Preparation of Some Bisaminoaryl Sulphones.

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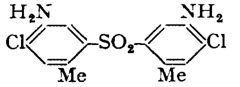
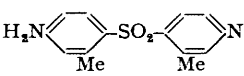
Aceto-*p*- and -*m*-toluidide condense with thionyl chloride in the presence of aluminium chloride to give di-(5-acetamido-4-chloro-2-methylphenyl) and di-(4-acetamido-2-methylphenyl) sulphoxide respectively. The corresponding acetamido-sulphones and amino-sulphones have been prepared.

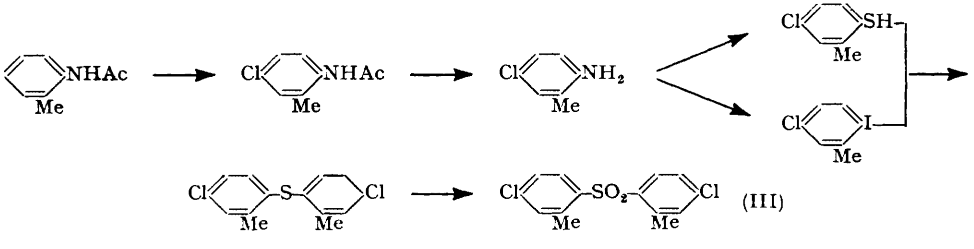
The high antibacterial activity of di-(4-aminophenyl) sulphone prompted us to prepare some analogous amino-sulphones. Reaction of acetanilide with thionyl chloride in the presence of aluminium chloride yields di-(*p*-acetamidophenyl) sulphoxide which on oxidation and subsequent deacetylation gives di-(*p*-aminophenyl) sulphone (Sugaswa and Sakurai, *J. Pharm. Soc. Japan*, 1940, **60**, 22). We investigated a similar reaction with the three isomeric acetotoluidides. Aceto-*o*-toluidide failed to undergo the reaction. Aceto-*p*- and -*m*-toluidide gave sulphoxides which were oxidised to the corresponding sulphones and then hydrolysed to the amino-sulphones (I) and (II) respectively, nuclear chlorination occurring in the former case. The structures (I) and (II) were established as follows: Deamination of the sulphone (I) gave di-(4-chloro-2-methylphenyl) sulphone (III) which was synthesised unequivocally as shown.

(I)





(II)



(III)

Replacement of the amino-groups in the sulphone (II) by chlorine gave the dichloro-sulphone (III) which was also obtained by oxidising the sulphoxide formed on condensation of *m*-chlorotoluene with thionyl chloride. Deamination of (II) gave di-*o*-tolyl sulphone identical with a sample synthesised unequivocally from *o*-thiocresol and *o*-iodotoluene. Purgotti (*Gazzetta*, 1890, **20**, 31) reported the melting point of di-*o*-tolyl sulphone as 134—135° whereas we found it to melt at 104·5—105·5°. Purgotti obtained his compound by the oxidation of the supposed di-*o*-tolyl sulphide boiling at 285°. The authenticity of his sulphide is questionable in view of the fact that di-*o*-tolyl sulphide melts at 64° (cf. Zeiser, *Ber.*, 1895, **28**, 1674; Mauthner, *Ber.*, 1906, **39**, 3595).

EXPERIMENTAL

Thionyl chloride was distilled, first, from quinoline and then from linseed oil; the fraction of b. p. 76—78° was used.

Di-(5-acetamido-4-chloro-2-methylphenyl) Sulphoxide.—Thionyl chloride (59·5 g.) in carbon disulphide (50 c.c.) was added dropwise during 45 min. to a well-stirred mixture of aceto-*p*-toluidide (74·5 g.), finely powdered aluminium chloride (100 g.), and carbon disulphide (500 c.c.) kept at 40—45°. The mixture was then stirred for 4 hr. at 50°; after cooling, the carbon disulphide layer was decanted from the insoluble, viscous sulphoxide–aluminium chloride complex which was decomposed by crushed ice. Next morning the solid was filtered off, agitated with a mixture of acetone (20 c.c.) and ether (100 c.c.), collected, and washed successively with ether and water. The *sulphoxide* (45 g., 44% based on aceto-*p*-toluidide) melted at 208·5—210° (from ethanol) (Found: C, 52·5; H, 4·4; $C_{18}H_{18}O_3N_2Cl_2S$ requires C, 52·3; H, 4·4%).

