again being protected from the air with a nitrogen mantle. The tubes were stoppered immediately, shaken vigorously and centrifuged at 2800 r. p. m. for ten minutes. The clear supernatant liquid was decanted into a flask containing 75 cc. of water. A 20-cc. portion of dry ether was added to the solid residue remaining in the centrifuge tube, which was again shaken, centrifuged for five minutes and decanted into the flask containing water. Further washing of the precipitate with ether failed to remove significant quantities of basic magnesium or halogen, showing that there was little if any occlusion, except in analyses using pyridine in quantities sufficient to precipitate diphenylmagnesium. In the latter case the amount of basic magnesium taken into solution increased with each washing of the precipitate, so that the analyses with more than 1.6 equivalents of pyridine have no exact quantitative significance.

In the pyridine analyses, the ether was first boiled off, after which the aqueous mixture was boiled for thirty minutes to remove the pyridine, acidified with an excess of standard sulfuric acid, again boiled for five minutes and back titrated with standard alkali. Bromide analyses were made on the same samples, after cooling, by Volhard titration. The method was proved to be accurate by analysis of a Grignard reagent of known normality after the addition of pyridine. The end-points in the acidimetric titration were not as sharp as in the dioxane analyses. Solutions precipitated with dioxane were acidified initially with an excess of standard sulfuric acid and boiled long enough to expel completely the ether before back titrating with standard alkali.

**Precipitations with Isoquinoline.**—Isoquinoline gives a bulky solid precipitate with phenylmagnesium bromide in ether solution. The precipitate may be separated by centrifuging, and the solutions analyzed as in the pyridine procedure if they are boiled for one hour before acidification, although the end-points are obscure in the acidimetric titration. Interpretation of the analyses is difficult, because a relatively large proportion of the bromide ion remains in solution. The following data are representative. A solution of phenylmagnesium bromide 0.2060 *N* in basic magnesium and 0.2138 *N* in bromide ion was precipitated as described above with 1.0 and 1.1 equivalents of isoquinoline. The solutions after centrifuging contained: (1 equivalent of isoquinoline) basic magnesium 0.1720 *N* (with respect to the volume of the original sample); bromide ion 0.0522 *N;* (1.1 equivalents of isoquinoline) basic magnesium 0.1690 *N;* bromide ion 0.0443 *N.*

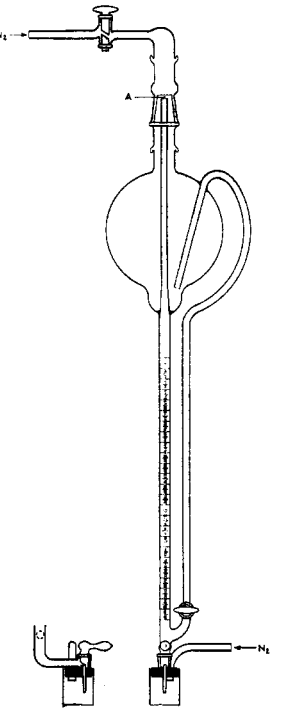

Fig. 2.—Apparatus.

## Summary

Pyridine behaves like dioxane in precipitating the halomagnesium components of the equilibrium, $2C_6H_5MgBr \rightleftarrows (C_6H_5)_2Mg + MgBr_2$. The two precipitants indicate 78–79% and 70–74% disproportionation in the above equilibrium, respectively. This rough check with two different precipitants indicates that the Schlenk dioxane precipitation method, for this Grignard reagent at least, gives approximately correct results.

BRYN MAWR, PENNSYLVANIA RECEIVED JUNE 18, 1938

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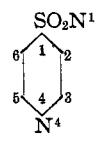
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE CALCO CHEMICAL COMPANY, INC.]

