0.5 g. of calcium carbonate were added to 100 ml. of 50% aqueous ethyl alcohol and the mixture heated under reflux on a steam-bath for eight hours. The reaction mixture was cooled, diluted with 50 ml. of water and filtered. The residue was dissolved in 10% sodium hydroxide (the solution was deep blood-red in color), treated with 0.5 g. of activated charcoal and the solution filtered. On acidification of the solution to congo red with concd. hydrochloric acid, a canary-yellow solid precipitated. After allowing the acidified mixture to stand overnight in the ice-box, the product was filtered off and dried at 130° for twelve hours giving a yield of 3.8 g. (41%). This compound did not melt below 250°.

Anal.[6] Calcd. for $C_{12}H_{10}O_7N_3As$: As, 19.58. Found: As, 19.44.

B.—I was also prepared from *p*-arsanilic acid and 2,4-dinitrochlorobenzene using sodium acetate as the condensing agent. In this reaction a considerable quantity of a red-orange solid was formed as a by-product. The product was isolated and purified, the same procedure used in method A giving a yield of 30%.

Anal. Calcd. for $C_{12}H_{10}O_7N_3As$: As, 19.58. Found: As, 19.16.

N-2,4-Diaminophenylarsanilic Acid.—One gram of I was reduced using 10.1 g. of ferrous sulfate in the method of Jacobs, Heidelberger and Rolf.[7] The product was a dark-red solid which rapidly turned black in the presence of air. The yield was 0.3 g. (36%).

Anal. Calcd. for $C_{12}H_{14}O_3N_3As$: As, 23.22. Found: As, 23.10.

N-4-Dimethylaminophenyl-3-nitroarsanilic Acid.—Four grams of 3-nitro-4-chlorophenylarsonic acid was dissolved in 10 ml. of 10% sodium hydroxide and 8 ml. of water, 3 ml. of *p*-aminodimethylaniline added and the mixture heated under reflux in an oil-bath at 140° for eight hours. On addition of concd. hydrochloric acid to the neutral point, a sticky dark-brown solid precipitated. This product was purified by twice redissolving in 5% sodium hydroxide, charcoaling the solution, filtering and reacidifying. The red-brown solid was filtered off, washed well with water and alcohol and dried at 100° for twenty-four hours to yield 3 g. of product (56%).

Anal. Calcd. for $C_{14}H_{16}O_5N_3As$: As, 19.40. Found: As, 19.29.

N-4-Diethylaminophenyl-3-nitroarsanilic Acid.—This product was prepared by the same method used for the dimethylamino compound. It was a red-brown solid. The yield was 3.5 g. (60%).

Anal. Calcd. for $C_{16}H_{20}O_5N_3As$: As, 18.32. Found: As, 18.36.

Summary

The reaction of *p*-arsanilic acid with 2,4-dinitrochlorobenzene to form N-2,4-dinitrophenylarsanilic acid has been studied. N-2,4-Diaminophenylarsanilic acid has been prepared.

N-4-Dimethylaminophenyl-3-nitroarsanilic acid and N-4-diethylaminophenyl-3-nitroarsanilic acid have been prepared.

LOUISVILLE, KY. RECEIVED AUGUST 3, 1949

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[6] Cislak and Hamilton, THIS JOURNAL, **52**, 638 (1930).

[7] Jacobs, Heidelberger and Rolf, *ibid.*, **40**, 1581 (1918).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK AND CO., INC.]

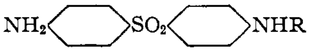
Monosubstituted Diaminodiphenyl Sulfones

BY JOHN WEIJLARD AND EDWARD SWANEZY

The antistreptococcal and antitubercular efficacy of substituted 4,4'-diaminodiphenyl sulfones appears to be increased if one amino group is free; consequently a number of monosubstituted diaminodiphenyl sulfones have been reported upon recently.[1,2] These compounds have generally been prepared either by reducing 4-nitro-4'-halodiphenyl sulfone followed by reaction of the resultant 4-amino-4'-halodiphenyl sulfone with the requisite amine,[1] or by alkylation of 4-nitro-4'-aminodiphenyl sulfone followed by reduction of the nitro group.[2] In either case the methods are laborious, the replacement reactions are often sluggish and the yields poor. This is particularly noticeable when 4-nitro-4'-aminodiphenyl sulfone is subjected to hydroxyethylation with compounds such as ethylene bromohydrin.[2]

