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

Derivatives of Biphenylsulfonamide. II.[1] Derivatives of *p*-(*o*-Aminophenyl)-benzenesulfonamide.[2]

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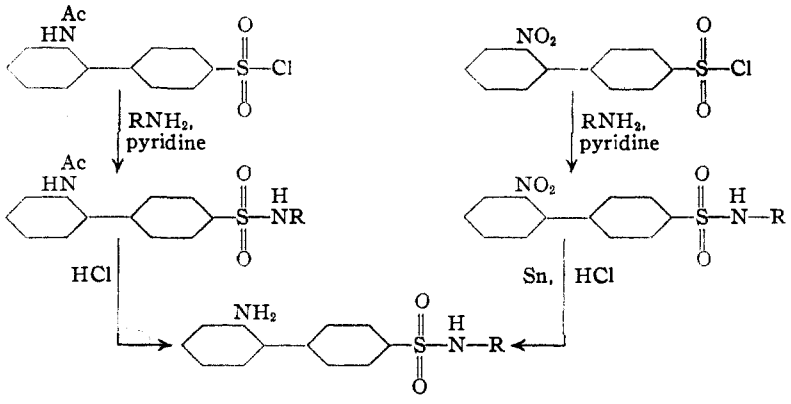
The preparation of *p*-(*o*-aminophenyl)-benzenesulfonamide has been described.[1] The present work is concerned with some derivatives of this compound in which a hydrogen of the sulfonamide nitrogen was replaced by an aromatic group. These were prepared by two methods, the first employing *p* - (*o* - acetamidophenyl) - benzenesulfonyl chloride, and the second, *p*-(*o*-nitrophenyl)-benzenesulfonyl chloride. The identities of the sulfonamide derivatives prepared by the two processes were proved by melting points and mixed melting points.



The following amino compounds were used in the preparations: (1) aniline, (2) benzylamine, (3) 2-aminobiphenyl, (4) 4-aminobiphenyl, (5) *p*-aminobenzenesulfonamide and (6) *p*-(*o*-aminophenyl)-benzenesulfonamide. These were chosen in order that the resulting derivatives be isomeric with some of the compounds prepared by Van Meter and Lowy.[3]

Bactericidal tests[4] on *p*-(*o*-aminophenyl)-benzenesulfonamide and the derivatives reported here indicate that these compounds are inactive *in vitro* against concentrations of *E. Coli* and *in vivo* against streptococcal infected mice. A similar inactivity was reported for *p*-(*p*-aminophenyl)-benzenesulfonamide,[5] indicating that the shift in the position of the amino group does not increase the activity.

It was noted during the deacetylation that the six amino derivatives gave hydrochlorides which were non-ionic in behavior, *i. e.*, they had distinct melting points and were insoluble in water. This distinction from the water-soluble hydrochlorides of the parent compound, *p*-(*o*-aminophenyl)-benzenesulfonamide and the isomer *p*-(*p*-aminophenyl)-benzenesulfonamide[6] may be attributed to the increase in molecular weight.

The insoluble hydrochlorides were used to advantage in isolation of the amino compounds obtained by reduction. The customary procedure requires the precipitation of tin with hydrogen sulfide. In the present work, the alcoholic solution of the tin reduction was concentrated. The hydrochloride which precipitated was washed with water until free of tin salts. The desired derivatives then were obtained in substantially pure forms and in good yields.

It was reported previously[1] that *p*-(*o*-acetamidophenyl)-benzenesulfonyl chloride could not be purified in the conventional manner since air-drying or vacuum-drying gave decomposition. This instability is now confirmed. A purified sample of the above, recrystallized several times from benzene, was found to undergo decomposition when stored in a closed glass container for one month. This was evidenced by the liberation of acid vapors and a decrease of five degrees in the melting point.

