

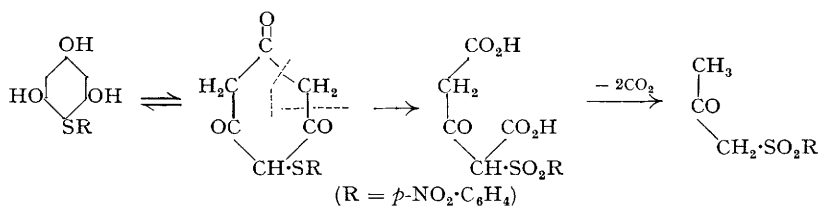
121. Compounds Related to 4:4'-Diaminodiphenylsulphone.

By HAROLD BURTON and ERIC HOGGARTH.

Various *p*-aminophenylarylsulphones and related sulphonic esters have been prepared by known methods. With one exception, none of the compounds is as active as 4:4'-diaminodiphenylsulphone as an antibacterial agent.

IN connection with an investigation on the effect of substituting hydroxyl, methoxyl, chloro- and amino-groups into arylalkyl- and diaryl-sulphones (compare Burton and Hoggarth, this vol., p. 14) various compounds of the type $p\text{-NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{SO}_2\text{Ar}$ were synthesised. In one case the group Ar was *p*-chlorophenyl, in another case (probably) 4-amino-2-hydroxyphenyl (the alternative 2:4-structure not being excluded); in other examples, Ar was mono-, di-, and 2:4:6-tri-hydroxyphenyl. The antibacterial activity of 4:4'-diamino-2-hydroxydiphenylsulphone is of the same order as that of 4:4'-diaminodiphenylsulphone, that of 4-amino-2':4'-dihydroxydiphenylsulphone somewhat less, and all other compounds show only feeble activity. In the earlier communication on this subject the isolation of sulphonic esters as by-products in attempts to prepare certain sulphones was reported. The great stability shown by these compounds led to the preparation of sulphonates analogous to the more active sulphones. A number of such compounds containing amino- and hydroxyl-groups are now described. None of these compounds showed more than a trace of antibacterial activity. Biological testing of these compounds was carried out by Dr. A. R. Martin at Blackley.

A novel oxidative degradation of 4-nitro-2':4':6'-tri-hydroxydiphenyl sulphide has been observed. When this compound was treated with "perhydrol" in hot acetic acid, approximately 30% of *p*-nitrobenzenesulphonyl-acetone was isolated. This presumably arises in the following way:



4-Nitro-2':4'-dihydroxydiphenyl sulphide under the same conditions gave only *p*-nitrobenzenesulphonic acid (69%). The fully acetylated derivatives of both sulphides can be oxidised to sulphones in good yield.

EXPERIMENTAL.

4-Chloro-4'-nitrodiphenylsulphone.—To a solution of sodium (5 g.) in absolute alcohol (250 c.c.) was added *p*-chlorothiophenol (29 g.), followed by *p*-chloronitrobenzene (32 g.), and the mixture refluxed for 3 hours. The reaction mixture was poured into water, the sulphide collected, washed with water, and crystallised from methyl alcohol, giving pale yellow plates (40 g.), m. p. 88° (Found: Cl, 13.6; S, 12.1. C₁₂H₈O₂NCIS requires Cl, 13.4; S, 12.05%). This sulphide (39 g.) was oxidised in boiling acetic acid (130 c.c.) by perhydrol (75 c.c.). When the violent reaction subsided, the clear yellow solution was refluxed for ½ hour and poured on ice, and the solid collected and crystallised from ethyl alcohol. 4-Chloro-4'-nitrodiphenylsulphone formed almost colourless needles (40 g.), m. p. 154° (Found: Cl, 12.1; S, 11.0. C₁₂H₈O₄NCIS requires Cl, 11.9; S, 10.75%).

4-Chloro-4'-aminodiphenylsulphone.—The above nitro-sulphone (30 g.) was reduced in methyl alcohol (400 c.c.), Raney nickel catalyst being used at ordinary pressure and temperature (absorption, corrected to N.T.P., 6,805 c.c.; theoretical, 6,720 c.c.). The clear filtrate was evaporated, and the residue crystallised from methyl alcohol, giving long colourless needles (21.4 g.), m. p. 182–183°, of 4-chloro-4'-aminodiphenylsulphone (Found: Cl, 13.7; S, 12.0. C₁₂H₁₀O₂NCIS requires Cl, 13.3; S, 12.0%).

