[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE CALCO CHEMICAL COMPANY, INC.]

# Sulfanilamide Derivatives. III. *strepto*-N-Polysulfanilylsulfanilamides and Related Compounds[1]

BY M. L. CROSSLEY, E. H. NORTHEY AND MARTIN E. HULTQUIST

Fourneau and his co-workers[2] describe the compound which we would name $N^4$-(N-acetylsulfanilyl)-sulfanilamide as having little therapeutic effect. Later Rosenthal[3] studied $N^4$-sulfanilylsulfanilamide and more recently[4] $N^1$-(2-hydroxyethyl)-$N^4$-sulfanilylsulfanilamide, and *strepto*-$N^4$-disulfanilylsulfanilamide.

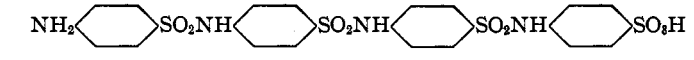
In the meantime investigators at the I. G. had studied $N^4$-sulfanilylsulfanilamide and its $N^4$-mono- and dimethyl derivatives.[5]

Gray, Buttle and Stephenson[6] also made $N^4$-sulfanilylsulfanilamide, which they named *p*-aminobenzenesulfonyl - *p'* - sulfonamidophenylamide. This is an example of what one encounters in trying to name such derivatives by conventional methods. The name is sufficiently formidable to make even chemists think twice, or reach for paper and pencil.

We have synthesized, independently of the others, not only the parent compound but a large number of derivatives using as starting materials many of the compounds described in the first two papers of this series.

The method of synthesis was to treat N-acetylsulfanilyl chloride with sulfanilamide or any of its $N^1$-derivatives at *p*H 8–10, followed by hydrolysis of the acetyl group with either acid or base depending on the character of the compound.

By increasing the chain of sulfanilyl groups the compounds become increasingly difficult to crystallize. Thus *strepto*[7]-N-trisulfanilylsulfanilic acid




forms an emulsion in water which is difficult to work with. However, its sodium salt is nearly impossible to handle, since it forms a pearly dispersion closely resembling a vanishing cream, which resists all attempts to filter.

In the synthesis of $N^1$-hydroxyalkyl-*strepto*-N-polysulfanilylsulfanilamides crystallization of the product is difficult not only because of the tendency of the desired compound to form tars or oils, but because the crude products are often contaminated by sulfanilic esters. However, after crystals once have been obtained subsequent crystallizations are easy. In general, these compounds were purified by dissolving in alcohol, treating with activated carbon, and slowly diluting with water so as to prevent immediate precipitation of the bulk of the material as an oil.

The derivatives made and their pharmacology are indicated in the following table, where sulfanilamide = ++, comparison being made on β-hemolytic streptococcic infections in mice.[8,9]

Inferences which can be drawn from a study of the present results and the results described in our first two papers are:

1. There is an apparent increase of activity by adding a sulfanilyl group to the amino group in sulfanilamide, N-sulfanilylsulfanilic acid, $N^1$-(2-hydroxyethyl)-sulfanilamide and $N^1$-(2-hydroxypropyl)-sulfanilamide.

2. Activity is decreased by adding a sulfanilyl group to 2-sulfanilamidobenzoic acid, $N^1$,$N^1$-*bis*-2-hydroxyethylsulfanilamide, and disulfanilamide.

3. Addition of a third sulfanilyl group decreases the activity in $N^1$-2-hydroxyethyl-$N^4$-sulfanilylsulfanilamide; increases it in *strepto*-N-disulfanilylsulfanilic acid.

4. The much better activity of $N^3$-sulfanilylmetanilamide as compared with $N^4$-metanilylsulfanilamide is significant and was predicted. The first compound is behaving as a sulfanilamide substituted on the amido nitrogen while the second is behaving as a sulfanilamide substituted on the amino nitrogen. All previous results, including our own, indicate that new *sulfanilamide* derivatives of greater activity will be substituted by groups on the amido nitrogen and probably not elsewhere.

5. Certain of these compounds have been found effective against virus diseases.

(1) Presented in part before the Division of Medicinal Chemistry, A. C. S., April 20, 1938.

(2) Fourneau, *et al.*, *Compt. rend., soc. biol.*, **122**, 258 (1936).

(3) Rosenthal, *et al.*, *Pub. Health Repts., U. S. Treas. Dept.*, **52**, 662 (1937).

(4) Rosenthal, et al., *ibid.*, **53**, 40 (1938).

(5) Mietzsch, *Ber.*, **71**, 15 (1938); French Patent, 817,034, Aug. 24, 1937.