The following new compounds were prepared in this work:

I *p*-(*o*-acetamidophenyl)-benzenesulfon-N-phenylamide
II *p*-(*o*-nitrophenyl)-benzenesulfon-N-phenylamide
III *p*-(*o*-aminophenyl)-benzenesulfon-N-phenylamide
IV *p*-(*o*-acetamidophenyl)-benzenesulfon-N-benzylamide

(1) Paper I, THIS JOURNAL, 65, 2043 (1943).
(2) Presented before the Division of Organic Chemistry, Detroit meeting of the American Chemical Society, April, 1943.
(3) Van Meter and Lowy, THIS JOURNAL, 63, 1330 (1941).
(4) By Dr. W. Harry Feinstone, Stamford Laboratory, American Cyanamid Company.
(5) Kumler and Halverstadt, THIS JOURNAL, 63, 2182 (1941).
(6) Van Meter, Bianculli and Lowy, *ibid.*, 62, 3146 (1940).

V *p*-(*o*-nitrophenyl)-benzenesulfon-N-benzylamide
VI *p*-(*o*-aminophenyl)-benzenesulfon-N-benzylamide
VII *p*-(*o*-acetamidophenyl)-benzenesulfon-N-*o*-xenylamide
VIII *p*-(*o*-nitrophenyl)-benzenesulfon-N-*o*-xenylamide
IX *p*-(*o*-aminophenyl)-benzenesulfon-N-*o*-xenylamide
X *p*-(*o*-acetamidophenyl)-benzenesulfon-N-*p*-xenylamide
XI *p*-(*o*-nitrophenyl)-benzenesulfon-N-*p*-xenylamide
XII *p*-(*o*-aminophenyl)-benzenesulfon-N-*p*-xenylamide
XIII N^4-[*p*-(*o*-acetamidophenyl)-benzenesulfonyl]-sulfanilamide
XIV N^4-[*p*-(*o*-nitrophenyl)-benzenesulfonyl]-sulfanilamide
XV N^4-[*p*-(*o*-aminophenyl)-benzenesulfonyl]-sulfanilamide
XVI 2-[*p*-(*o*-acetamidophenyl)-benzenesulfonamido]-biphenyl-4'-sulfonamide
XVII 2-[*p*-(*o*-nitrophenyl)-benzenesulfonamido]-biphenyl-4'-sulfonamide
XVIII 2-[*p*-(*o*-aminophenyl)-benzenesulfonamido]-biphenyl-4'-sulfonamide

The formulas, melting points, yields, and analyses of these compounds are given in Table I.

Experimental

Condensation of *p*-(*o*-Acetamidophenyl)-benzenesulfonyl Chloride with Aromatic Amino Compounds.—*p*-(*o*-Acetamidophenyl)-benzenesulfonyl chloride[1] was condensed with the six amino compounds listed above, dry acetone being used as solvent and pyridine as condensing agent. The following is a general description of the reactions. A solution was made of 5.00 g., 0.0161 mole, of *p*-(*o*-acetamidophenyl)-benzenesulfonyl chloride, m. p. 143–145°, in 80 cc. of dry acetone. To this was added 5 cc. of pyridine followed by a solution of 0.0163 mole of the amino compound in 20–70 cc. of acetone. The addition produced no appreciable rise in temperature. The mixture was warmed to 50° and then permitted to stand at room temperature for twelve hours.

The resulting solution was concentrated to one-half the volume. Addition of 350 cc. of water produced an oil which solidified on standing for twenty-four hours. The weight of this material was recorded as the yield in Table I. This was justified by the close agreement of the melting point for the crude product with the melting point of the purified final product. Each compound was purified by treatment with Norite and several crystallizations from dilute methanol.

In this manner, compounds I, IV, VII, X, XIII and XVI were prepared and purified.

Condensation of *p*-(*o*-Nitrophenyl)-benzenesulfonyl Chloride with Aromatic Amino Compounds.—*p*-(*o*-Nitrophenyl)-benzenesulfonyl chloride[1] was condensed with the aromatic amino compounds used above and by essentially the same procedure. A solution was made of 4.80 g., 0.0161 mole, of *p*-(*o*-nitrophenyl)-benzenesulfonyl chloride, m. p. 75–77°, in 65 cc. of dry acetone. To this was added 5 cc. of pyridine and a solution of 0.0163 mole of the amino compound in acetone. The addition produced no appreciable rise in the temperature of the reaction mixture. This was then warmed to 60° and allowed to stand at room temperature for sixteen hours.