# Sulfanilamide Derivatives. I. Aminoarylsulfonamidoarylsulfonic Acids and Aminoarylsulfonamidoarylcarboxylic Acids*

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

**Nomenclature of Sulfanilamide Derivatives.**—Chemical and medical literature on sulfanilamide derivatives suffers from a confusion of names and naming systems which is bewildering to the medical reader and often misleading to chemists. The name "sulfanilamide" has been adopted officially by the American Medical Association and is now generally used. It would seem desirable, therefore, to continue with this and relate the names of new derivatives, where possible, to the parent sulfanilamide. In the interest of setting up such a system, we have corresponded with Austin M. Patterson, who has given valuable suggestions on the following:

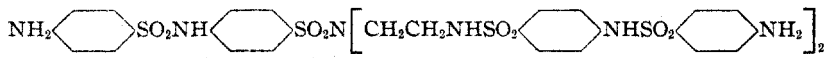
**a. Naming as substituted sulfanilamides**




In sulfanilamide the sulfonamide group, being the principal functional group, occupies the 1-posi-

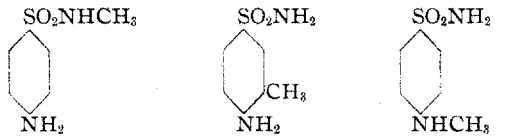
(*) Presented in part before the Division of Medicinal Chemistry, A. C. S., April 20, 1938.

tion in the ring. The nitrogens are differentiated by superscripts: $N^1$ referring to substituents on the amide nitrogen and $N^4$ to substituents on the amino nitrogen.



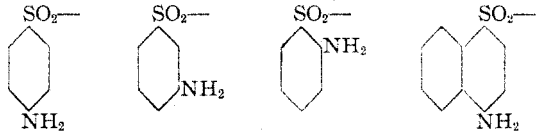
$N^1$,$N^1$-*bis*[2-($N^4$-Sulfanilylsulfanilamido)-ethyl]-$N^4$-sulfanilylsulfanilamide

The following examples illustrate the method



$N^1$-Methylsulfanilamide | 3-Methylsulfanilamide | $N^4$-Methylsulfanilamide

**b. Radical names.**—For simple derivatives the above method should be used, but it becomes unwieldy in naming compounds with complex substituents. In such cases radical names are useful. The following radicals are suggested

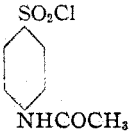


Sulfanilyl- | Metanilyl- | Orthanilyl- | Naphthionyl-

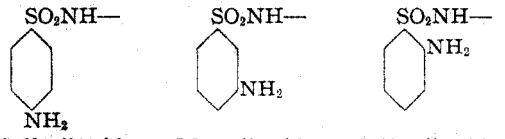
These names follow directly from the corresponding amino acids.

An example of their usefulness is shown by the compound

which we name N,N′-disulfanilylbenzidine-2,2′-disulfonic acid. This seems preferable to the name, N,N′-*bis*-(4-aminobenzenesulfonyl)-4,4′-diaminobiphenyl-2,2′-disulfonic acid. A simpler case is

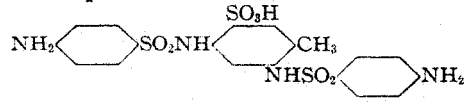


an important intermediate, which we call N-acetylsulfanilyl chloride instead of *p*-acetamidobenzenesulfonyl chloride. Other useful radicals are



Sulfanilamido- | Metanilamido- | Orthanilamido-

An example is



which we name 2,4-*bis*-sulfanilamidotoluene-5-sulfonic acid.

An example of the use of all three types of names is the following



$N^1$,$N^1$-*bis*[2-($N^4$-Sulfanilylsulfanilamido)-ethyl]-$N^4$-sulfanilylsulfanilamide

**New Derivatives.**—In spite of the fact that the literature on sulfanilamide and its derivatives now numbers over 300 references, a relatively few outstanding publications summarize most of the published work on new derivatives.[1-5]

The published work has indicated the following generalities on the relationship of structure and antistreptococcal activity. (1) Little or no activity was found in mononuclear compounds in which either the amino or sulfonamide groups of sulfanilamide were replaced. (The highly active diamino- and dinitrodiphenylsulfones, sulfoxides and sulfides have two rings joined through a sulfur linkage.) (2) Shifting the amino group to the meta or ortho position resulted in marked loss of activity. (3) A third group on the ring lowered the activity. (4) Substitution of the amino group with alkyl, aralkyl, substituted alkyl or aryl, acyl and alkylidene groups had less effect, but in general lowered the activity. (5) Substitution of the amide nitrogen had a variable effect. Methyl and ethyl groups did not change the activity while higher alkyl groups decreased the activity. *p*-Amino- and *p*-nitrophenyl groups increased the activity.

