142. *The Preparation of 4-Aminophenyl Sulphones. Part I. The Reaction between Aromatic Sulphinic Acids and Quinones or Quinoneimines.*

By S. Pickholz.

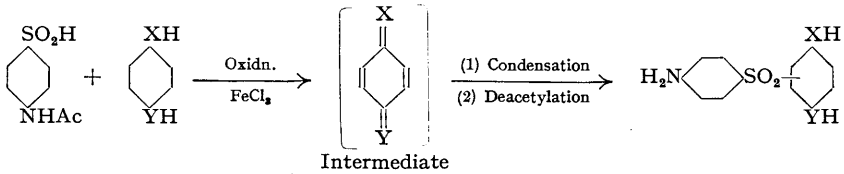
4-Aminophenyl sulphones have been prepared by the reaction between 4-acetamidobenzenesulphinic acid and quinones or quinoneimines or the corresponding dihydroxy- (or diamino-)benzenes. The compounds described possess high *in vitro* activity (against *B. subtilis*). Some of them are also active *in vivo* when tested on mice infected with *Str. Pyogenes* (var. *Aronson*).

The interest attached in recent years to the high antibacterial activity of 4 : 4′-diaminodiphenyl sulphone has led to extensive work on rendering this compound less toxic for clinical use. The diacetyl, formaldehyde-sulphoxylate, and *NN′*-diglucosesulphonic acid derivatives are probably the best known examples. Only recently more attention has been directed to the preparation of other sulphones as possible chemotherapeutic agents. Starting from the assumption that the 4-aminophenylsulphonyl group is an essential part of any potential antibacterial sulphone, various investigators have described the preparation of unsymmetrical sulphones of the general formula $H_2N{\cdot}C_6H_4{\cdot}SO_2R$, where R is an aliphatic, aromatic, or heterocyclic group (Buttle *et al.*, *Biochem. J.*, 1938, **32**, 1101; Fourneau *et al.*, *Compt. rend. Soc. Biol.*, 1938, **127**, 393; Jensen and Lundquist, *Dansk Tid. Farm.*, 1940, **14**, 129; Roblin *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 1930; Dewing *et al.*, *J.*, 1942, 239; Coggleshall and Maier, *J. Pharm. Exp. Ther.*, 1942, **76**, 161; Ochiai and Takubo, *J. Pharm. Soc. Japan*, 1941, **61**, 1; Bambas, *J. Amer. Chem. Soc.*, 1945, **67**, 668, 671; Burton and Hoggarth, *J.*, 1945, 14, 468; Goldberg and Besly, *ibid.*, p. 566; Walker, *ibid.*, p. 630).

The present paper represents a further contribution to the preparation of unsymmetrical 4-aminophenyl sulphones. The work was carried out in 1941 and 1942 * and is based in the main on the application of a method described first by Hinsberg in a number of papers (see Houben " Die Methoden der Organischen Chemie," 1930, 3e Aufl., Bd. III, 1281, 1329).

It consists in the oxidation–reduction of quinones or quinoneimines with aromatic sulphinic acids with the simultaneous formation of sulphones. The condensation will also take place by intermediate oxidation of the corresponding hydroxy- or amino-compounds in presence of the sulphinic acid. Potassium dichromate and ferric chloride are useful oxidising agents, and the method follows in principle the directions given by Hinsberg (*loc. cit.*; also Geigy A.-G., D.R.-P. 282,214). This feature considerably extends the scope of Hinsberg's reaction.

Starting with 4-acetamidobenzenesulphinic acid and deacetylating the condensation product, 4-aminophenyl sulphones are obtained which otherwise would be difficult to prepare. The reactions involved may be summarised as follows :



Intermediate quinone (quinoneimine)

In this way reactions were carried out with *p*-benzoquinone, *p*-toluquinone, quinol, *p*-aminophenol, *p*-phenylenediamine, and *p*-aminodimethyl- and *p*-aminodiethyl-aniline. Reaction with thymoquinone could not be effected (contrary to Hinsberg's claim, with benzenesulphinic acid). A few experiments with 4-chloro-, 4-nitro-, and 4-amino-benzenesulphinic acids have been included.

