JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

VOLUME 65 NOVEMBER 13, 1943 NUMBER 11

[CONTRIBUTION FROM THE RESEARCH DIVISION OF THE GENERAL PRINTING INK CORPORATION]

Derivatives of Biphenylsulfonamides. I. Preparation of *p*-(*o*-Aminophenyl)-benzenesulfonamide.[1]

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As part of another study it was necessary to prepare derivatives of *p*-phenylbenzenesulfonamide. Although these compounds were related only remotely to those "sulfa" drugs which are active against the microörganisms responsible for many infectious diseases, it was thought that they might possess desirable bactericidal properties. The present study, therefore, was undertaken to determine the chemotherapeutic value of some of the sulfonamide derivatives of biphenyl.

Work has already been done on *p*-(*p*-aminophenyl)-benzenesulfonamide,[2,3] which was reported as inactive when administered to streptococcal infected mice.[4] Some derivatives of this compound have been made[5,6] but no results of bactericidal tests have been reported.

The present paper is concerned with the preparation of *p*-(*o*-aminophenyl)-benzenesulfonamide, the parent substance of one series of compounds to be made in this study. This was prepared from 2-acetamidobiphenyl and 2-nitrobiphenyl by the action of chlorosulfonic acid. Diagram A shows the steps involved. The replacement of the para hydrogen in the adjacent ring in both instances is in accord with the bromination studies of Le Fèvre and Turner,[7] and the nitration studies of Scarborough and Waters.[8]

The position of the sulfonamide group was established by formation of the corresponding aminosulfonic acid which, by diazotization, hydrolysis and subsequent alkali fusion, was converted into the known 2,4′-dihydroxybiphenyl, further identified by the diacetyl derivative. The same dihydric phenol and the same diacetate were obtained by applying the identical set of reactions to the aminosulfonic acid resulting from the direct sulfonation of 2-aminobiphenyl at 120° during thirty-eight hours.

The preparation of derivatives of *p*-(*o*-aminophenyl)-benzenesulfonamide is described in another paper.[9] These and other derivatives now in preparation will be examined for effectiveness against different microörganisms.

Experimental

2-Acetamidobiphenyl (II).—This was made by the reaction of equal molecular quantities of 2-aminobiphenyl (technical product, Monsanto Chemical Company) and acetic anhydride. The yield of product was 93%; m. p., 120–121°.[10]

***p*-(*o*-Acetamidophenyl)-benzenesulfonyl Chloride (III).**—The procedure used in this preparation is a slight modification of the method of Smiles and Stewart[11] for *p*-acet-

(1) Presented before the Division of Organic Chemistry, Detroit meeting of the American Chemical Society, April, 1943.

(2) Van Meter, Bianculli and Lowy, THIS JOURNAL, **62**, 3146 (1940).

(3) Donnell, Dietz and Caldwell, *ibid.*, **63**, 1161 (1941).

(4) Kumler and Halverstadt, *ibid.*, **63**, 2182 (1941).

(5) Novelli and Somaglino, *ibid.*, **63**, 854 (1941).

(6) Van Meter and Lowy, *ibid.*, **63**, 1330 (1941).

(7) Le Fèvre and Turner, *J. Chem. Soc.*, 2041 (1926).

(8) Scarborough and Waters, *ibid.*, 89 (1927).

(9) Popkin and Perretta, THIS JOURNAL, **65**, 2046 (1943).

(10) *Cf.* Fichter and Sulzberger, *Ber.*, **37**, 879 (1904); also (8).

(11) Smiles and Stewart, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1925, Vol. V, p. 3.