The low solubility of sulfanilamide and its toxicity at effective dosage levels led us to attempt new derivatives of increased solubility which might also have a higher therapeutic index. Our first attempts were to combine N-acetylsulfanilyl chloride with various aminobenzenesulfonic acids and aminobenzenecarboxylic acids in aqueous solution at *p*H 8–10. The reaction went smoothly and after hydrolysis of the acetyl group with acid or base gave us the desired sulfanilyl derivative.

Orthanilyl and metanilyl derivatives were made by treating the corresponding nitrobenzenesulfonyl chlorides with the desired amino acid, followed by reduction of the nitroamide with ammonium polysulfide or in some cases iron in neutral solution.

(1) Tréfouël, Nitti and Bovet, *Ann. Inst. Pasteur*, **58**, 30 (1937).
(2) Buttle, Gray and Stephenson, *Lancet*, I, 1286 (1936); *Biochem. J.*, **31**, 724 (1937).
(3) Mietzsch, *Ber.*, **71**, 15 (1938).
(4) Bauer and Rosenthal, *U. S. Treasury Dept., Pub. Health Repts.*, **53**, 40 (1938).
(5) I. G. Fr. 817,034; *C. A.*, **32**, 1714 (1938).

| Compound | Formula | Therapeutic effect | Melting range, °C. | Purity by nitrite, % | Analyses: Calculated C | H | N | S | Na | Found C | H | N | S | Na |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sodium N-sulfanilylsulfanilate[a] | $C_{12}H_{11}O_5N_2S_2Na$ | + | >300 dec. | 99.9 | 41.2 | 3.14 | 8.00 | 18.21 | 6.57 | 41.3 | 3.5 | 8.0 | 18.1 | 6.2 |
| N-Sulfanilylmetanilic acid | $C_{12}H_{12}O_5N_2S_2$ | ++ | >300 dec. | 100.3 | 43.8 | 3.68 | 8.55 | 19.53 | | 43.6 | 3.8 | 8.45 | 19.4 | |
| N-Sulfanilylorthanilic acid | $C_{12}H_{12}O_5N_2S_2$ | +++ | >300 dec. | 96.3 | 43.8 | 3.68 | 8.55 | 19.53 | | 41.3 | 4.2 | 8.53 | 18.8 | |
| 2-Methyl-N-sulfanilylsulfanilic acid | $C_{13}H_{14}O_5N_2S_2$ | 0 | >300 dec. | 99.4 | 45.6 | 4.17 | 8.16 | 18.7 | | 45.2 | 4.4 | 8.17 | 18.7 | |
| 3-Methyl-N-sulfanilylsulfanilic acid | $C_{13}H_{14}O_5N_2S_2$ | + | >280 dec. | 100.1 | 45.65 | 4.15 | 8.18 | 18.7 | | 44.5 | 4.3 | 7.9 | 18.1 | |
| Sodium 5-methyl-N-sulfanilylorthanilate | $C_{13}H_{13}O_5N_2S_2Na$ | 0 | >300 dec. | 100.2 | | | 7.68 | 17.6 | 6.31 | | | 7.7 | 16.8 | 5.84 |
| Sodium 2,5-dimethyl-N-sulfanilylsulfanilate | $C_{14}H_{15}O_5N_2S_2Na\cdot H_2O$ | 0 | >300 dec. | 100.2 | 42.4 | 4.32 | 7.07 | 16.18 | 5.8 | 42.4 | 4.6 | 6.87 | 16.3 | |
| 6-Ethoxy-N-sulfanilylmetanilic acid | $C_{14}H_{16}O_6N_2S_2\cdot H_2O$ | 0 | >245 dec. | 103.0 | 42.9 | 4.61 | 7.15 | 16.3 | | 43.0 | 4.9 | 7.2 | 16.2 | |