There was no reaction under the conditions used for aceto-*m*-toluidide.

Di-(5-acetamido-4-chloro-2-methylphenyl) Sulphone.—A hot solution of the above sulphoxide (10 g.) in acetic acid (150 c.c.) was mixed with hydrogen peroxide (30%; 6 c.c.), left overnight, heated on a steam-bath for 1 hr., and diluted with water. The precipitated *sulphone* formed needles (6·2 g., 60%), m. p. 278—280° (decomp.), from acetic acid (Found: C, 50·5; H, 4·3; S, 7·4. $C_{18}H_{18}O_4N_2Cl_2S$ requires C, 50·4; H, 4·2; S, 7·5%).

Di-(5-amino-4-chloro-2-methylphenyl) Sulphone (I).—The foregoing acetamido-sulphone (6 g.) was hydrolysed by refluxing it with sulphuric acid (30 c.c.) and water (60 c.c.) for 45 min. The *amino-sulphone* formed pale yellow needles (4·6 g., 96%), m. p. 181—182°, from ethanol (Found: C, 48·6; H, 4·0; S, 9·3. $C_{14}H_{14}O_2N_2Cl_2S$ requires C, 48·7; H, 4·1; S, 9·3%).

Deamination of Di-(5-amino-4-chloro-2-methylphenyl) Sulphone.—The amino-sulphone (1 g.) in hydrochloric acid (*d* 1·08; 6 c.c.) was tetrazotised with sodium nitrite (0·52 g.) in water (2 c.c.), and the resulting solution was added to hypophosphorous acid (50%; 6 c.c.) at 0°. Next day, the precipitate formed was extracted with benzene, and the extract, after being washed with a 5% solution of sodium hydroxide and then with water, was evaporated to yield a residue which, after crystallisation from ethanol, melted at 135—137° alone or mixed with *di-(4-chloro-2-methylphenyl) sulphone* prepared as below (Found: C, 53·4; H, 3·6. $C_{14}H_{12}O_2Cl_2S$ requires C, 53·3; H, 3·8%).

*4-Chloro-*o*-toluidine* (NH_2 = 1).—It was obtained by the hydrolysis of 4-chloroaceto-*o*-toluidide with hydrochloric acid (cf. Reverdin and Crèpieux, *Ber.*, 1900, **33**, 2497), and had b. p. 140°/38 mm.

*4-Chloro-*o*-thiocresol* (SH = 1).—4-Chloro-*o*-toluidine (28·3 g.) in hydrochloric acid (*d* 1·08; 126 c.c.) was diazotised with sodium nitrite (15 g.) in water (15 c.c.), and the solution was added in a stream, with stirring, to potassium ethyl xanthate (50 g.) in water (50 c.c.) at 40—45°. This temperature was maintained for 1 hr. and the oil, after extraction with ether, washing with sodium hydroxide, and drying ($CaCl_2$), was dissolved in ethanol (200 c.c.), and treated at the b. p. with potassium hydroxide pellets (65 g.). After 8 hours' refluxing, most of the ethanol was removed and the residue was dissolved in the minimum of water, acidified with sulphuric acid, mixed with zinc dust (10 g.), and steam-distilled. After drying ($MgSO_4$), *4-chloro-*o*-thiocresol* (28 g., 88%) distilled at 117°/21 mm., n_D^{32} 1·590 (Found: C, 53·2; H, 4·7. C_7H_7ClS requires C, 53·0; H, 4·4%).

Di-(4-chloro-2-methylphenyl) Sulphide.—To a solution obtained by dissolving sodium (2 g.) in ethanol (40 c.c.) was added 4-chloro-*o*-thiocresol (12 g.), and all the ethanol was removed by distillation. The residue was mixed with copper powder (0·6 g.) and 5-chloro-2-iodotoluene (19·1 g.) (Beilstein and Kuhlberg, *Annalen*, 1870, **156**, 82), heated at 240—245° for 3½ hr., cooled, mixed with ethanol (60 c.c.), and strongly acidified with sulphuric acid (1 : 1). After the addition of zinc dust (2 g.), the mixture was steam-distilled to remove unchanged reactants, and the residue on ether-extraction and drying ($CaCl_2$) gave the *sulphide* (15·5 g., 72%), b. p. 213—215°/17 mm., n_D^{29} 1·6295 (Found: C, 59·3; H, 4·5. $C_{14}H_{12}Cl_2S$ requires C, 59·4; H, 4·2%).

