90. *The Sulphonation of* o-*Anisidine and Aceto-*o-*anisidide.*

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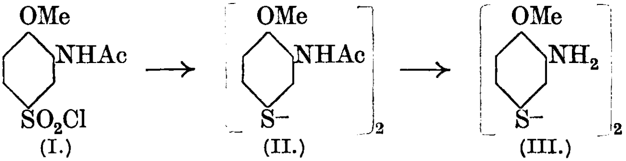
THE sulphur analogue of salvarsan, namely, 4 : 4′-dihydroxy-3 : 3′-diaminodiphenyl disulphide dihydrochloride, has not been described, and the author has attempted to prepare it by demethylation of 2 : 2′-diaminodianisyl 4 : 4′-disulphide (III). The latter substance, made by Gnehm and Knecht (*J. pr. Chem.*, 1906, **74**, 92), who did not record its melting point or analysis, has now been prepared by the following route, the sulphonyl chloride (I) being converted through the sulphinic acid and mercaptan into (II).



In this connexion, the sulphonation of *o*-anisidine and aceto-*o*-anisidide has been studied. The proof, hitherto lacking, that the acid obtained by the sulphonation of *o*-anisidine (D.R.-P. 291,963; Friedländer's "Fortschritte," XIII, 479) is 2-aminoanisole-4-sulphonic acid has now been furnished, since the product has been shown to be identical with 2-aminoanisole-4-sulphonic acid prepared by the reduction of 2-nitroanisole-4-sulphonic acid (Gnehm and

Knecht, *loc. cit.*) : both samples were converted on diazotisation and treatment with boiling cuprous chloride solution into 2-chloroanisole-4-sulphonic acid, isolated as the sodium salt, and converted into the *chloride* and the *amide.* 2-Chloroanisole-4-sulphonyl chloride was also obtained by the action of chlorosulphonic acid upon *o*-chloroanisole, a by-product of this reaction being 3 : 3′-*dichloro*-4 : 4′-*dimethoxydiphenylsulphone.* The latter was prepared by an alternative method which provides proof of its constitution, *viz.*, the chlorination of *pp*′-dimethoxydiphenylsulphone.

2-Aminoanisole-4-sulphonic acid from each of the two sources mentioned above was converted into 2-*acetamidoanisole*-4-*sulphonyl chloride* (I). This substance, however, is made most conveniently by the action of chlorosulphonic acid upon aceto-*o*-anisidide. It is remarkable that it may be prepared thus in good yield (75%) and unaccompanied by isomeric substances, for the nitration of aceto-*o*-anisidide (Ingold and Ingold, J., 1926, 1316) affords a mixture of nitro-compounds in which the 5-nitro-derivative predominates, and the derivative obtained by Orton and King (J., 1911, **99**, 1191) from the chlorination of aceto-*o*-anisidide appears to be the 5-chloro-compound, since its properties accord well with those of authentic 5-chloroaceto-*o*-anisidide (Reverdin and Eckhard, *Ber.*, 1899, **32**, 2625).

2-Acetamidoanisole-4-sulphonyl chloride was converted by the usual methods into a number of thio-derivatives, which call for no special comments and are described in the experimental section. 4 : 4′-*Dimethoxy*-3 : 3′-*diaminodiphenyl disulphide* has m. p. 105° (*acetyl* derivative, m. p. 153°), whereas the isomeric 5 : 5′-dimethoxy-4 : 4′-diaminodiphenyl disulphide (Hodgson and Handley, J., 1928, 626) melts at 88° (*acetyl* derivative, m. p. 136°), this non-identity providing further confirmation of the 4-structure of the derivatives here described.

EXPERIMENTAL.