| Sodium 2,4-*bis*-sulfanilamidobenzenesulfonate | $C_{18}H_{17}O_7N_4S_3Na$ | +++ | >320 dec. | 100.0 | 41.5 | 3.26 | 10.7 | 18.4 | 4.4 | 41.6 | 3.9 | 9.9 | 17.9 | |
| Sodium 2,4-*bis*-sulfanilamidotoluene-5-sulfonate | $C_{19}H_{19}O_7N_4S_3Na$ | 0 | >300 dec. | 100.4 | 42.7 | 3.6 | 10.5 | 18.0 | 4.3 | 42.1 | 3.9 | 10.7 | 17.7 | |
| 2,5-*bis*-Sulfanilamidobenzenesulfonic acid | $C_{18}H_{18}O_7N_4S_3\cdot H_2O$ | +++ | >240 dec. | 100.2 | 41.9 | 3.91 | 10.86 | 18.6 | | 41.9 | 4.03 | 11.5 | 19.1 | |
| Sodium 3,4-*bis*-sulfanilamidobenzenesulfonate | $C_{18}H_{18}O_7N_4S_3Na$ | ± | | 100.4 | 41.5 | 3.29 | 10.77 | 18.3 | 4.42 | | | | 18.4 | 4.3 |
| 2-Sulfanilamidosulfanilic acid | $C_{12}H_{13}O_5N_3S_2\cdot{}^1/_2H_2O$ | 0 | >270 dec. | 101.0 | 40.9 | 4.0 | 11.9 | 18.2 | | 40.8 | 4.3 | 12.5 | 18.1 | |
| Sodium-4-sulfanilamidonaphthalenesulfonate | $C_{16}H_{13}O_5N_2S_2Na\cdot{}^1/_2H_2O$ | ++ | >245 dec. | 101.1 | 44.9 | 3.79 | 6.55 | 15.05 | 5.38 | 44.5 | 3.72 | 5.72 | 14.4 | 5.4 |
| 2-Sulfanilamidonaphthalene-6-sulfonic acid | $C_{16}H_{14}O_5N_2S_2$ | − | >300 dec. | 100.5 | 50.8 | 3.74 | 7.42 | 16.95 | | 49.7 | 3.7 | 7.5 | 16.5 | |
| Sodium 5-sulfanilamidonaphthalene-1-sulfonate | $C_{16}H_{13}O_5N_2S_2Na\cdot 2H_2O$ | + | >300 dec. | | 44.1 | 3.92 | 6.43 | 14.7 | 5.27 | 44.0 | 3.79 | 6.77 | 14.9 | 5.24 |
| N,N′-Disulfanilylbenzidine-2,2′-disulfonic acid | $C_{24}H_{22}O_{10}N_4S_4$ | 0 | >300 dec. | 100.0 | 44.05 | 3.4 | 8.58 | 19.57 | | 43.5 | 3.4 | 8.7 | 19.4 | |
| 4,4′-Disulfanilamidostilbene-2,2′-disulfonic acid | $C_{26}H_{24}O_{10}N_4S_4\cdot 4H_2O$ | 0 | >330 dec. | 100.5 | 41.5 | 3.75 | 7.54 | 17.05 | | 41.2 | 3.81 | 7.53 | 17.06 | |
| 4-Sulfanilamidobenzoic acid[a,4] | $C_{13}H_{12}O_4N_2S$ | + | 198–200.5 | 100.0 | 53.4 | 4.14 | 9.58 | 10.98 | | 52.6 | 4.1 | 9.7 | 10.9 | |
| 3-Sulfanilamidobenzoic acid[a] | $C_{13}H_{12}O_4N_2S$ | + | 197.0–198.5 | 100.0 | 53.4 | 4.14 | 9.58 | 10.98 | | 52.8 | 4.2 | 9.31 | 10.8 | |
| 2-Sulfanilamidobenzoic acid[a] | $C_{13}H_{12}O_4N_2S$ | +++ | 225 dec. | 101.9 | 53.4 | 4.14 | 9.58 | 10.98 | | 53.7 | 3.7 | 9.3 | 10.8 | |
| 2-Metanilamidobenzoic acid | $C_{13}H_{12}O_4N_2S$ | ++ | 191.5–193.5 | 100.0 | 53.4 | 4.14 | 9.58 | 10.98 | | 52.6 | 4.5 | 9.7 | 11.0 | |
| 2-Orthanilamidobenzoic acid | $C_{13}H_{12}O_4N_2S$ | − | 176.7–178 | 99.8 | | | | | | | | | | |
| 2-Hydroxy-5-sulfanilamidobenzoic acid | $C_{13}H_{12}O_5N_2S$ | − | >285 dec. | | 50.6 | 3.93 | 9.08 | 10.42 | | 50.5 | 4.4 | 9.0 | 9.7 | |