DIAGRAM A

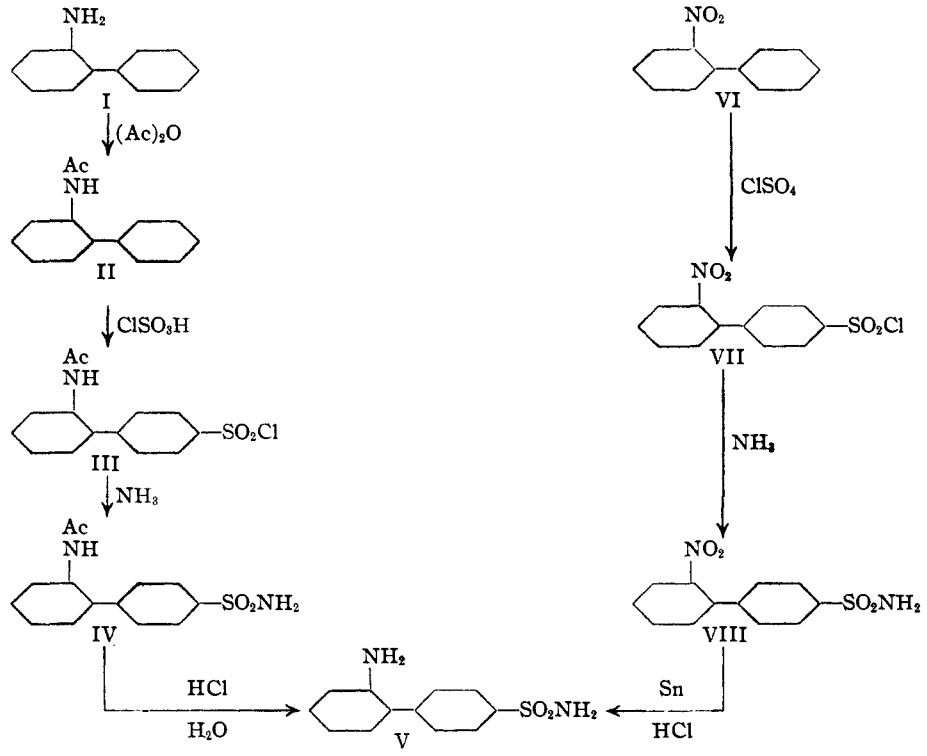
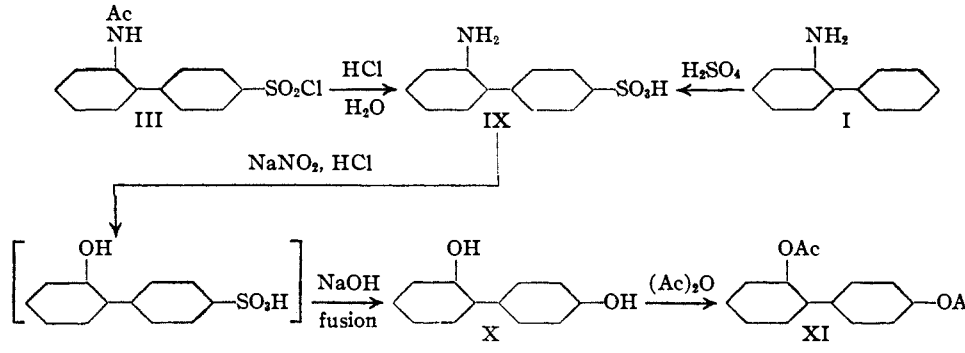


DIAGRAM B



amidobenzenesulfonyl chloride. Into a two-liter beaker was placed 1150 g. (650 cc., 9.86 moles) of chlorosulfonic acid. This was cooled to −20° with dry-ice and 410 g., 1.94 moles, of (II) was added during forty minutes. The temperature was maintained below 10° during the addition. The mixture was then heated at 60° for three hours, poured upon six kilograms of ice-water, and the resulting white precipitate separated by filtration. This wet filter cake could not be dried by the conventional methods since air-drying or vacuum-drying resulted in decomposition. However, most of the water was removed in a separatory funnel by addition of the filter cake to three liters of chloroform. The chloroform solution of (III) was further dried by treatment with anhydrous calcium chloride and by evaporation at reduced pressure. The dry solution then was concentrated and 331 g., 55% yield, of product was precipitated by the addition of dry benzene; m. p. 143–145°. Several crystallizations from benzene gave a pure sample of (III), m. p. 149–150.5°.

Anal. Calcd. for $C_{14}H_{12}ClNO_3S$: N, 4.52; S, 10.35; Cl, 11.45. Found: N, 4.37; S, 10.49; Cl, 11.55.

***p*-(*o*-Acetamidophenyl)-benzenesulfonamide (IV).**—To 2.03 g. of (III) contained in a 50-cc. Erlenmeyer flask was added 25 cc. of concd. ammonium hydroxide. The mixture was heated until a volume of approximately 10 cc. was attained and then made neutral with dilute acetic acid. A precipitate of (IV) was obtained, 1.76 g.; m. p. 199–200°. Several crystallizations from ethyl alcohol gave a purified sample of (IV), m. p. 201–202°.

Anal. Calcd. for $C_{14}H_{14}N_2O_3S$: N, 9.65; S, 11.04. Found: N, 9.45; S, 10.80.

***p*-(*o*-Aminophenyl)-benzenesulfonamide (V).**—To a solution of 1.57 g. of (IV) in 25 cc. of absolute methyl alco-

hol was added 10 cc. of concd. hydrochloric acid. The resulting solution was heated for fifteen minutes until a volume of approximately 15 cc. resulted. Addition of 25 cc. of water gave a clear solution indicating effective deacetylation. This was made ammoniacal and a precipitate was obtained weighing 1.24 g.; m. p. 178–180°. Successive crystallizations from methyl alcohol gave a purified sample of (V), m. p. 186–187°.

Anal. Calcd. for $C_{12}H_{12}N_2O_2S$: N, 11.28; S, 12.91. Found: N, 11.45, 11.52; S, 12.50, 12.62.

***p*-(*o*-Nitrophenyl)-benzenesulfonyl Chloride (VII).**—The action of 1150 g. of chlorosulfonic acid on 410 g., 2.06 moles, of 2-nitrobiphenyl (Monsanto Chemical Company) was carried out as above and the material was crystallized by addition of Petrolene, a petroleum fraction boiling between 65–90°, to a benzene solution of the crude oily product; 429 g., 70% yield; m. p. 70–77°. Further purification gave a purified sample of colorless (VII), m. p. 78–80°.

