amide), a name coined in 1937 (1). The history of sulfanilamide begins in 1906, when Schroeter (2) synthesized the molecule containing a 4-acetylamino-sulfanilamide portion.



In 1908, Gelmo (3) described sulfanilamide and 13 of its derivatives and gave solubility values for these compounds. In 1935, Domagk (4) detected antibacterial activity of a synthetic azo dye, prontosil, with the structure.



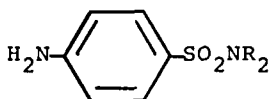
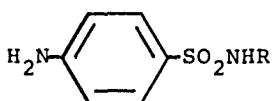
This compound had been tested for antibacterial activity (5), the "sulfanilamide" portion being responsible for its activity. This was confirmed (6) by isolation of sulfanilamide in the urine of patients. Fildes (7) and Wood (8), in 1940, demonstrated that the derivatives of sulfanilamide were antimetabolites of p-aminobenzoic acid (PABA) which is a step in the folic acid synthesis of bacteria. Thus, the structural similarity of PABA and sulfonamides caused interference by competitive antagonism and resulted in a bacteriostatic effect. The discoveries of antibacterial activity led to an exciting flood of research, and thousands of sulfanilamide derivatives have been synthesized. As early as 1948, the number of sulfonamide derivatives (9) was estimated to be several thousand. In the two decades after that, the number of synthesized sulfonamides have gone past 10,000(10)

Clinical trials of these sulfonamides and derivatives have been associated with low solubilities and some renal crystalluria. The low solubility, and its sensitivity to pH, could cause crystalline precipitation in the renal tubules in the filtration of blood into acidic urine. Some of the problems of limited solubility were overcome by complexation or salt formation, and solid state manipulations which in turn have stimulated investigations into solubility of the drugs in water, buffers and some binary solvent system. Analytical methodologies span a wide spectrum of techniques and the relevant references are in pharmaceutical, medical and chemical literature.

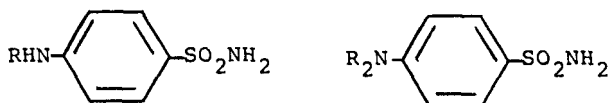
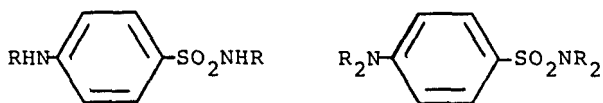
In all volumes the chemical structures, registry number and the molecular weight of the compounds considered are collected in the front of each volume. The compounds as they occur on the data sheets are given successively in each volume. In the first volume of this series there are 35 compounds. The second and third volumes have 58 compounds and 108 compounds, respectively.

NOMENCLATURE:

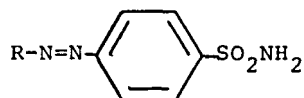
The nomenclature of sulfanilamide derivatives has conventionally been based on the following numbering system: substituents at the nitrogen atom of the amide group ($-\text{SO}_2\text{NH}_2$) are called N^1 -substituents, whereas substituents at the 4-amino nitrogen ($4-\text{H}_2\text{N}-$) are called N^4 -substituents. Substitution in either or both of the two positions lead to compounds referred to as "sulfonamides" (sometimes "sulfanilamides" or even "sulfamides"). Here are illustrative examples of this nomenclature.



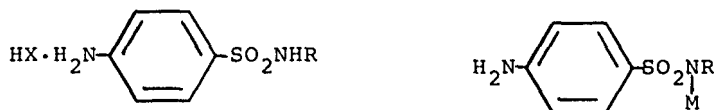
N^1 -substituted sulfonamides

 \underline{N}^4 -substituted sulfonamides $\underline{N}^1, \underline{N}^4$ -substituted sulfonamides

The 4-amino group can be diazotized to give derivatives of the formula



As the sulfonamide molecule carries a basic 4-NH₂ group and an acid -SO₂NH₂ one, it is capable of formation the respective salts or complexes, e.g.



where HX stands for an acid and M is a univalent metal atom.

In common use by health practitioners are nonproprietary names of sulfonamides which are brief and reflect the chemical nature of their molecules. Examples are: sulfacetamide, sulfapyridine, sulfathiazole, sulfadiazine, sulfaguanidine, etc. There are numerous trivial names; for example, sulfanilamide has as many as 140 synonyms, and sulfathiazole has 113. Negwer (11) has compiled an excellent guide to this nomenclature. In chemical literature, systematic names in line either with IUPAC (12) or Chemical Abstract rules (13) are used. The latter has been adopted in these volumes and the systematic name is, where appropriate, followed by the nonproprietary or trivial name.

ORGANIZATION OF THE VOLUMES:

The numerical data on the solubility of 2-aminobenzenesulfonamide, 3-aminobenzenesulfonamide, and 4-aminobenzenesulfonamide and its \underline{N}^1 and \underline{N}^4 - derivatives, salts and complexes, compiled up to 1985 inclusive, have been divided into three volumes on the basis of chemical structure of the compounds.

The first volume includes the solubility of 2-aminobenzenesulfonamide, 3-aminobenzenesulfonamide, 4-aminobenzenesulfonamide and the derivatives of the last-named compound substituted at either of the nitrogen atoms, or both, with non-cyclic substituents (see System Index at the end of the first volume). The aroyl substituents, -C(:O)aryl, have also been included here. The second volume includes sulfanilamide derivatives substituted with 5-membered heterocyclic rings at either of the nitrogen atoms, and their derivatives. The third volume covers the solubilities of the derivatives substituted with 6-membered rings, mixtures of sulfonamides, and miscellanea. The compilations do not include compounds devoid of the -NH₂, -NHR or -NR₂ group in the benzene ring.