No attempts were made to determine the orientation of the sulphone group where unsymmetrical quinones or amines were used, and the constitutions ascribed to the compounds are therefore only tentative. For the *p*-toluquinone derivatives Walker's formulation (*loc. cit.*) is adopted. In the reactions with *p*-amino-dimethyl- and -diethyl-aniline it is assumed that the sulphone group owing to the directing influence of the amino groups

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enters the *o*-position. This formulation is in accordance with the formation of *S*-(2-amino-5-dimethylaminophenyl)thiosulphuric acid (an intermediate in the preparation of methylene blue) by the oxidation of *p*-aminodimethylaniline with ferric chloride in presence of sodium thiosulphate (cf. Bernthsen, *Annalen*, 1889, **251**, 51). In *p*-aminophenol the sulphone group may be in the *o*-position to the hydroxyl group, which here would be expected to have the stronger directive influence. These formulations are in agreement with results to be described in a second paper, dealing with the reaction between sulphinic acids and aromatic nitroso compounds.

Except the sulphones from benzo- and tolu-quinone (Buttle *et al.*, *loc. cit.*; Burton and Hoggarth, *loc. cit.*; Walker, *loc. cit.*) none of the compounds has been described before. A German Patent (Schering A.G., D.R.-P. 740,515, 2nd Sept., 1943) claims the preparation of sulphones according to Hinsberg's method. So far only a short abstract with no experimental details (*Chem. Abs.*, 1945, **39**, 2296) has been available.

Tests *in vitro* for antibacterial activity (against *B. subtilis*) and *in vivo* for toxicity (on mice) support the claims put forward by Walker (*loc. cit.*) for the quinol derivatives. An attempt was made to condense the 4-amino-2′ : 5′-dihydroxydiphenyl sulphone with glucose. Though the solubility was increased, the antistreptococcal activity remained negligible. It is of particular interest that the 4-amino group apparently remained uncombined in this experiment.

The sulphones derived from the amines showed even higher antibacterial activities *in vitro* than the hydroxysulphones. Their activity *in vivo* [mice infected with *Str. pyogenes* (var. *Aronson*)] is remarkably increased, with 4 : 2′ : 5′-triaminodiphenyl sulphone approaching that of sulphanilamide, although they are generally more toxic.

Experimental.

4-Acetamidobenzenesulphinic acid was prepared from crude *p*-acetamidobenzenesulphonyl chloride (*Org. Synth.*, Coll. Vol. I, 7), and had m. p. 140—143° (decomp.). Material with higher m. p. as claimed in *Org. Synth.* was regularly found to be more or less decomposed. It is interesting to note that reductions carried out with pure sulphonyl chloride (recrystallised from chloroform) took much longer and gave much lower yields of the sulphinic acid. 4-Aminobenzenesulphinic acid was prepared by alkaline hydrolysis of the foregoing acetyl compound (Jensen and Lundquist, *loc. cit.*); owing to its low solubility in water and organic solvents it is less convenient to use. 4-Nitrobenzenesulphinic acid was prepared by the method of Zincke (*Annalen*, 1913, **400**, 1). 4-Chlorobenzenesulphinic acid was prepared from 4-chlorobenzenesulphonyl chloride by reduction with sodium sulphite; the acid melts at 106—108° (Gattermann, *Ber.*, 1899, **32**, 1142, gives m. p. 96—98°).

4-*Acetamido*-2′ : 5′-*dihydroxydiphenyl Sulphone*.—(*a*) 4-Acetamidobenzenesulphinic acid (20 g.) was dissolved in a mixture of hot water (100 c.c.) and ethanol (50 c.c.), and a hot solution of benzoquinone (10 g.) in ethanol (40 c.c.) added all at once with vigorous shaking. The deep brown mixture was almost instantly decolourised and the sulphone crystallised shortly afterwards. After ½ hour on the water-bath the product was filtered off and dissolved in dilute sodium hydroxide solution, and the red-brown solution filtered (charcoal). The solution was acidified with acetic acid; and the cream-coloured precipitate collected and dried (24 g.). A sample, recrystallised from 50% aqueous alcohol, had m. p. 271—272° (Found: S, 10·6. Calc. for $C_{14}H_{13}O_5NS$: S, 10·4%). (*b*) 4-Acetamidobenzenesulphinic acid (20 g.) and quinhydrone (20 g.) were caused to react as described under (*a*); the product was identical. (*c*) 4-Acetamidobenzenesulphinic acid (10 g.) was dissolved in a mixture of warm water (200 c.c.) and ethanol (20 c.c.), and a solution of quinol (4·5 g.) in warm water (100 c.c.) added. A solution of potassium dichromate (6 g.) in 4% sulphuric acid (120 c.c.) was slowly added to the mixture with continuous stirring at 50—60°. The dichromate was quickly reduced and a brownish precipitate formed. After complete addition, stirring was continued for 15 minutes, and the precipitate collected, washed with water, dried, and extracted with 90% ethanol (140 c.c.). The hot solution was filtered (charcoal), and the clear, slightly pinkish filtrate diluted with water (300 c.c.). After some hours the sulphone crystallised out. Recrystallisation from 50% aqueous alcohol gave 7 g., m. p. 270—272° [Buttle *et al.*, *Biochem. J.*, 1938, **32**, 1108, record m. p. 282° (corr.); Burton and Hoggarth, *loc. cit.*, 274°; Walker, *loc. cit.*, 273°].