TABLE I

Compd.	Formula	M. p., °C.	Yield, %	Yield by reduction, %	Yield by deacetylation, %	Analyses, % Nitrogen Calcd.	Nitrogen Found		Sulfur Calcd.	Sulfur Found	
I	$C_{20}H_{18}N_2O_3S$	163.5–164.5	89			7.65	7.62	7.69	8.75	8.46	8.54
II	$C_{18}H_{14}N_2O_4S$	155.5–156.5	95			7.91	8.26	8.16	9.05	8.85	8.96
III	$C_{13}H_{16}N_2O_2S$	100.0–100.5		98	94	8.64	8.58	8.69	9.88	9.49	9.59
IV	$C_{21}H_{20}N_2O_3S$	161 –162	59			7.36	7.16	7.28	8.43	8.25	8.44
V	$C_{19}H_{16}N_2O_4S$	128.5–130	68			7.61	7.86	7.62	8.70	8.65	8.54
VI	$C_{19}H_{18}N_2O_2S$	106.5–107.0		99	92	8.28	8.73	8.32	9.47	9.20	9.31
VII	$C_{26}H_{24}N_2O_3S$	173.5–175.0	86			6.33	6.19	6.21	7.25	6.97	7.13
VIII	$C_{24}H_{18}N_2O_4S$	161 –162	85			6.51	6.56	6.51	7.45	7.30	7.38
IX	$C_{24}H_{20}N_2O_2S$	165 –165.5		98	98	7.00	7.04	7.14	8.01	7.73	7.92
X	$C_{26}H_{22}N_2O_3S$	196 –196.5	92			6.33	6.55	6.48	7.25	6.92	7.00
XI	$C_{24}H_{18}N_2O_4S$	164 –165	90			6.51	6.43	6.46	7.45	7.38	7.45
XII	$C_{24}H_{20}N_2O_4S$	169 –170		97	98	7.00	7.08	7.11	8.01	7.84	7.89
XIII	$C_{27}H_{23}N_3O_5S_2$	231.5–232.5	78			9.43	9.63	9.44	14.39	14.12	14.36
XIV	$C_{25}H_{21}N_3O_6S_2$	239.5–240	92			9.70	9.92	9.94	14.80	14.97	15.06
XV	$C_{25}H_{23}N_3O_4S_2$	197.2–198.2		84	87	10.42	10.50	10.70	15.89	15.70	15.89
XVI	$C_{26}H_{23}N_3O_5S_2$	148.5–150 d.	92			8.06	7.92	7.94	12.29	12.13	12.42
XVII	$C_{31}H_{25}N_3O_6S_2$	173 –174	86			8.25	8.32	8.30	12.58	12.73	12.76
XVIII	$C_{29}H_{25}N_3O_4S_2$	263 –264		97	96	8.76	8.90	8.82	13.37	13.70	13.90

To the resulting solution was added 450 cc. of water, and the oil which separated was allowed to stand until solidification resulted. The solid was separated and washed with water until the odor of pyridine was gone. The resulting weight was recorded as the yield in Table I. Again, this was justified by the close agreement of the melting point of the crude product with that of the purified product. Purification to a constant melting point was obtained by treatment with Norite and recrystallization from dilute methanol.

Compounds II, V, VIII, XI, XIV and XVII were prepared by the above procedure.

Preparation of *p*-(*o*-Aminophenyl)-benzenesulfon-N-arylamides. Method I. The acetamido compounds ob-

tained above were deacetylated by the action of hydrochloric acid on a solution of the compound in methanol. The procedure was essentially the same for all derivatives, except for minor differences in the quantities of methanol used.