4-Nitro-4-methoxydiphenylsulphone.—This compound was obtained from *p*-methoxythiophenol in the same way as for 4-chloro-4'-nitrodiphenylsulphone and formed pale yellow needles from benzene (62%), m. p. 162° (Found: C, 53.0; H, 3.6. C₁₃H₁₁O₃NS requires C, 53.2; H, 3.8%).

4-Amino-4-methoxydiphenylsulphone.—The above nitromethoxy-sulphone was reduced catalytically as described for 4-chloro-4'-aminodiphenylsulphone, and the product crystallised from ethyl alcohol, giving colourless needles (69.2%), m. p. 150° (Found: C, 59.6; H, 5.35. C₁₃H₁₃O₃NS requires C, 59.3; H, 4.9%).

4-Amino-4'-hydroxydiphenylsulphone.—The above aminomethoxy-sulphone (2.6 g.) and 46% hydrobromic acid were refluxed with stirring for 6 hours. Excess of hydrobromic acid was evaporated under reduced pressure, the residue dissolved in warm water (100 c.c.), filtered, and treated with a saturated solution of sodium acetate until precipitation was complete. The solid was collected, dissolved in sodium hydroxide solution (50 c.c. of 2½%), filtered with charcoal, and precipitated with acetic acid. The solid was collected and crystallised from water containing a little ethyl alcohol, forming colourless needles (1.2 g.), m. p. 166° (Found: C, 57.5; H, 4.5. Calc. for C₁₃H₁₁O₃NS: C, 57.8; H, 4.4%). Raiziss, Clemence, Severac, and Moetsch (J. Amer. Chem. Soc., 1939, 61, 2764; U.S.P. 2,248,283) have described this compound, prepared by another route, as having m. p. 192°, diacetyl derivative m. p. 171°. The diacetyl derivative of the compound prepared as above, acetic anhydride being used at 100°, had m. p. 169–170° (Found: C, 57.6; H, 4.2. Calc. for C₁₅H₁₃O₅NS: C, 57.7; H, 4.5%).

4-Amino-2'-hydroxy-5'-methyldiphenylsulphone.—4-Nitro-2'-hydroxy-5'-methyldiphenylsulphone (Levi and Smiles, J., 1932, 1488) (5.8 g.), iron powder (12 g.), alcohol (75 c.c.), water (10 c.c.), and concentrated hydrochloric acid (1 c.c.) were heated, with stirring, under reflux for 3 hours. The mixture was made alkaline with ammonia, and the liquid filtered hot and evaporated to dryness. The residue was dissolved in boiling dilute hydrochloric acid (charcoal), and the amine liberated with sodium acetate. The sulphone (3.8 g.) had m. p. 198° after crystallisation from methyl alcohol (Found: C, 59.5; H, 5.0. C₁₃H₁₃O₃NS requires C, 59.3; H, 4.9%). Acetylation with acetic anhydride in aqueous solution gave the acetyl derivative, m. p. 241° after crystallisation from acetic acid (Found: C, 58.4; H, 4.95. C₁₅H₁₅O₄NS requires C, 59.0; H, 4.9%).

4-Nitro-2'- β -diethylaminoethoxy-5'-methylidiphenylsulphone.—The nitrohydroxy-sulphone (7.5 g.) was dissolved in the solution prepared from potassium (1 g.) and methyl alcohol (22 c.c.); xylene (20 c.c.) was then added, the methyl alcohol removed by distillation, and a 40% solution (21.5 g.) of β -diethylaminoethyl chloride in xylene added to the residue. The mixture was boiled under reflux for 24 hours, the xylene removed in a vacuum, and the residue treated with 1:1 dilute hydrochloric acid. The insoluble *hydrochloride* (6.2 g.) was collected, washed with ether, and recrystallised from boiling 1:1 dilute hydrochloric acid, forming colourless needles, m. p. 217° after sintering at ca. 120° (Found for material dried at 120°/vac.; N, 6.35; S, 7.15; Cl, 7.7. $C_{19}H_{24}O_5N_2S \cdot HCl$ requires N, 6.5; S, 7.3; Cl, 8.3%). The free base crystallised from light petroleum in pale yellow plates, m. p. 119–120° (Found: N, 6.95; S, 8.1. $C_{19}H_{24}O_5N_2S$ requires N, 7.15; S, 8.2%).