4-*Amino*-2′ : 5′-*dihydroxydiphenyl Sulphone*.—(*a*) A mixture of the foregoing acetyl compound (25 g.), 32% hydrochloric acid (25 c.c.), 95% ethanol (40 c.c.), and water (70 c.c.) was refluxed for 2 hours, and the solution treated with charcoal, filtered, diluted with water (150 c.c.), and neutralised with sodium bicarbonate. The precipitate, recrystallised from hot water (charcoal), gave finally cream-coloured crystals (16—18 g.), m. p. 175—177° (Found: S, 12·2. Calc. for $C_{12}H_{11}O_4NS$: S, 12·1%). (*b*) A suspension of 4-aminobenzenesulphinic acid (8 g.) in hot water (80 c.c.) was shaken with a solution of benzoquinone (5 g.) in ethanol (50 c.c.). The sulphone was quickly formed, the colour being discharged. The solution was filtered hot with two additions of charcoal. The slightly pinkish solution was cooled; the sulphone then crystallised (11—12 g.), m. p. 178—180° after one more recrystallisation from 50% alcohol (Buttle *et al.* give m. p. 180°; Burton and Hoggarth, 180°; Walker, 176—177°).

4-*Acetamido*-2′ : 5′-*dihydroxy*-4′(?)-*methyldiphenyl Sulphone*.—(*a*) The sulphinic acid (6 g.) was dissolved in hot water (150 c.c.) and a solution of *p*-toluquinone (3·5 g.) in warm 50% ethanol (50 c.c.) added with stirring. Reaction took place immediately. The precipitate, recrystallised from 50% aqueous alcohol, had m. p. 236—238° (Walker gives m. p. 237—239°). Yield 8·5 g. (*b*) An identical product was obtained starting from 2 : 5-dihydroxytoluene and oxidising it with potassium dichromate in presence of the sulphinic acid (Found: S, 10·2. Calc. for $C_{15}H_{15}O_5NS$: S, 9·97%).

4-*Amino*-2′ : 5′-*dihydroxy*-4′(?)-*methyldiphenyl Sulphone*.—(*a*) Deacetylation was carried out as before in hydrochloric acid–ethanol–water. After recrystallisation from 50% aqueous alcohol 6·5 g. of aminosulphone were obtained from 10 g. of acetyl compound. (*b*) Condensation with 4-aminobenzenesulphinic acid and *p*-toluquinone gave the same product. Cream coloured crystals, m. p. 185—186° (Walker gives m. p. 187—188°) (Found: S, 11·3. Calc. for $C_{13}H_{13}O_4NS$: S, 11·5%).

4-*Acetamido*-2′ : 5′-*diacetoxydiphenyl Sulphone*.—4-Acetamido-2′ : 5′-dihydroxydiphenyl sulphone (9 g.) was boiled with acetic anhydride (15 c.c.) for 1 hour. The red solution was diluted with an equal amount of water and left overnight. The acetylated product crystallised out and was filtered off. It was dissolved in acetone (40 c.c.) and the solution filtered (charcoal). The filtrate was concentrated on the water-bath; the *sulphone* (8 g.) then separated. It had m. p. 181—182° (Found: N, 4·1; S, 8·3. $C_{18}H_{17}O_7NS$ requires N, 3·84; S, 8·2%). Hydrolysis with 2N-sodium hydroxide solution gave 4-amino-2′ : 5′-dihydroxydiphenyl sulphone.

4-*Acetamido*-2′ : 5′-*diethoxydiphenyl Sulphone*.—4-Acetamido-2′ : 5′-dihydroxydiphenyl sulphone (3·1 g.) was dissolved in 10% sodium hydroxide solution (10 c.c.) and ethyl sulphate (2·9 c.c.) added with shaking at 40—50°. The diethoxy compound suddenly precipitated; it was collected and recrystallised from 95% alcohol (50 c.c.) (charcoal). The *product*, pale, cream-coloured crystals, had m. p. 206—207° (2·5 g.) (Found: S, 9·05. $C_{18}H_{21}O_5NS$ requires: S, 8·8%).