Reduction of 2-*Nitroanisole*-4-*sulphonic Acid* (compare Gnehm and Knecht, *loc. cit.*).—*o*-Nitroanisole (50 g.) and chlorosulphonic acid (40 g.) were cautiously mixed and after a few minutes the reddish deliquescent mass was dissolved in water (150 c.c.), freed from unchanged nitroanisole by means of ether, and treated with concentrated hydrochloric acid (200 c.c.) and, in portions, granulated tin (120 g.). Reduction was vigorous at first and cooling was necessary. When most of the tin had dissolved, 5*N*-hydrochloric acid (200 c.c.) was added, and the solution heated on the steam-bath for 3—4 hours. The mixture was kept in the ice-chest over-night; the crystalline deposit was then collected and dissolved in water, tin removed as sulphide, and the filtrate concentrated to 300 c.c. and allowed to crystallise. Yield, 25 g. (38%). It is not economical to treat the mother-liquor.

2-Aminoanisole-4-sulphonic acid separates from water (16 parts) in colourless rhombs, decomp. about 300°. 100 Parts of water dissolve 2·56 g. at 22° (Found: N, 6·8; equiv., 203. Calc. for $C_7H_9O_4NS$: N, 6·9%; equiv., 203).

Sulphonation of o-*Anisidine.*—*o*-Anisidine (40 g.) was dissolved in sulphuric acid (80 c.c.), 20% oleum (80 c.c.) added, and the mixture kept at 80° for 10 minutes, cooled, and poured on ice. The acid (56 g.), which gradually separated, was recrystallised from water (600 c.c.; charcoal), 40 g. (61%) of pure sulphonic acid being obtained (Found: N, 6·9%; equiv., 203).

Conversion of the Sulphonic Acid from either Source into 2-*Chloroanisole*-4-*sulphonic Acid.*—(A) *Acid from the reduction of* 2-*nitroanisole*-4-*sulphonic acid.* The acid (20 g.) was dissolved in *N*-sodium hydroxide (100 c.c.), sodium nitrite (7 g.) added, the solution cooled to 0°, and concentrated hydrochloric acid (30 c.c.) run in at such a rate that the temperature did not rise above 5°; the yellow diazo-salt which at first separated, redissolved. The clear diazo-solution was run into a boiling solution of cuprous chloride (16 g.), concentrated hydrochloric acid (75 c.c.), and water (25 c.c.). Addition of saturated brine (450 c.c.) to the cooled solution precipitated sodium 2-chloroanisole-4-sulphonate, which was collected, dissolved in the minimal amount of water (charcoal), and reprecipitated by addition of brine (2 vols.). Yield, 15·6 g. (65%).

The sodium salt was triturated with phosphorus pentachloride (24 g.); the mixture became liquid and after 1 hour it was treated with ice-cold water, and the chloride collected (14 g., m. p. 73—76°). This material, fractionally crystallised from light petroleum, gave a recovery of 12·4 g. in four crops differing only 3° in m. p.

2-*Chloroanisole*-4-*sulphonyl chloride* formed colourless stout prisms, m. p. 81—82° (corr.), from light petroleum (10 parts, b. p. 40—60°) (Found: Cl, 29·45; S, 13·0. $C_7H_6O_3Cl_2S$ requires Cl, 29·4; S, 13·3%). The corresponding *amide*, matted needles from water, had m. p. 130—131° (corr.) (Found: C, 38·1; H, 3·8; N, 6·3. $C_7H_8O_3NClS$ requires C, 37·9; H, 3·7; N, 6·3%).

(B) *Acid from the sulphonation of* o-*anisidine.* This acid (20 g.), treated in the manner described under (A), gave 16 g. (67% of the theoretical yield) of sodium chloroanisolesulphonate, which, on treatment with phosphorus pentachloride (25 g.), afforded 13·5 g. of chloride, m. p. about 77°. This material also was homogeneous, fractionation from light petroleum giving four crops differing only 1° in m. p. The first crop (8·5 g.) had m. p. and mixed m. p. 81°; the amide prepared from it had m. p. and mixed m. p. 130°.