(6) Gray, Buttle and Stephenson, *Biochem. J.*, **31**, 724 (1937).

(7) We have used the prefix "*strepto*" to indicate that the sulfanilyl- groups are in a chain rather than separately attached. It has no therapeutic connotation as used.

(8) The pharmacology will be reported by D. R. Climenko elsewhere.

(9) Microanalyses were made under the direction of G. L. Royer.

| Compound | Formula | Therapeutic effect | Melting range, °C. | Assay by nitrite, % | Analyses, % Calcd. C | H | N | S | Found C | H | N | S |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $N^4$-Sulfanilylsulfanilamide[a] | $C_{12}H_{13}O_4N_3S_2$ | +++ | 132.5–136 | 99.6 | 44.0 | 4.0 | 12.86 | 19.6 | 43.3 | 4.3 | 12.9 | 19.2 |
| *strepto*-$N^4$-Disulfanilylsulfanilamide[a,b] | $C_{18}H_{18}O_6N_4S_3$ | +++ | 210.0–211.5 | 100.4 | 44.8 | 3.76 | 11.62 | 19.9 | 44.8 | 4.0 | 11.6 | 19.4 |
| $N^4$-Metanilylsulfanilamide | $C_{12}H_{13}O_4N_3S_2$ | + | 142–144 | 100.0 | 44.1 | 4.01 | 12.86 | 19.6 | 43.7 | 4.0 | 12.7 | 19.5 |
| $N^3$-Sulfanilylmetanilamide | $C_{12}H_{13}O_4N_3S_2\cdot{}^1/_2H_2O$ | ++ | 134–156 | 100.0 | 42.9 | 4.2 | 12.5 | 19.1 | 43.4 | 4.6 | 12.5 | |
| Sodium-*strepto*-N-disulfanilylsulfanilate | $C_{18}H_{16}O_7N_3S_3Na$ | + | >220 dec. | 99.5 | 42.72 | 3.18 | 8.32 | Na, 4.55 | 42.1 | 3.9 | 8.22 | Na, 4.3 |
| *strepto*-N-Trisulfanilylsulfanilic acid | $C_{24}H_{22}O_9N_4S_4\cdot 2H_2O$ | ++ | >250 dec. | 105 | 42.6 | 3.89 | 8.32 | 19.6 | 42.4 | 4.6 | 8.24 | |
| 2-($N^4$-Sulfanilylsulfanilamido)-benzoic acid | $C_{19}H_{17}O_6N_3S_2$ | ++ | 200–203 | 100.2 | 51.0 | 3.83 | 9.40 | 14.32 | 49.3 | 4.4 | 9.3 | 12.9 |
| $N^1$-(2-Hydroxyethyl)-$N^4$-sulfanilylsulfanilamide[b] | $C_{14}H_{17}O_5N_3S_2$ | +++ | 140–143 | 100.2 | 45.3 | 4.61 | 11.31 | 17.28 | 45.2 | 4.8 | 11.2 | 17.3 |
| $N^1$-(2-Hydroxyethyl)-$N^3$-metanilylmetanilamide | $C_{14}H_{17}O_5N_3S_2$ | ± | 125–127.2 | 100.4 | 45.3 | 4.61 | 11.31 | 17.28 | 44.7 | 4.9 | 11.31 | |
| $N^1$-(2-Hydroxyethyl)-*strepto*-$N^4$-disulfanilylsulfanilamide | $C_{20}H_{22}O_7N_4S_3$ | ± | 137–143 | 99.1 | 45.6 | 4.21 | 10.65 | 18.27 | 45.35 | 4.27 | 11.1 | |
| $N^1$,$N^1$-*bis*-2-Hydroxyethyl-$N^4$-sulfanilylsulfanilamide[a] | $C_{18}H_{21}O_6N_3S_2$ | + | 122.5–128 | 96.4 | 46.25 | 5.16 | 10.1 | 15.41 | 46.3 | 5.6 | 10.0 | 14.9 |
| $N^1$,$N^1$-*bis*-2-Hydroxyethyl-*strepto*-$N^4$-disulfanilylsulfanilamide | $C_{22}H_{25}O_8N_4S_3$ | + | 115.5–120.5 | 99.5 | 46.3 | 4.6 | 9.81 | 16.84 | 45.5 | 5.0 | 9.8 | 16.1 |
| $N^1$-(2-Hydroxypropyl)-$N^4$-sulfanilylsulfanilamide | $C_{15}H_{19}O_5N_3S_2$ | + | 127.3–129.6 | 100.2 | 46.8 | 5.00 | 10.9 | 16.6 | 45.5 | 4.82 | 10.95 | 16.8 |
| $N^1$-Phenyl-$N^1$-(2-hydroxyethyl)-$N^4$-sulfanilylsulfanilamide | $C_{20}H_{21}O_5N_3S_2$ | ++ | 183–185 | 100.0 | 53.0 | 4.0 | 9.47 | 14.38 | 52.8 | 5.0 | 9.55 | 14.3 |
| $N^1$,$N^1$-*bis*-2-Hydroxyethyl-$N^4$-*p*-toluenesulfonylsulfanilamide | $C_{17}H_{22}O_6N_2S_2$ | ± | 187–190 | | | | | | | | | |
| $N^1$-Sodium-$N^1$,$N^4$-dimetanilylsulfanilamide | $C_{18}H_{17}O_6N_4S_3Na$ | + | 280 dec. | 100.4 | 42.8 | 3.39 | 11.1 | Na, 4.57 | 41.4 | 3.5 | 11.1 | Na, 3.9 |
| $N^1$,$N^4$,$N^{4'}$-Trisodium-$N^4$,$N^{4'}$-disulfanilyldisulfanilamide | $C_{24}H_{20}O_8N_5S_4Na_3$ | 0 | 340 dec. | 100.4 | | Na, 9.81 | | | | Na, 9.05 | | |
| $N^4$-Sulfanilyldisulfanilamide | $C_{18}H_{18}O_6N_4S_3$ | + | 198.5–206 | 99.2 | 44.7 | 3.72 | 11.6 | 19.8 | 43.4 | 3.7 | 11.1 | 19.8 |