4-*Amino*-2′ : 5′-*diethoxydiphenyl Sulphone*.—(*a*) By deacetylation in the usual way. White crystals, m. p. 204—205°;

(*b*) by ethylation of 4-amino-2′ : 5′-dihydroxydiphenyl sulphone in essentially the manner described above. The *products* were identical; mixed m. p. 204° (Found : S, 9·8. $C_{16}H_{19}O_4NS$ requires S, 10·0%).

5′-Amino-4-acetamido-2′-hydroxydiphenyl Sulphone.—(*a*) *p*-Aminophenol (5 g.) and 4-acetamidobenzenesulphinic acid (10 g.) were dissolved in warm water (150 c.c.), the solution was acidified with 50% sulphuric acid (40 c.c.), and 10% potassium dichromate solution (70 c.c.) was added with stirring (excess of dichromate should be avoided). The mixture was neutralised with sodium bicarbonate, and the brown precipitate collected, washed with water, and dried. The product was dissolved in ethanol (150—200 c.c.), and the dark solution repeatedly decolourised with charcoal until only slightly brown. The final filtrate was concentrated to *ca.* 50 c.c. and left for 24 hours in the cold. The crystals were collected and recrystallised from alcohol to yield white to cream-coloured needles (6—8 g.), m. p. 234—236°. (*b*) A solution of *p*-aminophenol (5 g.) and 4-acetamidobenzenesulphinic acid (10 g.) in warm water (200 c.c.) was acidified with concentrated hydrochloric acid (10 c.c.). A solution of anhydrous ferric chloride (16 g.) in water (160 c.c.) was added during 15 minutes with stirring, the temperature being kept at 50—60°. The stirring was continued for 1 hour, the dark coloured mixture cooled, and sodium bicarbonate added to give a pH of *ca.* 5·5—6; the dark precipitate was collected and worked up as before. The *substance*, crystallised from 80—85% aqueous acetone, had m. p. 235—236° (decomp.) (Found : S, 10·6. $C_{14}H_{14}O_4N_2S$ requires S, 10·5%).

4 : 5′-*Diamino-2′-hydroxydiphenyl Sulphone.*—Deacetylation of the foregoing compound (5 g.) with 10% hydrochloric acid (50 c.c.) and neutralisation of the filtered solution with sodium bicarbonate yielded the *sulphone*. Recrystallisation from ethanol or methanol gave white crystals (3 g.), m. p. 210—212° (decomp.) (Found : S, 12·1. $C_{12}H_{12}O_3N_2S$ requires S, 12·1%).

2 : 5′-*Diamino-4-acetamidodiphenyl Sulphone.*—Solutions of *p*-phenylenediamine (11 g.) dissolved in 5% hydrochloric acid (350 c.c.) and 4-acetamidobenzenesulphinic acid (22 g.) suspended in water (350 c.c.) with 10% sodium hydroxide (40 c.c.) were mixed and a solution of ferric chloride (35 g.) in water (140 c.c.) was added dropwise with vigorous stirring, the temperature being kept at 40—60°. The mixture was left for some hours, and the yellow solution then decanted from some tarry precipitate and filtered (charcoal). The filtrate was adjusted to pH *ca.* 5·5—6 with 10% sodium hydroxide (*ca.* 250 c.c.), and the brown precipitate collected, washed with water, dried, and twice recrystallised from 70% alcohol (100—150 c.c.). The *product* was dissolved in 10% hydrochloric acid (*ca.* 100 c.c.), the brownish solution decolourised with charcoal, and the filtrate neutralised with sodium bicarbonate. The white to cream crystals (12—16 g.) were collected, washed with water, and dried; m. p. 222—223° (Found : S, 10·6; N, 14·0. $C_{14}H_{15}O_3N_3S$ requires S, 10·5; N, 13·8%).

4 : 2′ : 5′-*Triaminodiphenyl Sulphone.*—The acetyl derivative (10 g.) was deacetylated in the usual way. The product was precipitated from the solution with ammonia and recrystallised twice from 25% alcohol. Almost white needles (6 g.) were obtained. The *sulphone* had m. p. 150—152° (Found : S, 12·0; N, 16·1. $C_{12}H_{13}O_2N_3S$ requires S, 12·2; N, 16·0%).