Chlorosulphonation of o-*Chloroanisole.*—*o*-Chloroanisole (5·25 g.) was added carefully to chlorosulphonic acid at 0°, and the mixture heated at 50° for a few minutes, cooled, and poured on ice. The product (6·3 g.) had m. p. 66—72° (not clear); 0·5 g. of the material was undissolved by light petroleum (75 c.c.) and had m. p. 155—157° (uncorr.). The crude chloride which separated (4 g., m. p. 73—76°), after a further recrystallisation, had m. p. 77—80°, not depressed by either of the samples previously described. It was converted into the amide, which, after crystallisation, had m. p. 130° (corr.), not depressed by admixture with an authentic sample.

The high-melting product after two crystallisations from alcohol had m. p. 165—166° (corr.). It was unattacked by boiling 20% caustic soda solution, and was shown to be 3 : 3'-*dichloro*-4 : 4'-*dimethoxydiphenylsulphone* (Found : Cl, 20·3; S, 9·3. $C_{14}H_{12}O_4Cl_2S$ requires Cl, 20·4; S, 9·2%) by the following alternative synthesis.

pp'-Dimethoxydiphenylsulphone [from *pp'*-dihydroxydiphenylsulphone (250 g.), 5*N*-caustic soda (500 c.c.), and methyl sulphate (250 c.c.) at 100°], m. p. 129°, (14 g.) in boiling glacial acetic acid (100 c.c.) was treated for 2 hours with a steady stream of chlorine. The crude product (12·75 g.) precipitated by water, after several crystallisations from alcohol, had m. p. 164—165° (corr.), not depressed by admixture with the material described above.

Chlorosulphonation of Aceto-o-*anisidide.*—Aceto-*o*-anisidide (13 g.) was added slowly to chlorosulphonic acid (30 c.c.), the temperature being kept below 50°; the mixture was kept at 50° for ½ hour, cooled, and poured on ice. The crude product (14 g.) had m. p. 148° (uncorr.). The average yield of several experiments was 75%, and careful fractionation of 240 g. of the crude material failed to show the presence of an isomeride. 2-*Acetamidoanisole*-4-*sulphonyl chloride* (I) separated from benzene (10 parts) in colourless needles, m. p. 152—153° (corr.) (Found : Cl, 13·3. $C_9H_{10}O_4NClS$ requires Cl, 13·4%). The corresponding *amide*, prepared in the usual manner, melted, after recrystallisation from alcohol, at 226° (corr.) (Found : N, 11·3. $C_9H_{12}O_4N_2S$ requires N, 11·5%).

The following alternative method of preparation establishes the constitution of these derivatives. Dried and powdered sodium 2-aminoanisole-4-sulphonate (22·2 g.) was treated with acetic anhydride (15 c.c.); after 1 hour, the gummy product was granulated by treatment with acetone and dried in a vacuum. The crude acetylated salt was triturated with a large excess of phosphorus pentachloride and after 1 hour water was added; the crude chloride (21·2 g.), after two recrystallisations from benzene, had m. p. 152—153° and was identical with the material obtained by chlorosulphonation of aceto-*o*-anisidide.

*4-Thio-derivatives of Aceto-*o*-anisidide.*—*2-Acetamidoanisole-4-sulphinic acid.* The sulphonyl chloride (24 g.) was shaken with sodium sulphite (60 g.) and water (120 g.) until it dissolved, the mixture being kept just alkaline by the occasional addition of 20% caustic soda solution. The *sulphinic acid,* isolated in the usual manner, separated from water in colourless needles, containing $1H_2O$, m. p. 117—119° (corr.; efferv.) (Found: equiv., 246·0. $C_9H_{11}O_4NS,H_2O$ requires equiv., 247·1). The acid gradually decomposes at 100°.