[a] I. G. Fr. 817,034, Aug. 24, 1937.

[b] Bauer and Rosenthal, ref. 4.

It should be pointed out that the therapeutic effectiveness of these various sulfanilamide compounds is described in terms of a series of preliminary pharmacological experiments carried out on large groups of mice experimentally infected with a very virulent strain of β-hemolytic streptococci, using massive infecting doses and single protective doses of the therapeutic agent. In all cases the control animals died in sixteen hours. Reported results are in terms of animals surviving at the end of seventy-two hours. Much further experimental evidence will be needed to establish the usefulness of these products in human medication, since acute toxicity studies in mice tell nothing of the complications of human administration, such as fever, cyanosis, dermatitis, acidosis and peripheral neuritis.

## Experimental

**General Method of Preparation.**—The general method for making the present derivatives was the same as that described in the first paper of this series for the preparation of sodium N-sulfanilylsulfanilate.[10] Syntheses of compounds involving important variations of this method are given below.

**$N^4$-Metanilylsulfanilamide.**—Seven-tenths mole of sulfanilamide was dissolved in 500 cc. of water at about 95°; 0.5 mole of freshly prepared *m*-nitrobenzenesulfonyl chloride was added rapidly with vigorous agitation. When the mixture had crystallized (ten to fifteen minutes) sufficient sodium hydroxide was added to dissolve the solid. The solution was clarified and poured into 400 cc. of concentrated hydrochloric acid. $N^4$-*m*-Nitrobenzenesulfonylsulfanilamide precipitated while excess sulfanilamide remained dissolved. The precipitate was filtered and washed with hot water. It was reduced with ammonia and hydrogen sulfide by the general procedure for metanilyl derivatives.[11]

Attempts to prepare this compound by the usual procedure lead to $N^1$,$N^4$-di-(*m*-nitrobenzenesulfonyl)-sulfanilamide as the main product.

$N^1$-(2-Hydroxyethyl)-$N^4$-sulfanilylsulfanilamide and similar derivatives were made by the general method while maintaining a *p*H of 7–9 (when foaming occurred sufficient sodium hydroxide solution was added to give a faint pink spot test on phenolphthalein paper). It was thought that a somewhat lower *p*H led to formation of less of the sulfanilic esters which gave difficulty in purification of the final products. The crude hydrolyzed products were oils or sticky masses which were partially purified by dissolving as the sodium salts in water, treating with activated charcoal, and reprecipitating with acid. Initial crystallization was frequently very slow, extending in some cases to weeks. Most favorable conditions found for inducing initial crystallization were established by dissolving the material in about twice the amount of 60–80% alcohol, treating with decolorizing carbon, and diluting with water

(10) Crossley, Northey and Hultquist, THIS JOURNAL, **60**, 2220 (1938).

(11) Crossley, Northey and Hultquist, THIS JOURNAL, **60**, 2220 (1938).

at room temperature until the solution remained slightly milky. It was then allowed to stand with occasional agitation and scratching of the walls until crystallization started. Once seed crystals were obtained subsequent recrystallizations were comparatively easy.