A simple and rapid method has now been found for these compounds consisting of treating the readily available 4-acetylaminobenzene sulfonyl chloride with monochlorobenzene in presence of aluminum chloride to give 4-acetylamino-4'-chlorodiphenyl sulfone in 88% yield and of reacting the latter with, for instance, ethanolamine or isopropanolamine in presence of copper to yield the corresponding 4-amino-4'-(β-hydroxyethylamino)- or (β-hydroxypropylamino)-diphenyl sulfone, respectively, in 70 to 85% yields. Other amines, such as N-aminoethylmorpholine, reacted readily to give 4-amino-4'-(β-morpholineëthylamino)-diphenyl sulfone in high yield. With ammonia water, 4,4'-diaminodiphenyl sulfone was obtained in good yield. It is noteworthy that deacetylation takes place simultaneously with the alkylations.

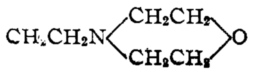
A simplified method for the preparation of the parent substance, 4,4'-diaminodiphenyl sulfone, is thus available, and in addition a general method for preparing a large number of monosubstituted diaminodiphenyl sulfones, by selecting the proper amine and catalyst. The preparation of four compounds in this class is described.



I R = H

II R = CH_2CH_2OH

III R = $CH_2CH(OH)CH_3$



IV R = $CH_2CH_2N(CH_2CH_2)_2O$

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[1] Amstutz, Fehnel and Woods, THIS JOURNAL, **69**, 1922 (1947).

[2] Jackson, *ibid.*, **70**, 680 (1948).

The new compounds, III and IV, show activity *in vitro* against *M. Tuberculosis;* compound III has also been found to be active against *D. pneumoniae* and *Staph. aureus.*[3] Compound II is being investigated elsewhere.

Experimental

4-Acetylamino-4'-chlorodiphenyl Sulfone.[4]—Four hundred sixty-seven grams of 4-acetylaminobenzene sulfonyl chloride (2 moles) was mixed with 1500 cc. of monochlorobenzene and warmed to 50°; 533 g. of anhydrous aluminum chloride (4 moles) was added in portions over a period of one hour at 55–65° with rapid stirring. The mixture was stirred at 70–80° for an additional three hours, then the excess monochlorobenzene was distilled *in vacuo.* The hot residual sirup was poured into a mixture of 2 kg. of crushed ice and 400 cc. of concentrated hydrochloric acid and stirred till completely disintegrated. The product was collected, washed with liberal quantities of water, then alcohol, and dried at 50°; yield 544 g. (88%), m. p. 194°.

Anal. Calcd. for $C_{14}H_{12}O_3NSCl$: N, 4.57. Found: N, 4.87.

4,4'-Diaminodiphenyl Sulfone.—Thirty-one grams of 4-acetylamino-4'-chlorodiphenyl sulfone (0.1 mole) was mixed with 100 cc. of concentrated ammonia water containing 0.5 g. of cuprous chloride, and the mixture was held in a mechanically agitated steel bomb at 180–190° for twelve hours. The cooled reaction mixture was filtered, washed with water and dried; yield 22 g. of crude sulfone (89%). The crude product was dissolved in 400 cc. of hot 50% methanol, the copper was precipitated with hydrogen sulfide, 2 g. of decolorizing black was added, and the solution was filtered through a heated filter. The clear filtrate was poured into 1400 cc. of water containing a trace of hydrosulfite, and the precipitated sulfone was filtered and washed with water; yield 18.6 g. (84.5%) of white sulfone, m. p. 172°.

Anal. Calcd. for $C_{12}H_{12}O_2N_2S$: C, 58.06; H, 4.87; N, 11.30. Found: C, 57.78; H, 4.84; N, 10.99.