2′-Amino-5′-dimethylamino-4-acetamidodiphenyl Sulphone.—Dimethylaniline (16 g.) was converted into *p*-nitrosodimethylaniline, which was reduced with iron powder–hydrochloric acid to *p*-aminodimethylaniline. To the acid solution (corresponding to 14 g. of *p*-aminodimethylaniline), 4-acetamidobenzenesulphinic acid (22 g. in the equivalent amount of sodium hydroxide, total volume 220 c.c.) was added at once and the mixture stirred at 40—60°. 10% Ferric chloride (300 c.c.), acidified with concentrated hydrochloric acid (20 c.c.), was added in 15—20 minutes and the stirring continued for 1 hour more. After some time the greenish-white crystals of hydrochloride were filtered off. The product could be recrystallised from dilute alcohol or water; yield 15—16 g. This hydrochloride (8 g.) was dissolved in water (150 c.c.) with a few drops of concentrated hydrochloric acid, and the acid solution made neutral or slightly alkaline with ammonia or sodium hydroxide. The yellowish-green *acetyl* derivative was collected and washed with water, alcohol, and ether; 6·5 g., m. p. 217—219° (Found : S, 9·7; N, 12·8. $C_{16}H_{19}O_3N_3S$ requires S, 9·6; N, 12·6%).

4 : 2′-*Diamino-5′-dimethylaminodiphenyl Sulphone.*—The foregoing compound (3 g.) was deacetylated and the *sulphone* precipitated from the acid solution by excess of ammonia. The precipitate, recrystallised from ethanol, formed yellowish-green plates (2 g.), m. p. 190—192° (Found : S, 10·7; N, 14·5. $C_{14}H_{17}O_2N_3S$ requires S, 11·0; N, 14·4%).

2′-Amino-5′-diethylamino-4-acetamidodiphenyl Sulphone.—*p*-Aminodiethylaniline was prepared and condensed with 4-acetamidobenzenesulphinic acid under the same conditions as in the foregoing example (amine : acid : ferric chloride = 1 : 1 : 2). The *compound* (yield *ca.* 50%) formed yellow plates from benzene, m. p. 124—126° (Found : S, 9·1. $C_{18}H_{23}O_3N_3S$ requires S, 8·9%).

4 : 2′-*Diamino-5′-diethylaminodiphenyl Sulphone.*—Hydrolysis in the usual way yielded the *sulphone*, yellowish-green crystals from ethanol, m. p. 150—152° (Found : S, 10·2. $C_{16}H_{21}O_2N_3S$ requires S, 10·0%).

4-*Nitro-2′* : 5′-*diaminodiphenyl Sulphone Hydrochloride.*—4-Nitrobenzenesulphinic acid (8 g.) and *p*-phenylenediamine (4·4 g.) were dissolved in hot water (160 c.c.) and the solution acidified with concentrated hydrochloric acid (30 c.c.); 20% ferric chloride solution (65—70 c.c.) was added at 70—80° with stirring during 15 minutes, the stirring continued without further heating for another 15 minutes, and the still warm solution filtered (charcoal). The yellow *product*, which crystallised out on cooling, was collected and recrystallised from 12—15% hydrochloric acid to give pale yellowish needles (6—8 g.), m. p. 257—260° (Found : Cl, 10·5; S, 9·9. $C_{12}H_{11}O_4N_3S,HCl$ requires Cl, 10·8; S, 9·8%). This compound was reduced with tin and hydrochloric acid to 4 : 2′ : 5′-triaminodiphenylsulphone, thus confirming the assumed structure.

4-*Chloro-2′* : 5′-*diaminodiphenyl Sulphone.*—4-Chlorobenzenesulphinic acid (8 g.) and *p*-phenylenediamine (4 g.) were dissolved in 25% alcohol (100 c.c.) and the warm (50%) solution acidified with concentrated hydrochloric acid (20 c.c.). 20% Ferric chloride (40—50 c.c.) was added as before. The hydrochloride of the sulphone, m. p. 238—240°, crystallised out and was collected after some time. The *sulphone*, prepared by addition of a slight excess of dilute ammonia to a warm solution of the hydrochloride, crystallised from 90% ethanol in pale yellow crystals (7 g.), m. p. 146—148° (Found : S, 11·2. $C_{12}H_{11}O_2N_2ClS$ requires S, 11·3%).

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