[CONTRIBUTION FROM THE DIVISION OF PHARMACOLOGY, NATIONAL INSTITUTE OF HEALTH, UNITED STATES PUBLIC HEALTH SERVICE]

Organic Compounds in Chemotherapy. II. The Preparation of Formaldehyde Sulfoxylate Derivatives of Sulfanilamide and of Amino Compounds

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The combination of aromatic amino compounds with sodium formaldehyde sulfoxylate usually is brought about by the action of sodium formaldehyde sulfoxylate on the hydrochloride of the amino compound in aqueous solution, or by heating a suspension of the amine in water with the calculated amount of sodium formaldehyde sulfoxylate.

In preparing the formaldehyde sulfoxylate derivatives of sulfanilamide and of 4,4′-diaminodiphenylsulfone, a convenient method was found by carrying out the reaction in a solution of glacial acetic acid. Sodium formaldehyde sulfoxylate dissolves readily in glacial acetic acid. The small amount of decomposition which can be observed does not influence the reaction. The combination of the calculated amounts of the components takes place in about fifteen to thirty minutes, and by addition of ether and alcohol the acetic acid is removed easily, while the reaction product is obtained as a crystalline precipitate. By crystallization from warm water or dilute alcohol the formaldehyde sulfoxylate derivatives can be obtained in a pure state. The sensitivity of these compounds to acids requires complete neutralization of the acetic acid. Their stability is increased by the addition of a small excess of sodium bicarbonate.

Studies of these compounds in experimental bacterial infections have already been published.[1] By attaching the sodium formaldehyde sulfoxylate to the amino group, water soluble compounds are obtained which can be administered subcutaneously. In the case of sulfanilamide the chemotherapeutic index is diminished by this substitution. In the case of the 4,4′-diaminodiphenylsulfone, a better result is obtained; while the absolute value of the chemotherapeutic activity is diminished, the high toxicity of the sulfone decreases to a much greater extent, and the chemotherapeutic index is improved. This result agrees with the result obtained by E. Fourneau[2] by acetylation of the diaminodiphenyl sulfone.

The sodium formaldehyde bisulfite derivative of the 4,4′-diaminodiphenyl sulfone was also prepared. It was found to possess surprisingly little action against streptococci and pneumococci.

The table gives a summary of the toxicity and chemotherapeutic activity of the 4,4′-diaminodiphenyl sulfone and its derivatives in comparison to sulfanilamide.

Experimental

Sodium Sulfanilamide Formaldehyde Sulfoxylate.—An intimate mixture of sulfanilamide (5.0 g.) and sodium formaldehyde sulfoxylate (5.5) was added gradually, while stirring, to glacial acetic acid (15 cc.). After about twenty-five minutes of stirring a clear solution was obtained which was mixed with ether until a solid precipitate was formed. Then sufficient ether for complete precipitation was added. The solid was separated by suction, washed with ether, dissolved in a small amount of water and neutralized by addition of sodium bicarbonate. By the addition of three volumes of alcohol and cooling, a precipitate of inorganic salts appeared which was filtered off. The filtrate was mixed with ether and yielded a crystalline precipitate of the reaction product, which was separated by suction, washed with a mixture of equal parts of alcohol and ether and dried in vacuum. The yield was 7.7 g.

The sodium sulfanilamide formaldehyde sulfoxylate thus obtained was readily soluble in water with weakly alkaline reaction. It was not soluble in 95% alcohol, but dissolved in it after addition of a little water.

The salt was purified by dissolving 5 g. in 10 cc. of warm water and cooling. Small crystals of silky luster were obtained which were dried in air. The compound contains two molecules of water of crystallization which can be removed at 100°.

Anal. Calcd. for $C_7H_9O_4N_2S_2Na + 2H_2O$: H_2O, 11.68; S, 20.80; Na, 7.46. Found: H_2O, 11.75; S, 20.92; Na, 7.19.

While standing in air, the water-free compound attracts one molecule of water. Calcd.: H_2O, 6.21. Found: H_2O, 6.88.

Sodium 4,4′-Diaminodiphenyl Sulfone *bis*-Formaldehyde Sulfoxylate.—This product is obtained in the same way as described above by combining 4,4′-diaminodiphenyl sulfone (12 g.) with sodium formaldehyde sulfoxylate (15 g.) in glacial acetic acid (35 cc.). Upon the addition

(1) S. M. Rosenthal, H. Bauer and S. E. Branham, *Pub. Health Repts.*, U. S. Treas. Dept., **52**, 662 (May 21, 1937); H. Bauer and S. M. Rosenthal, *ibid.*, **53**, 40 (Jan. 14, 1938).

(2) E. Fourneau, M. and Mme. J. Tréfouel, F. Nitti and D. Bovet, *Compt. rend. acad. sci.*, **205**, 299 (1937).