The solvent systems include all solvents with the exception of body fluids. The order of solvents for a particular solute are as follows: water; water-mineral acid; water-mineral base; water-mineral salt; water-miscellaneous mineral components; water-mineral and organic compounds; water-organic components; organic solvents; carboxylic acid and their salts; aliphatic acids; aromatic acids; other acids; alcohols, phenols (mono-, di-, polyhydric); amides; amines; aliphatic amines (primary, secondary, tertiary); aromatic amines (primary, secondary, tertiary); other amines; aminoalcohols; carboxylic acid esters; ethers (excluding tensides); hydrocarbons; aliphatic hydrocarbons; aromatic hydrocarbons; miscellaneous hydrocarbons; halogenated hydrocarbons (fluoro-, chloro-, bromo-, iodo-); aliphatic halogenated hydrocarbons; aromatic halogenated hydrocarbons; ketones; tensides (surface-active agents); miscellaneous organic solvents.

SIGNIFICANT FIGURES AND GRAPHICAL DATA:

In most cases, solubility values given in the primary source by various workers are overstated with respect to significant figures. Since the author(s) original values are given on the data sheets, it is difficult to consider significant figures and analytical limitations in a completely consistent fashion. Therefore, the reader should be aware that in most cases the number of significant figures used for calculations was not that given by the original author(s). This was done to maintain coherence and consistency as data were given to varying significant figures. In many cases graphic data of sufficient size and clarity are reproduced. The data can be regarded of sufficient accuracy to serve as a starting point for more precise determinations. In many instances, the effect of additive concentration, pH, temperature, etc. can be depicted.

POLYMORPHISM:

Many sulfonamides exhibit several crystalline forms or polymorphs. There are several studies referenced in these volumes that specifically deal with the solubility difference between polymorphic modifications of the same compound. The solubility differences between polymorphs have been found to vary over a large range of values.

AMPHOLYTES:

Solubility of ampholytic sulfonamides as a function of pH varies enormously, sometimes by several orders of magnitude. Unless the pH is known experimentally, the solubility value may be suspect especially at low (1-3) and high pH (10-12) values. In these cases, the solubility is a rapidly changing value, frequently with small incremental changes of pH. The abrupt change of solubility with pH is usually associated with the formation of water soluble anionic and cationic species. Buffers, especially at higher concentrations may alter solubility by salting effect and the pH is also affected by ionic strength.

EQUILIBRATION TIME:

In general, it appears that many of these determined solubilities may not have been under equilibrium conditions. Unfortunately, in too many instances the equilibration time appears too low. Typically, solutes possess low aqueous solubilities and require long dissolution time to reach saturation. Saturation time should be experimentally determined in each case and for each compound. In many cases up to 24 hours may be required.

The editors consider the vast majority of the solubility values given in these volumes as tentative. It should be stressed, however, that they represent a useful starting point for more accurate determinations of a vast array of substituted 4-aminobenzene-sulfonamides with many structurally and chemically related compound of various types. They amply illustrate the many factors and parameters affecting solubility and the direction and magnitude of these effects.

This compilation and evaluation is not only the result of the joint efforts of the compiler and evaluator, but also of all those who read the manuscripts, expressed their criticism, who procured copies of hard-to-get journals, who translated texts from Japanese as well as of those who in any other way assisted in the compilation and evaluation. We would like to express our gratitude in particular to the following colleagues: Prof. S. Kertes, Dr. M. Salomon, Prof. S. Yalkowsky, Prof. H. Akaiwa, Prof. C. Kalidas, Prof. W. Riess, Prof. A. Guerrero-Laverat, Prof. P. Rohdewald, Prof. J. Püttner, Dr. K. L. Loening, Dr. A. Brodin, Dr. D. Zimma, Mr. K. Hazelton, Dr. R. Fernandez-Prini, and Mr. E. MacMullan.

REFERENCES TO THE PREFACE:

1. Council on Pharmacy and Chemistry, *J. Am. Med. Assoc.* 1937, *108*, 1888.
2. Schroeter, G. *Ber. Dtsch. Chem. Ges.* 1906, *39*, 1559.
3. Gelmo, P. *J. Prakt. Chem.* [2], 1908, *77*, 369.
4. Domagk, G. *Dtsch. Med. Wschr.* 1935, *61*, 250 and 829.
5. Tréfouël, T. J.; Nitti, F.; Bovet, D. *Compt. Rend. Soc. Biol.* 1935, *120*, 756.
6. Fuller, A. T. *Lancet*, 1937, 194.
7. Fildes, P. *Lancet*, 1940, 955.
8. Woods, D. D. *J. Expt. Path.* 1940, *21*, 74.
9. Langecker, H. *Arch. Exptl. Pat. Pharmakol.* 1948, *205*, 291.
10. Rolski, S. *Chemia Srodkow Leczniczych (Chemistry of Medicinal Agents)*, 3rd ed., PZWL, Warsaw, 1968.
11. Negwer, M. *Organisch-chemische Arzneimittel und ihre Synonyma (Organic-chemical Drugs and their Synonyms)*, Akademie-Verlag, Berlin, 1978.
12. *Nomenclature of Organic Chemistry, Definitive Rules for Section C. Characteristic Groups Containing Carbon, Hydrogen, Oxygen, Nitrogen, Halogen, Sulfur, Selenium, and/or Tellurium IUPAC Commission on the Nomenclature of Organic Chemistry*, London, Butterworths, 1971, rule 641.8.
13. *J. Chem. Documentation* 1974, *14*, 3.