**$N^4$-Sulfanilyldisulfanilamide.**—One-half mole of sulfanilamide was dissolved in 500 cc. of water with sufficient sodium hydroxide to give a *p*H of 10–12; 1.2 moles of freshly prepared N-acetylsulfanilyl chloride was added over half an hour at 35–40° while maintaining the above *p*H by addition of 50% sodium hydroxide as necessary. Stirring was continued for one hour, then 100 g. of sodium hydroxide was added, and the mixture boiled for two hours. The hydrolysis mixture was neutralized with concentrated hydrochloric acid, cooled, crystals of crude $N^1$-sodium-$N^4$-sulfanilyldisulfanilamide filtered off, and recrystallized several times from water, using activated charcoal. The free amide was made by acidification of a solution of the sodium salt. The initial amorphous mass was crystallized by rubbing in alcohol.

**$N^1$,$N^4$,$N^{4'}$-Trisodium $N^4$,$N^{4'}$-disulfanilyldisulfanilamide.**—This was made by the general procedure starting with an equivalent of $N^1$-sodium disulfanilamide. Attempts to prepare a crystalline monosodium salt or crystalline free amide failed. The trisodium salt (actually a mixture with some of the disodium salt) was crystallized from a concentrated aqueous solution at *p*H 9–10, by dilution with alcohol.

**$N^1$-(2-Hydroxyethyl)-$N^3$-metanilylmetanilamide.**—One-third mole of $N^1$-(2-hydroxyethyl)-metanilamide was dissolved in 300 cc. of water containing 30 g. of boric acid; $^1/_3$ mole of *m*-nitrobenzenesulfonyl chloride was added over an hour at 55–65° with vigorous agitation while maintaining a *p*H of 6–8 by addition of 50% sodium hydroxide solution as required. The nitro compound which separated on cooling was reduced with 150 g. of fine iron, 500 cc. of water, and 1 cc. of glacial acetic acid at 95–100°. After complete reduction excess sodium hydroxide was added to dissolve completely the product, the mixture was filtered, and the filtrate neutralized. A sticky mass separated which crystallized on standing overnight. This crude product was recrystallized by dissolving in hot alcohol, treating with activated charcoal, then diluting gradually with water, cooling and seeding. After several recrystallizations, colorless crystals were obtained.

Boric acid was used in the hope that by forming a complex with the hydroxyl groups, it would aid in preventing formation of sulfonic esters. Success in obtaining a crystalline product through its use, where previously there had been failure, leads us to believe that it was of value.

## Summary

A series of *strepto*-N-polysulfanilyl derivatives of aminobenzenesulfonic acids and carboxylic acids, hydroxyalkylamines, sulfonamides, and disulfonamides are described, together with preliminary results of the pharmacological study of their effect in mice infected with β-hemolytic streptococci.

No general conclusions can be drawn concerning the effect of increasing the number of sulfanilyl groups.

Better activity was shown by $N^3$-sulfanilylmetanilamide than by $N^4$-metanilylsulfanilamide This was predicted from previous results.

Certain of these compounds appear effective in virus diseases, but caution is expressed against assuming that the results of these preliminary studies in mice are translatable to human therapy.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF WISCONSIN]

# Ethylenediamine and Propylenediamine Vanadates

BY EUGENE H. HUFFMAN

In the course of an investigation, some diamine vanadates were desired. A search of the literature did not reveal the previous preparation of these, though some alkyl amine vanadates[1] and a pyridinium vanadate[2] have been described. This paper describes the preparation and some properties of hydrated hexavanadates of ethylenediamine and propylenediamine and the metavanadate of ethylenediamine.

(1) Bailey, *J. Chem. Soc.*, **45**, 690 (1884); *Compt. rend.*, **104**, 1844 (1887).

(2) Katzoff and Roseman, THIS JOURNAL, **58**, 1785 (1936).

### Preparation

**Ethylenediamine and Propylenediamine Hexavanadates.**—Ten grams of vanadium pentoxide (either C. P. grade or prepared by gently heating ammonium metavanadate) is added to a solution of 5 cc. of 69.8% ethylenediamine and 15 cc. of water, or 8 g. of vanadium pentoxide to 5 cc. of 70–75% propylenediamine and 15 cc. of water. Then 15 cc. of 30% hydrogen peroxide is added slowly, with stirring, over a period of half an hour, while keeping the temperature below 60°. The mixture is filtered, washed with 25 cc. of water, to which is added 3 cc. of 30% hydrogen peroxide, and the filtrate and washings diluted to 150 cc. After just neutralizing the solution to