A solution of 2.5–4.0 g. of acetamido compound in 25–100 cc. of absolute methanol was treated with 5–15 cc. of concd. hydrochloric acid. This was heated to boiling and concentrated until the insoluble hydrochloride was obtained either as crystals or an oil. In the latter instances, addition of 100–200 cc. of water usually gave crystals. In each case, the hydrochloride was found to have a distinct melting point.

The hydrochloride was converted in the usual manner to the corresponding *p*-(*o*-aminophenyl)-benzenesulfon-N-arylamide which was separated by filtration, washed with water, dried and weighed. The resulting weight was recorded as the yield in Table I. Except for III, which was purified by treating the alkaline solution with Norite, the compounds obtained here were purified by treatment in a dilute methanol solution with Norite and by recrystallization therefrom.

This procedure was used for making compounds III, VI, IX, XII, XV and XVIII.

Method II.—The nitro compounds obtained above were reduced with tin and hydrochloric acid. Except for a slight variation in the quantity of solvent used, the procedure is the same for the different nitro compounds.

To a solution of 3–5 g. in 100–150 cc. of methanol was added 3–4.5 g. of tin and 25 cc. of concd. hydrochloric acid. This was boiled for three and one-half hours and allowed to stand for sixteen hours. The resulting solution was concentrated to a volume of 25 cc. On cooling, the hydrochloride separated either as crystals or as an oil. To the mixture was then added 150 cc. of water. This usually caused the oil to solidify. The hydrochloride was separated by a vacuum filtration, washed free of tin salt with water, and then converted to the corresponding amine in the usual manner. The weight of the resulting *p*-(*o*-aminophenyl)-benzenesulfon-N-arylamide was recorded as the yield in Table I. An ignition of this material showed an ash content of less than 1%, proving that the tin salt can be removed effectively from the hydrochloride by washing with water.

Compounds III, VI, IX, XII, XV and XVIII were prepared by this method. These were shown to be identical, by melting points and mixed melting points, with the corresponding compounds made by deacetylation.

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Summary

Six derivatives of *p*-(*o*-aminophenyl)-benzene sulfonamide, in which a hydrogen of the sulfonamide nitrogen was replaced by an aryl group were prepared from *p*-(*o*-acetamidophenyl)-benzenesulfonyl chloride and from *p*-(*o*-nitrophenyl)-benzenesulfonyl chloride. These and the parent compound were inactive when tested *in vitro* against *E. Coli* and *in vivo* against streptococcal infected mice.

Eighteen new derivatives of biphenyl-4′-sulfonamide have been prepared.

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Reduction Products of 2-Nitrophenyl Esters of Arylsulfonic Acids

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When two different acyls derived from carboxylic acids are introduced into 2-aminophenol only one mixed diacyl derivative can generally be obtained, regardless of the order of introduction of these radicals; and in this product the heavier and more acidic of these groups is usually found attached to nitrogen. Migration of acyl from nitrogen to oxygen must occur in one of these reactions.[1] If one of these acyls is derived from a sulfonic acid isomeric mixed diacyl derivatives are obtained and no rearrangement is observed.[2]

Reduction of the 2-nitrophenyl ester of a carboxylic acid gives the related 2-aminophenyl derivative as the first product, but under the ordinary laboratory conditions this rearranges to the isomeric 2-N-acylaminophenol or 2-hydroxyphenylurethan, depending on the starting material. In this case acyl must wander from oxygen to nitrogen.[3] In reduction of 2-nitrophenyl 4-tolylsulfonate Bell[4] obtained a product having an exposed amino radical, indicating that no rearrangement had occurred. Both the above reactions have now been tested in

(1) Raiford and Couture, THIS JOURNAL, **46**, 2305 (1924).

(2) Raiford and co-workers, *ibid.*, **47**, 1111 (1925); **53**, 3420 (1931); *J. Org. Chem.*, **4**, 207 (1939); **5**, 300 (1940).

(3) Ransom, *Ber.*, **31**, 1058 (1898); *Am. Chem. J.*, **23**, 43 (1900).

(4) Bell, *J. Chem. Soc.*, 1983 (1930).