Anal. Calcd. for $C_{12}H_8ClNO_4S$: N, 4.71; S, 10.77; Cl, 11.91. Found: N, 4.60; S, 11.02; Cl, 11.68.

***p*-(*o*-Nitrophenyl)-benzenesulfonamide (VIII).**—To 2.01 g. of (VII) in a 50-cc. Erlenmeyer flask was added 25 cc. of concd. ammonium hydroxide. This was heated for twenty minutes and then made neutral with dilute acetic acid. The resulting precipitate weighed 1.86 g.; m. p. 202–203°. Two crystallizations from ethyl alcohol and one purification with activated carbon raised the melting point of (VIII) to 203–204°.

Anal. Calcd. for $C_{12}H_{10}N_2O_4S$: N, 10.07; S, 11.52. Found: N, 10.29, 10.07; S, 11.52, 11.50.

Reduction of (VIII) to (V).—This procedure is the same as the one used for the reduction of *p*-(*p*-nitrophenyl)-benzenesulfonamide.[3] A solution of 10.0 g. of (VIII) in 200 cc. of ethyl alcohol was reduced with 8 g. of tin and 50 cc. of concd. hydrochloric acid. This gave 3.2 g. of (V) which showed no depression in the melting point when mixed with another sample of (V) prepared above.

***p*-(*o*-Aminophenyl)-benzenesulfonic Acid (IX). Method I.**—To 20.0 g. of (III) in a 500-cc. Erlenmeyer flask was added a solution of 75 cc. of concd. hydrochloric acid and 75 cc. of water. A clear yellow solution resulted after five minutes of refluxing, indicating formation of the soluble hydrochloride. After ten minutes of heating crystals appeared, indicating the formation of acid-insoluble (IX). The reaction mixture was heated for a total of twenty minutes and then cooled to 5°. The weight of (IX) obtained was 11.4 g. This compound does not have a melting point and chars above 250°.

Method II.—To 590 g., 3.49 moles, of (I) was added 2000 g., 19.6 moles, of concd. sulfuric acid (96%). The solution which formed was heated at 120° for thirty-eight hours. The reaction product was poured upon 1500 g. of ice-water. The resulting precipitate was separated by filtration and dispersed in 3500 cc. of water, in which it was insoluble. This was heated to 75° and addition of concd. ammonium hydroxide until the mixture was slightly alkaline gave a clear solution. After one purification with activated carbon, (IX) was reprecipitated by the addition of 250 cc. of concd. hydrochloric acid; weight, 578 g., 66% yield.

Anal. Calcd. for $C_{12}H_{11}NO_3S$: N, 5.65; S, 12.87. Found: N, 5.53, 5.61; S, 12.81, 12.88.

Conversion of (IX) to (X) and (XI).—To 10.0 g. of (IX), obtained from (III), was added during one minute and at room temperature, 88 cc. of 10% sulfuric acid and 15 cc. of 20% sodium nitrite solution. A vigorous reaction resulted and the solution turned brown in color. The temperature was kept at 60° for one hour during which time nitrogen gas was evolved and the diazonium group was replaced by the hydroxyl group. The resulting solution was made alkaline with 10% sodium hydroxide and concentrated to dryness. This gave *p*-(*o*-hydroxyphenyl)-benzenesulfonic acid as the sodium salt. This was fused with 50 g. of sodium hydroxide and 5 g. of water during fifteen minutes at 270–290°. The melt was cooled, treated with 400 cc. of water and neutralized with 30% sulfuric acid. The mixture was heated to boiling and a resinous product removed by filtration. The clear filtrate was cooled to 10°, extracted three times with 150 cc. of ether and the combined ether extracts concentrated to give brown crystals, m. p. 144–159°. One crystallization from dilute methyl alcohol gave purified 2,4′-dihydroxybiphenyl (X), m. p. 161.5–162.5°, which is in agreement with the value 162–163° previously recorded in the literature.[12] The corresponding diacetate (XI) was made with 0.3 g. of (X) and 10 cc. of acetic anhydride. The product, crystallized from methyl alcohol, gave m. p. 94.5–96.5°, which agrees with the value 94° reported in the literature.[12]

The above reactions were repeated for a sample of (IX) obtained by sulfonation of (I). The products (X) and (XI) obtained had the same m. p. values as above and mixed m. p. of the two mixtures showed no depression.

Summary

1. *p*-(*o*-Aminophenyl)-benzenesulfonamide, the parent compound of a new series of biphenylsulfonamides, and a number of these latter have been prepared.

2. The action of chlorosulfonic acid on 2-acetamidobiphenyl and 2-nitrobiphenyl and the action of sulfuric acid on 2-aminobiphenyl gave substitution at the 4′ position. This agreed with previous studies of the bromination and nitration of 2-acetamidobiphenyl.

NEW YORK, N. Y. RECEIVED JANUARY 14, 1943

(12) Fichter and Brunner, *Bull. soc. chim.*, **19**, 281 (1916).