[a] Kolloff, THIS JOURNAL, **60**, 950 (1938).

In the form of the neutral salts of the sulfonic or carboxylic acids, these derivatives had high water solubility, while the free acids were, in general, only slightly soluble.

The table shows the derivatives and the results of preliminary tests in mice infected with β-hemolytic streptococci. The signs and their meaning are: +++ indicates compounds superior to sulfanilamide, ++ equal to, + somewhat inferior to sulfanilamide; while ± designates compounds with very slight activity, 0 no activity, and − identifies compounds which killed the animals faster than the controls died.[6,7]

The compounds are named as substituted sulfonic or carboxylic acids. The acid function, therefore, occupies the 1-position in the ring.

Sodium N-sulfanilylsulfanilate is extremely water soluble—so much so that a solution of it may be evaporated to a very thick sirup. The addition of benzene to a moderately concentrated aqueous solution caused precipitation of a white crystalline compound containing benzene of crystallization. This was stable to drying at 60°, but was decomposed on dissolving in boiling water, when the benzene was evolved with effervescence, like a carbonate dissolving in acid.

While sodium N-sulfanilylsulfanilate was synthesized primarily for trial in bacterial diseases, this unusual property gave us the idea that it might be effective against viruses, for if it had the power of coördinating with an inert substance such as benzene, might it not coördinate with, or inactivate, the infinitely more complex molecules of a virus?

We suggested, therefore, to Dr. Dochez that he try it against the common cold and influenza viruses. The latter being capable of investigation in experimental animals was tried first and the compound found ineffective. The thing might have died a natural death at this point but, fortunately, Dr. Dochez tried it against dog distemper virus, with striking results.[8]

We have tested other of the above compounds in other virus diseases with promising results. Our most interesting compound in this respect is 2,5-*bis*-sulfanilamidobenzenesulfonic acid, which not only appears to be more efficient than sulfanilamide in antistreptococcal effect, but which shows definite activity against the Francis strain of influenza virus in mice.

Attempts to correlate antistreptococcal activity with structure, based on the above series, indicate that in the parent aminobenzenesulfonamide the para position gives the greater therapeutic effect with the meta position next and the ortho position least. In the second ring, however, this is reversed completely and the more effective compounds are obtained when a carboxyl or sulfonic group is ortho to the amido group. These compounds, in fact, seem to be more effective than sulfanilamide.

Addition of a methyl, chlorine, OH or OR to these derivatives gives less active compounds.

Addition of $NH_2$ also gives an inactive derivative. However, a very active derivative is obtained by placing an additional sulfonamido group on this ring as in 2,4-*bis*-sulfanilamidobenzenesulfonic acid. Addition of a fourth group, $CH_3$, to this ring again completely destroys the activity.