4-Amino-4'-(β-hydroxyethylamino)-diphenyl Sulfone.—Thirty-one grams of 4-acetylamino-4'-chlorodiphenyl sulfone (0.1 mole) was mixed with 37 g. of ethanolamine (0.6 mole) and 0.5 g. of cuprous chloride, and the mixture was stirred and refluxed at 160–168° for twenty-two hours. The cooled reaction mixture was diluted with 400 cc. of water and cooled in ice overnight. The mother liquor was decanted and the gummy residue was dissolved in 180 cc. of hot 50% ethanol. The solution was treated with hydrogen sulfide and 2 g. of decolorizing black, filtered, scratched until crystallization was well under way, then chilled at 0° for forty-eight hours. The crystals were collected, washed with iced 50% ethanol and dried *in vacuo;* yield 21.0 g. (73%), m. p. 128–131°. After recrystallization in absolute alcohol the product melted at 131–132°.[5]

Anal. Calcd. for $C_{14}H_{16}O_3N_2S$: C, 57.52; H, 5.52; N, 9.58. Found: C, 57.55; H, 5.31; N, 9.73.

The X-ray diffraction pattern was identical with that from the sulfone made by the Jackson method,[2] and the solubility analysis indicated a purity of over 95%.[6]

4-Amino-4'-(β-hydroxypropylamino)-diphenyl Sulfone.—One-tenth of a mole of 4-amino-4'-chlorodiphenyl sulfone was mixed with 45 g. of isopropanolamine (0.6 mole) and 0.5 g. of cuprous chloride, and the mixture was stirred and refluxed at 165–175° for fifteen hours. The reaction mixture was worked up essentially as above, except that the crude product was dissolved in a hot mixture of 200 cc. of alcohol and 100 cc. of acetone. After removal of the copper and treatment with Darco, the solution was diluted with two volumes of water and cooled overnight in ice; yield 26.0 g. (85%), m. p. 183–186°. After recrystallization in absolute alcohol, the m. p. rose to 190–192°.

Anal. Calcd. for $C_{15}H_{18}O_3N_2S$: C, 58.80; H, 5.92; N, 9.14. Found: C, 58.87; H, 5.88; N, 9.22.

4-Amino-4'-(β-morpholineethylamino)-diphenyl Sulfone.—One-tenth of a mole of 4-amino-4'-chlorodiphenyl sulfone, 65 g. of N-aminoethylmorpholine (0.5 mole), and 0.5 g. of cuprous chloride were mixed and held at 200° for fifteen hours with stirring. The reaction mixture was diluted with 600 cc. of water and the precipitated product was separated by decantation and dissolved in 250 cc. of hot alcohol. The copper was removed with hydrogen sulfide, the clear filtrate was concentrated *in vacuo,* and during the concentration the sulfone crystallized suddenly. The crystals were filtered, washed with cold alcohol and dried at 50°; yield 30.1 g. (83%), m. p. 204–205°.

Anal. Calcd. for $C_{18}H_{23}O_3N_3S$: N, 11.63. Found: N, 11.54.

Acknowledgment.—We are indebted to Dr. Max Tishler for his interest and valuable suggestions.

Summary

A new and rapid method for the preparation of monosubstituted diaminodiphenyl sulfones is described. Two new sulfones have been prepared.

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[3] The study of the chemotherapeutic activity of these compounds is being carried out by Dr. Morris Solotorovsky and Miss Bettina M. Frost of the Merck Institute for Therapeutic Research.

[4] Heymann and Fieser, *ibid.*, **67**, 1979 (1945), isolated the 4-amino-4'-chlorodiphenyl sulfone from a mixture of incompletely ammonolyzed 4,4'-dichlorodiphenyl sulfone.

[5] Two forms of this compound have been observed, one of m. p. 145–146°, the other of m. p. 131–132°. The form of lower m. p. appears to be the more stable.

[6] We are indebted to Mr. F. A. Bacher of the Research Laboratories of Merck and Co., Inc., for carrying out these measurements.