2-Acetamidoanisyl-4-methylsulphone was obtained by heating silver 2-acetamidoanisole-4-sulphinate (8 g.) with an excess of methyl iodide under reflux for 4 hours. The excess of the latter was distilled off, and the residue extracted with boiling water (500 c.c.); the filtered extract on cooling deposited the *sulphone* in shimmering colourless plates (3·42 g.), m. p. 186° (corr.), very sparingly soluble in cold water (Found: N, 5·7. $C_{10}H_{13}O_4NS$ requires N, 5·8%).

2-Acetamidoanisyl 4-disulphoxide was obtained (30% yield) from the sulphinic acid by treatment in aqueous solution with sulphurous and hydriodic acids in the usual manner. It formed colourless short prisms, m. p. 226° (corr.; decomp.), from acetic acid (Found: N, 6·5. $C_{18}H_{20}O_6N_2S_2$ requires N, 6·6%). The disulphoxide was not altered by exposure to light, which accords with the observation of Child and Smiles (J., 1926, 2696) that phototropy is only exhibited by disulphoxides having the sulphur atom para to nitrogen.

Reduction of the sulphonyl chloride with zinc dust and alcoholic hydrochloric acid (compare Zincke and Müller, *Ber.*, 1913, **46**, 784) and oxidation of the final alcoholic solution by means of ferric chloride gave the crude disulphide, m. p. about 145°, which was difficult to purify. It was found preferable to reduce the sulphinic acid with the same reagents; 2-acetamidoanisyl 4-mercaptan was then obtained in 80% crude yield, which after purification by means of caustic soda, and crystallisation from 30% aqueous alcohol, formed pale yellow leaflets, m. p. 121—122°. Acetylation of the mercaptan by means of acetic anhydride and sodium acetate afforded the diacetyl derivative of 4-thiol-2-aminoanisole, m. p. 85—86° in agreement with Gnehm and Knecht (*loc. cit.*).

2-Acetamidoanisyl 4-methyl sulphide, obtained from the mercaptan and methyl sulphate, had m. p. 109—110° (corr.) (Found: S, 15·0. $C_{10}H_{13}O_2NS$ requires S, 15·2%).

Oxidation of the mercaptan in alcoholic solution by means of ferric chloride yielded (in nearly theoretical amount) 2 : 2′-*diacetamidodianisyl* 4 : 4′-*disulphide* (II), rosettes of pale yellow needles, m. p. 153° (corr.), from alcohol (20 parts) (Found: S, 15·9.

$C_{18}H_{20}O_4N_2S_2$ requires S, 16·3%). This substance (11·2 g.) was boiled for ½ hour with hydrochloric acid (75 c.c.) and alcohol (50 c.c.). After cooling, the crystalline deposit of 2 : 2′-*diaminodianisyl* 4 : 4-*disulphide dihydrochloride* was collected (9·4 g.) and recrystallised from 5*N*-hydrochloric acid, from which it formed minute needles, m. p. 268° (corr.; decomp.) (Found: Cl, 18·2. $C_{14}H_{16}O_2N_2S_2$,2HCl requires Cl, 18·6%). This hydrochloride, previously prepared but inadequately described by Gnehm and Knecht (*loc. cit.*), was readily soluble in water, giving an acid solution which on dilution became turbid owing to separation of the free base; it was sparingly soluble in concentrated hydrochloric acid and in alcohol; addition of ferric chloride to an aqueous solution produced a green colour. The free 2 : 2′-*diaminodianisyl* 4 : 4′-*disulphide* (III) formed pale yellow prisms, m. p. 105° (corr.), from alcohol (Found: N, 9·05. $C_{14}H_{16}O_2N_2S_2$ requires N, 9·1%); it was readily re-acetylated and it was found that the crude 2-acetamido-disulphide, m. p. about 145° (see above), could be satisfactorily purified by hydrolysis, crystallisation, and re-acetylation of the amino-disulphide.

All attempts to prepare 4 : 4′-dihydroxy-3 : 3′-diaminodiphenyl disulphide dihydrochloride in a pure state by demethylation of the methoxy-disulphide were unsuccessful.

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