Further interesting evidence on the relation of structure to therapeutic effect in these compounds is furnished by 1,3-*bis*-sulfanilamidobenzene which rates only ± while its sulfonic acid is +++; 1,4-*bis*-sulfanilamidobenzene rates ++, while its sulfonic acid as stated above has a superior antistreptococcal effect coupled with viruscidal activity.

In the naphthalene series position isomerism also has a pronounced effect on the therapeutic activity. The 1,4-position was much superior to the 1,5-, while the 2,6-derivative was toxic. An attempt to prepare N-sulfanilyl-2-naphthylamine-1-sulfonic acid failed when the sulfonic group was lost during hydrolysis of the acetyl derivative. This compound would have been of interest in view of our results in the benzene series.

## Experimental

**Preparation of Sulfanilyl Derivatives.**—The general method of preparing sulfanilyl derivatives of aminoarylsulfonic acids and aminoarylcarboxylic acids is illustrated below for the synthesis of sodium N-sulfanilylsulfanilate.

**Sodium N-Sulfanilylsulfanilate.**—One hundred seventy-three grams (1 mole) of sulfanilic acid, 40 g. (1 mole) sodium hydroxide and 20 g. sodium carbonate were dissolved in 800 cc. of water. The solution was cooled to 40° and 1 mole of N-acetylsulfanilyl chloride in the form of a freshly prepared and analyzed paste was added over one hour, with vigorous agitation. The temperature was held at 40–45° by addition of ice, and the *p*H maintained between 8 and 11 by addition of 50% sodium hydroxide solution as required.

(6) The pharmacological study was carried out by D. R. Climenko and will be reported elsewhere.

(7) Micro-analyses were made under the direction of G. L. Royer.

(8) Dochez and Slanetz, *Science*, **87**, 142 (1938).

After stirring for fifteen minutes a 2-cc. sample of the reaction mixture was diluted to 50 cc., acidified and titrated with 0.1 *N* sodium nitrite at about 20°. This gave an estimation of unreacted amino nitrogen. If the value corresponded to more than 5% of the starting amount, more N-acetylsulfanilyl chloride was added until the nitrite titration reached a minimum, or until 25% excess had been added.

Isolation of N-acetylsulfanilylsulfanilic acid at this point offered no advantage in purity of the final compound. Hydrolysis was therefore made by adding 100 g. (2.5 moles) of sodium hydroxide and boiling the solution for one and one-half hours, or until there was no further increase in diazotizable amine.

N-Sulfanilylsulfanilic acid was isolated from the hydrolysate by acidifying to about *p*H 1 with hydrochloric acid, filtering the precipitate and washing five or six times with 100-cc. portions of water at 80–90° to remove sulfanilic acid.

The crude N-sulfanilylsulfanilic acid was dissolved as the sodium salt at *p*H 5–6, treated with decolorizing carbon and reprecipitated twice. The resulting filter cake was dissolved with solid sodium hydroxide to give a 2.2 *N* solution having a *p*H of 6.5. An equal volume of 95% ethyl alcohol was added to the warm solution. On cooling, crystallizing, filtering, washing with alcohol and drying finally at 100°, 110 g. of anhydrous sodium-N-sulfanilylsulfanilate resulted. Approximately an equal amount was recovered from the mother liquor, giving a yield over all of 60%.

**Notes on General Procedure. 1.**—This type procedure was followed with the other sulfanilyl derivatives listed, substituting an equivalent amount of the corresponding amino or diaminosulfonic acid. Some variation was necessary in concentration because of the difference in solubility of intermediates and final compounds. Thus, in the case of N-sulfanilylorthanilic acid, N-sulfanilylmetanilic acid and 6-ethoxy-N-sulfanilylmetanilic acid, the free acids were moderately soluble and were therefore recrystallized from water without passing through the sodium salt. Sodium salts listed, with the exception of sodium-N-sulfanilylsulfanilate, were crystallized from concentrated aqueous solutions without use of alcohol.