4-Amino-2'- β -diethylaminoethyl-5'-methylidiphenylsulphone.—The nitro-compound (6 g.) was reduced with iron powder as described above. The free amine crystallised from benzene–light petroleum in colourless needles, m. p. 135–136° (Found: N, 8.05; S, 8.7. $C_{19}H_{24}O_3N_2S$ requires N, 7.7; S, 8.8%).

4-Amino-2': 5'-dihydroxydiphenylsulphone.—Hot solutions of *p*-acetamidobenzenesulphonic acid (5 g.) in water (100 c.c.) and *p*-benzoquinone (2.7 g.) in water (50 c.c.) were mixed; the *N*-acetyl derivative (6.8 g.) of the sulphone separated almost immediately. It melted at 274° (after darkening from 240°) to a black liquid. Hydrolysis with boiling 6*N*-hydrochloric acid gave the amino-sulphone (4.4 g.), which crystallised from water in nearly colourless prisms, m. p. 180° (Found: C, 54.1; H, 4.1. $C_{12}H_{11}O_4NS$ requires C, 54.4; H, 4.15%).

4-Nitro-3': 5'-dimethoxydiphenylsulphone.—3:5-Dimethoxythiophenol (3.4 g.) was added to a solution of sodium (0.6 g.) in absolute alcohol (30 c.c.), followed by *p*-chloronitrobenzene (3.2 g.), and the mixture refluxed for 3 hours. The oily sulphide isolated by pouring into water and extraction with benzene had b. p. 220–225°/1 mm. (3.2 g.). From absolute alcohol a small sample gave large yellow prisms, m. p. 74° (Found: S, 10.9. $C_{14}H_{13}O_4NS$ requires S, 11.0%). The remainder of the crude sulphide (3.0 g.) was oxidised in hot acetic acid (15 c.c.) with "perhydrol" (5.5 c.c.). **4-Nitro-3': 5'-dimethoxydiphenylsulphone**, isolated in the usual manner, crystallised from ethyl alcohol in golden-yellow needles (1.6 g.), m. p. 153° (Found: N, 4.6; S, 10.1. $C_{14}H_{13}O_4NS$ requires N, 4.3; S, 9.9%).

4-Amino-3': 5'-dimethoxydiphenylsulphone.—The above nitromethoxy-sulphone was reduced in methanol with Raney nickel at ordinary pressure and temperature, and the sulphone crystallised from ethyl alcohol, giving faintly yellow needles (82%), m. p. 134° (Found: C, 57.0; H, 5.05. $C_{14}H_{15}O_4NS$ requires C, 57.3; H, 5.1%).

4-Amino-3': 5'-dihydroxydiphenylsulphone.—Demethylation of the above aminomethoxy-compound as described for 4-amino-4'-hydroxydiphenylsulphone gave 4-amino-3': 5'-dihydroxydiphenylsulphone, which separated from chloro-benzene–light petroleum as a nearly colourless, crystalline powder, m. p. 238° (Found: C, 53.9; H, 4.2. $C_{12}H_{11}O_4NS$ requires C, 54.4; H, 4.15%).

4-Nitro-4'(or 2')-amino-2'(or 4')-hydroxydiphenyl Sulphide.—*p*-Nitrobenzenesulphenyl chloride (from 15.4 g. of 4:4'-dinitrodiphenyl disulphide), *m*-aminophenol (21.8 g.; 2 mols.), and ether were boiled for 2 hours. The residue after removal of the ether from the filtrate was dissolved in the minimum amount of warm acetic acid; on keeping, crystalline material separated. Recrystallisation from 50% acetic acid gave the sulphide (9.5 g.), m. p. 148–150° (Found: N, 10.75; S, 12.0. $C_{15}H_{10}O_3N_2S$ requires N, 10.7; S, 12.2%). A solution of the sulphide in hot acetic acid (50 c.c.) was treated with acetic anhydride (10 c.c.), and the mixture allowed to cool; recrystallisation of the acetyl derivative from acetic acid gave orange needles, m. p. 235° (Found: N, 9.25; S, 10.3. $C_{14}H_{12}O_4N_2S$ requires N, 9.2; S, 10.5%).