TABLE I

TOXICITY AND THERAPEUTIC ACTIVITY COMPARED TO SULFANILAMIDE IN STREPTOCOCCAL INFECTIONS OF MICE

MTD = Maximum tolerated dose; MED = Minimum effective dose.

Compound	Toxicity to mice g. per kg.	Therapeutic activity g. per kg.
Sulfanilamide	MTD subcut. (oil) 2.5; orally 2.5	MED subcut. 0.5; oral 0.75
Sodium sulfanilamide formaldehyde sulfoxylate		Inferior
4,4′-Diaminodiphenyl sulfone	MTD orally 0.15	MED 0.025
4,4′-Diacetyldiaminodiphenyl sulfone	MTD orally >4.0	MED 0.2
Sodium 4,4′-diaminodiphenyl sulfone *bis*-formaldehyde sulfoxylate	MTD subcut. 3.0	MED 0.2
Sodium 4,4′-diaminodiphenyl sulfone diformaldehyde bisulfite		Little activity

of alcohol to the neutralized aqueous solution, the reaction product crystallized in fine needles; the needles contain two molecules of water of crystallization. The compound is readily soluble in water.

Anal. Calcd. for $C_{14}H_{14}O_6N_2S_3Na_2 + 2H_2O$: N, 5.78; S, 19.86; Na, 9.50. Found: N, 5.64; S, 19.80; Na, 9.24.

To keep the formaldehyde sulfoxylate derivatives stable either in solution or in a solid state, a small amount of sodium bicarbonate must be added.

Sodium 4,4′-Diaminodiphenyl Sulfone *bis*-Formaldehyde Bisulfite.—A mixture of 4,4′-diaminodiphenyl sulfone (2.5 g.), sodium formaldehyde bisulfite (3.5 g.) and water (15 cc.) was heated on a steam-bath for about two hours, until solution occurred. Upon cooling, a part of the condensation product crystallized out; the main portion was precipitated in fine needles by addition of alcohol. The colorless crystals are freely soluble in water; they contain 4 molecules of water of crystallization which can be removed by heating on a steam-bath. Upon standing in air, the water-free material attracts again 4 molecules of water.

Anal. Calcd. for $C_{14}H_{14}O_8N_2S_3Na_2 + 4H_2O$: S, 17.41; H_2O, 13.05. Found: S, 17.17; H_2O, 12.82.

Summary

A new method of preparing sodium formaldehyde sulfoxylates of aromatic amino compounds has been described. The method was used for the preparation of the derivatives of sulfanilamide and 4,4′-diaminodiphenyl sulfone. Results of their chemotherapeutic action are given. The sodium formaldehyde bisulfite derivative of 4,4′-diaminodiphenyl sulfone also has been prepared.

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The Influence of Substituents on the Rates of Decomposition of the Potassium Salts of Dihydroxamic Acids. The Lossen Rearrangement

BY ROBERT D. BRIGHT AND CHARLES R. HAUSER

The general course for the Hofmann and Lossen reactions of compounds of the type RCONHX (where X is halogen, benzoate, etc.) in the presence of alkali, may be represented as follows

$$\mathrm{RCONHX + KOH \longrightarrow (RCONX)^-K^+ + HOH}$$

$$\mathrm{(RCONX)^-K^+ \longrightarrow (RCON) + K^+X^-}$$

$$\mathrm{(RCON) \longrightarrow RNCO}$$

First, an acid–base reaction occurs forming the salt $(RCONX)^-K^+$; many salts of this type can be isolated. Second, the anion of the salt releases X with a complete octet of electrons (*i. e.*, as an anion) leaving the nitrogen atom with only a sextet of electrons. Third, the molecule is stabilized by rearrangement to an isocyanate[1]; this is considered to involve a shift of an electron pair, together with the group R attached, from carbon to nitrogen.[2] It is possible that the "univalent nitrogen derivative," although never isolated, might have a brief existence; on the other hand, it is also possible that the release of X from the anion of the salt and the migration of R are simultaneous processes. Regardless of the intimate mechanism, however, there seems little doubt that the rate measured[3] in the decomposi-

(1) Generally, the isocyanate is decomposed under the experimental conditions employed; in the presence of excess alkali, the corresponding primary amine is formed, while, in the presence of ammonia, which is used in the experiments described in this paper, urea derivatives are formed.

(2) See Whitmore, THIS JOURNAL, **54**, 3281 (1932).

(3) The release of X may be the rate determining step, and the rearrangement of the "univalent nitrogen complex," a relatively rapid or simultaneous process. On the other hand, the experimental results might also be accounted for on the basis that the irreversible rearrangement of the "univalent nitrogen complex" is the relatively slow step. This would be possible, however, only if the release of X were a reversible reaction whose equilibrium is far on the side of unchanged dihydroxamate anion; the concentration of the "univalent nitrogen complex" would then be dependent upon the ease of release of X.