**2.**—Yields averaging 60–70% were obtained in most cases but were of no special significance since recoveries from the numerous mother liquors were not made unless these contained more than 10% of the yield as determined by nitrite titration. Yields of derivatives where a sulfonic acid or other large group was in the ortho position to the sulfanilamido group were generally poor, probably because of steric hindrance.

**3.**—In making sulfanilyl derivatives of aminonaphthalenesulfonic acids, and diaminosulfonic acids, care was taken to prepare or purify these immediately before use, since highly colored impurities were difficult to remove later. Use of small amounts of sodium hydrosulfite following treatment with decolorizing carbon was helpful in removing color and preventing further oxidation, both on intermediates and final compounds.

**4.**—Usage of sodium hydroxide in hydrolysis was based on one mole for each acetyl group, plus one mole for each —$SO_2NH$— (or other acidic group not neutralized), plus one-half mole excess. This excess was sufficient to promote complete hydrolysis of the acetyl groups in about one hour at 102–103°, for the concentrations used.

**5.**—Hydrolysis of acetyl groups was also effected by boiling in 15% hydrochloric acid, but this was generally less satisfactory since many of the products were only slightly soluble in acid. The resulting thick slurry bumped on boiling and was otherwise difficult to handle. Hydrolysis did not proceed to completion in some cases because the particles of intermediate were protected by a coating of the product.

**2-Sulfanilamidosulfanilic Acid.**—This was prepared by the type procedure starting with 1 mole of 2-amino-4-acetylaminobenzenesulfonic acid per mole of N-acetylsulfanilyl chloride; 3.5 moles of sodium hydroxide was used for hydrolysis of the acetyl groups.

**Orthanilyl and Metanilyl Derivatives.**—These derivatives were made following the general procedure outlined above but with substitution of *o*-nitrobenzenesulfonyl chloride or *m*-nitrobenzenesulfonyl chloride in equivalent amount for N-acetylsulfanilyl chloride. Since these acid chlorides were somewhat more resistant to hydrolysis, the reaction temperature was raised to 45–50°. The resulting nitrosulfonamide was isolated by acidification of the reaction mixture and reduced to the amino derivative by the method illustrated below.

**2-Metanilamidobenzoic Acid.**—The 2-(*m*-nitrobenzenesulfonamido)-benzoic acid resulting from one mole of anthranilic acid was dissolved in 500 cc. of 28% ammonia. A stream of hydrogen sulfide was passed in with vigorous agitation and cooling. When the initial reaction had moderated, the flask contents were heated to a gentle boil under a reflux condenser with a continued slow stream of hydrogen sulfide, for an hour and a half. Boiling was then maintained while a rapid stream of air was passed through the solution until sulfides had been oxidized to sulfur and most of the excess ammonia removed. Sulfur was removed by filtration. The filtrate was acidified slowly with hydrochloric acid and the crude product filtered off. This was twice recrystallized by dissolving as the sodium salt, treating with activated charcoal and reprecipitating. A yellow color still persisted. The material was dissolved as the sodium salt, made slightly acid with acetic acid and boiled with about 1 g. of zinc dust. This decolorized the solution. The product was isolated as the acid and recrystallized twice from 1 liter of alcohol using activated charcoal.

Attempts to reduce the nitro compound with iron failed because of the formation of an insoluble iron salt.

## Summary

A naming system for sulfanilamide derivatives is proposed which relates the names where possible to the parent sulfanilamide. For more complex derivatives, the radicals "sulfanilyl," $NH_2C_6H_4SO_2$—, and "sulfanilamido," $NH_2C_6H_4SO_2NH$—, are used.

Highly soluble salts of sulfanilamidobenzenesulfonic acids and sulfanilamidobenzenecarboxylic acids are described. Preliminary tests in mice

indicate that while in the parent ring highest antistreptococcal activity is found in the para derivative, this is reversed completely in the second ring, where compounds in which the acid function is ortho to the nitrogen have the highest activity.

Addition of $-CH_3$, —OH, —OR or —Cl to the second ring greatly lowers or destroys the activity.