4:4'(or 2')-Diamino-2'(or 4')-hydroxydiphenylsulphone.—The above acetyl derivative (7.5 g.) was oxidised with "perhydrol" in acetic acid, giving the acetyl-sulphone (6.2 g.), fine hair-like needles from alcohol, m. p. 245° (Found: S, 9.5. $C_{14}H_{12}O_6N_2S$ requires S, 9.5%), which was reduced with iron powder (12 g.), in a boiling mixture of alcohol (75 c.c.), water (10 c.c.) and concentrated hydrochloric acid (1 c.c.) during 3 hours. The residue from the evaporated, basified (ammonia) solution was hydrolysed with 6*N*-hydrochloric acid, and the diaminohydroxy-sulphone liberated with sodium acetate; recrystallisation from water (charcoal) gave colourless needles, m. p. 132–133° (Found: N, 10.7; S, 12.3. $C_{12}H_{12}O_3N_2S$ requires N, 10.6; S, 12.1%).

4-Nitro-2': 4'-dihydroxydiphenyl Sulphide.—Finely powdered resorcinol (11 g.) and a filtered solution of *p*-nitrobenzenesulphenyl chloride (19 g.) in dry benzene (200 c.c.) were shaken together in a pressure bottle for 5 hours. The solid was collected and crystallised from dilute acetic acid, giving yellow needles (17.2 g.), m. p. 184°. After this sulphide (10.6 g.) had been oxidised in hot acetic acid (30 c.c.) with "perhydrol" (20 c.c.), the reaction liquid gave no appreciable precipitate on dilution with cold water. The clear filtered solution was evaporated under reduced pressure, and the residue crystallised from ethyl acetate–benzene, forming colourless prisms (5.6 g.), m. p. 106–108° (Found: N, 7.3; S, 15.6. Calc. for $C_6H_5O_3NS$: N, 6.9; S, 15.8%). On heating this compound (1 g.) with phosphorus pentachloride, *p*-nitrobenzenesulphonyl chloride (0.6 g.), m. p. 79–80° (not depressed by admixture with an authentic sample), was obtained.

4-Nitro-2': 4'-diacetoxydiphenylsulphone.—The above nitrodihydroxy-sulphide (17 g.) in acetic anhydride (60 g.) was heated to boiling, one drop of concentrated sulphuric acid added, and after 5 minutes the reaction liquid was poured into water. The solid was collected, washed with water, and crystallised from methyl alcohol, giving large colourless prisms (18.1 g.), m. p. 115°. Oxidation of this was effected (17.5 g.) by addition of "perhydrol" (23 c.c.) to a boiling solution in glacial acetic acid (40 c.c.), well stirred, under reflux. When the reaction had subsided, the clear yellow solution was stirred just below refluxing temperature for 1 hour and poured into water, and the solid collected and washed with water. This material appeared to be partially deacetylated, as it could be crystallised only with difficulty. It was dissolved in acetic anhydride (50 g.), heated just to boiling with 1 drop of sulphuric acid, and poured into ice-water, and the solid collected. From methyl alcohol it readily crystallised in long colourless needles (8.8 g.), m. p. 124° (Found: C, 50.8; H, 3.5; S, 8.3. $C_{16}H_{13}O_8NS$ requires C, 50.7; H, 3.4; S, 8.4%).

4-Amino-2': 4'-diacetoxydiphenylsulphone.—The above nitrodiaacetoxy-sulphone (9.5 g.) was reduced in methyl alcohol (50 c.c.) by hydrogen at ordinary temperature and pressure in the presence of Raney nickel catalyst (2 g.) (absorption, corrected to N.T.P., 1,670 c.c.; theoretical, 1,680 c.c.). The filtered solution was evaporated under reduced pressure; the residue crystallised from methyl alcohol in long colourless needles (6.9 g.), m. p. 136° (Found: C, 54.8; H, 4.4; S, 9.3. $C_{14}H_{15}O_6NS$ requires C, 55.0; H, 4.3; S, 9.2%) (0.132 g. of this compound absorbed 7.9 c.c. of *m*/20-sodium nitrite; theoretical, 7.7 c.c. The acetyl group has therefore not migrated to the amino-group).