Sodium 2,4-*bis*-sulfanilamidobenzenesulfonate and 2,5-*bis*-sulfanilamidobenzenesulfonic acid appear to have activity against influenza virus in mice, as well as to have high antistreptococcal powers.

BOUND BROOK, N. J. RECEIVED APRIL 27, 1938

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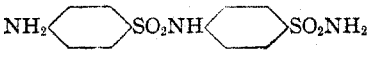
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE CALCO CHEMICAL COMPANY, INC.]

# Sulfanilamide Derivatives. II. Disulfanilamides and Related Compounds[1]

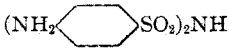
BY M. L. CROSSLEY, E. H. NORTHEY AND MARTIN E. HULTQUIST

The compound called by Rosenthal[2] "Disulfanilamide"



is incorrectly named. We suggest that it be called $N^4$-sulfanilylsulfanilamide.

We have synthesized true disulfanilamide



and have prepared a number of derivatives having the disulfonamide linkage, $-SO_2NHSO_2-$. These compounds as a class behave as strong acids, forming neutral sodium salts of the type $-SO_2NNaSO_2-$. The salts have high water solubility and are very stable to heat, decomposing at temperatures above 300°. However, if the hydrogen of the disulfonamide is replaced by alkyl, the compound becomes water and alkali insoluble and is broken down more readily by strong acids or bases.

Disulfanilamide was synthesized by treating more than two moles of N-acetylsulfanilyl chloride with one mole of ammonia, keeping the *p*H at 10–11 by addition of sodium hydroxide solution and holding the temperature below 45°. It was also made starting with N-acetylsulfanilyl chloride and $N^4$-acetylsulfanilamide. The resulting $N^1$-sodium-$N^4$,$N^{4'}$-diacetyldisulfanilamide was hydrolyzed by boiling with sodium hydroxide and was purified by recrystallization as the sodium salt.

Alkylation was accomplished by boiling the $N^1$-sodium-$N^4$,$N^{4'}$-diacetyldisulfanilamide with excess dimethyl sulfate in xylene. The resulting $N^1$-methyl-$N^4$,$N^{4'}$-diacetyldisulfanilamide was hydrolyzed to $N^1$-methyldisulfanilamide by adding the theoretical amount of 36% hydrochloric acid, dropwise, to a boiling alcoholic solution so that the acidity at no time was sufficient to give a green spot on methyl violet paper. Boiling aqueous 20% hydrochloric acid caused rapid breakdown at the amide linkage giving sulfanilic acid and $N^1$-methylsulfanilamide. The same type of decomposition occurred during hydrolysis with sodium hydroxide but at a much slower rate.

Dimetanilamide was made by treating an excess of *m*-nitrobenzenesulfonyl chloride with *m*-nitrobenzenesulfonamide at 50–60° in aqueous solution and at *p*H 10–11. The *p*H was maintained by addition of sodium hydroxide as necessary. The resulting 3,3′-di-*m*-nitrodibenzenesulfonamide was reduced to dimetanilamide with ammonia and hydrogen sulfide.

The compounds synthesized and their relative effectiveness as indicated by preliminary studies on β-hemolytic streptococcal infections in mice are shown in the table, where sulfanilamide = ++.[3,4]

The inferences drawn from the results are:

1. Acetylation of the amino groups lowered the therapeutic effect. This was in agreement with all other work on sulfanilamide derivatives.

2. Alkylation of the amide nitrogen had no apparent effect on the therapeutic efficiency although the compound had lost its water solubility almost completely.

3. Metanilyl derivatives had a lower effectiveness than the corresponding sulfanilyl derivatives. However, dimetanilamide had about the same activity as sulfanilamide.

In addition to the sodium and magnesium salts

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

(2) Rosenthal, *et al.*, *Pub. Health Repts., U. S. Treas. Dept.*, **52** 662 (1937); *ibid.*, **53**, 40 (1938).

(3) A complete report on the pharmacology will be presented by Dr. D. R. Climenko, elsewhere.

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