4-Amino-2': 4'-dihydroxydiphenylsulphone.—The above aminodiaacetoxy-compound (6.0 g.) in methyl alcohol (200 c.c.) was kept cold whilst dry hydrogen chloride was passed until the solution was saturated. After refluxing for 5 hours, the solvent was evaporated under reduced pressure, the residual hydrochloride treated with a solution of sodium carbonate (4 g.) in water (200 c.c.), and the solid collected, dried in a vacuum at 80°, and crystallised from light petroleum (b. p. 60–80°)–benzene–ethyl acetate, forming colourless needles (3.4 g.), m. p. 134–136° (Found after drying in a vacuum at 100°: C, 53.8; H, 4.3; S, 11.8. $C_{12}H_{11}O_4NS$ requires C, 54.4; H, 4.15; S, 12.1%). A sample not dried as above was apparently a hydrate).

4-Nitro-2': 4'-dihydroxydiphenylsulphone.—The 4-nitro-2': 4'-diacetoxydiphenylsulphone above (2.5 g.) was hydrolysed by dry hydrogen chloride in methyl alcohol (50 c.c.) under reflux during 4 hours. The solid left on evaporation crystallised from benzene in colourless plates (1.7 g.), m. p. 182° (Found: C, 48.4; H, 3.05; S, 10.5. $C_{12}H_9O_6NS$

requires C, 48.8; H, 3.1; S, 10.8%). This compound was reduced to 4-amino-2':4'-dihydroxydiphenylsulphone in the usual manner (68%), m. p. 134—136°.

4-Nitro-2':4':6'-trihydroxydiphenyl Sulphide.—*p*-Nitrobenzenesulphenyl chloride (from 15.4 g. of 4:4'-dinitrodiphenyl disulphide) and anhydrous phloroglucinol (12.6 g.) in ether (250 c.c.) were heated on the steam-bath for 6 hours. The residue after removal of the ether was extracted with warm 2*N*-sodium hydroxide. The *sulphide* (ca. 15 g.) liberated from the alkaline solution did not crystallise well; material obtained from dilute aqueous alcohol had m. p. 245° after previous softening and was not quite pure (Found: N, 5.0; S, 10.75. $C_{12}H_9O_5NS$ requires N, 5.0; S, 11.5%). Acetylation with acetic anhydride and anhydrous sodium acetate gave the *triacetate*, which crystallised from methyl alcohol (charcoal) containing a little acetone in colourless prismatic needles, m. p. 120—121° (Found: C, 53.3; H, 3.9; S, 8.1. $C_{18}H_{15}O_8NS$ requires C, 53.3; H, 3.7; S, 7.9%).

When the sulphide (20 g.) was oxidised with "perhydrol" in acetic acid, a vigorous reaction (external cooling was necessary) took place, and after 30 minutes at 100° was complete. Dilution with water gave *p*-nitrobenzenesulphonylacetone (5.1 g.), m. p. 117—118°, almost colourless needles from alcohol (Found: C, 44.3; H, 3.5; N, 5.8; S, 13.3. $C_9H_9O_5NS$ requires C, 44.4; H, 3.7; N, 5.8; S, 13.2%), identical with a specimen prepared by oxidation of *p*-nitrophenylthioacetone. Reduction (iron powder) gave *p*-aminobenzenesulphonylacetone, colourless needles from alcohol, m. p. 134—135° (Found: C, 50.3; H, 5.2; N, 6.55; S, 15.0. $C_9H_{11}O_3NS$ requires C, 50.7; H, 5.2; N, 6.6; S, 15.0%).

4-Nitro-2':4':6'-trihydroxydiphenylsulphone.—The sulphide triacetate (16 g.) in acetic acid (100 c.c.) and acetic anhydride (20 c.c.) was oxidised with "perhydrol" (18 c.c.) as described for 4-nitro-2':4'-diacetoxydiphenylsulphone; reacylation was unnecessary. The *sulphone triacetate* crystallised from alcohol-acetone in colourless needles, m. p. 188° (Found: C, 49.5; H, 3.45; N, 3.2. $C_{18}H_{15}O_{10}NS$ requires C, 49.4; H, 3.4; N, 3.2%). Hydrolysis with dilute sulphuric acid in boiling alcohol (2 hours) gave 4-nitro-2':4':6'-trihydroxydiphenylsulphone (8 g.), which recrystallised from water in fine needles containing water of crystallisation; an air-dried specimen had m. p. 120° (efferv.), raised to 224—225° on drying at 120° (Found for material dried at 120°: N, 4.4; S, 10.45. $C_{12}H_9O_7NS$ requires N, 4.5; S, 10.3%).

4-Amino-2':4':6'-trihydroxydiphenylsulphone.—The nitrotrihydroxy-sulphone was reduced (iron powder) as above. The *aminotrihydroxy-sulphone* crystallised from water in needles, m. p. 209—210° after drying at 120° (Found for material dried at 120°: N, 4.9; S, 11.3. $C_{12}H_{11}O_5NS$ requires N, 5.0; S, 11.4%).

***p*-Nitrophenyl *p*-Nitrobenzenesulphonate.**—*p*-Nitrophenol (9.1 g.) was dissolved in dry pyridine (11 c.c.) by gentle heat, and powdered *p*-nitrobenzenesulphonyl chloride (14.7 g.) added at such a rate that the temperature remained below 80—90°. After standing for 12 hours, the reaction mixture was diluted with water, and the solid collected and crystallised from β -ethoxyethyl alcohol, giving large colourless prisms (15.5 g.), m. p. 158° (Found: C, 44.6; H, 2.2. $C_{12}H_8O_7N_2S$ requires C, 44.5; H, 2.5%).

***p*-Aminophenyl Sulphanilate.**—The above ester (10.8 g.) was reduced in methyl alcohol (250 c.c.), Raney nickel catalyst being used at ordinary pressure and temperature (absorption, 4515 c.c.; theoretical, 4480 c.c.). *p*-Aminophenyl sulphanilate crystallised from ethyl alcohol in long colourless needles (8.6 g.), m. p. 117° (Found: C, 54.4; H, 4.65. $C_{12}H_{12}O_3N_2S$ requires C, 54.55; H, 4.5%).

***p*-Hydroxyphenyl *p*-Nitrobenzenesulphonate.**—Quinol (5.5 g.) was dissolved in pyridine (12 c.c.) and treated with *p*-nitrobenzenesulphonyl chloride (9.5 g.; 1 mol.) as above. The crude product was dissolved in 4*N*-sodium hydroxide (25 c.c.) and water (100 c.c.), filtered from the insoluble disulphonic ester, and *p*-hydroxyphenyl *p*-nitrobenzenesulphonate precipitated with acetic acid. It crystallised from benzene-light petroleum in clumps of pale yellow needles (2.1 g.), m. p. 134° (Found: S, 10.8. $C_{12}H_9O_6NS$ requires S, 10.8%).

***p*-Hydroxyphenyl Sulphanilate.**—The above nitrohydroxy-ester was reduced in methyl alcohol with Raney nickel catalyst in the usual way. *p*-Hydroxyphenyl sulphanilate crystallised from benzene containing a little ethyl acetate in plates (65%), m. p. 170° (Found: C, 54.55; H, 4.45; S, 12.0. $C_{12}H_{11}O_4NS$ requires C, 54.35; H, 4.1; S, 12.1%).

***m*-Hydroxyphenyl Sulphanilate.**—This compound was obtained by the same route as the *p*-hydroxy-isomer and crystallised from benzene-light petroleum in colourless plates, m. p. 119° (Found: C, 53.95; H, 4.3; S, 12.1. $C_{12}H_{11}O_4NS$ requires C, 54.35; H, 4.1; S, 12.1%).

THE UNIVERSITY, LEEDS, 2.

IMPERIAL CHEMICAL INDUSTRIES LIMITED,

RESEARCH LABORATORIES, BLACKLEY, MANCHESTER, 9.

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