Di-(4-chloro-2-methylphenyl) Sulphone (III).—The foregoing sulphide (5 g.) in hot acetic acid (100 c.c.) was oxidised with 5% potassium permanganate solution (excess). The *sulphone* (5·2 g., 93%) crystallised as needles, m. p. 139—140°, from ethanol or light petroleum (b. p. 140—150°) (Found : C, 53·0; H, 4·0%).

Di-(4-*acetamido*-2-*methylphenyl*) *Sulphoxide*.—With aceto-*m*-toluidide (14·9 g.), aluminium chloride (26·6 g.), carbon disulphide (150 c.c.), and thionyl chloride (6 g. in 10 c.c. of carbon disulphide) the reaction was effected as in the earlier condensation, except that the refluxing was stopped 2 hr. after the addition of thionyl chloride. The *sulphoxide* (14 g., 81%) melted at 209—211° (from acetone–water) (Found : C, 62·7; H, 6·05; S, 9·3. $C_{18}H_{20}O_3N_2S$ requires C, 62·8; H, 5·8; S, 9·3%).

Di-(4-*acetamido*-2-*methylphenyl*) *Sulphone*.—The above sulphoxide (9 g.) in hot acetic acid (90 c.c.) was oxidised with potassium permanganate (5·4 g.) in water (160 c.c.). The *acetamidosulphone* (7 g., 74%) melted at 243—244° (from acetic acid) (Found : C, 59·8; H, 5·5. $C_{18}H_{20}O_4N_2S$ requires C, 60·0; H, 5·6%).

Di-(4-*amino*-2-*methylphenyl*) *Sulphone* (II).—This *compound*, obtained in 91% yield by the hydrolysis of the acetamido-sulphone with hydrochloric acid (1 : 1), crystallised from ethanol as pale yellow needles, m. p. 280° (decomp.) (Found : C, 60·6; H, 5·9; S, 11·2. $C_{14}H_{16}O_2N_2S$ requires C, 60·9; H, 5·8; S, 11·6%).

Deamination. The procedure used for the deamination of (I) was followed. The product after crystallisation from methanol melted at 103—104·5°, alone or mixed with di-*o*-tolyl sulphone prepared as below (Found : C, 68·0; H, 5·8. $C_{14}H_{14}O_2S$ requires C, 68·3; H, 5·7%).

Di-o-*tolyl Sulphone*.—Di-*o*-tolyl sulphide (3 g.), m. p. 64—64·5° (Mauthner, *loc. cit.*), was oxidised in acetic acid (100 c.c.) with 5% potassium permanganate solution. The *sulphone* (3·2 g., 94%) melted at 104·5—105·5° (from methanol) (Found : C, 68·6; H, 5·6; S, 13·3. $C_{14}H_{14}O_2S$ requires S, 13·0%).

Di-(4-*chloro*-2-*methylphenyl*) *Sulphone*.—The tetrazo-solution obtained from the aminosulphone (II) (1 g.) was mixed with a solution of cuprous chloride [prepared from copper sulphate (4 g.) and sodium chloride (1·1 g.)] in hydrochloric acid (4 c.c.), then heated on a water-bath until the evolution of nitrogen ceased, and the precipitate formed was collected, washed with alkali and water, and extracted with boiling light petroleum (b. p. 140—150°). The residue, after evaporation of the solvent and crystallisation from ethanol–water, yielded di-(4-chloro-2-methylphenyl) sulphone (0·4 g.), m. p. 138—139°, undepressed on admixture with the synthetic sample (Found : C, 53·2; H, 4·0%).

Di-(4-*chloro*-2-*methylphenyl*) *Sulphoxide*.—Thionyl chloride (10 g.) was added during 45 min. to *m*-chlorotoluene (10 g.), aluminium chloride (20 g.), and carbon disulphide (100 c.c.); the whole was heated for a further 3 hr. and then poured into ice-water. After removal of the carbon disulphide, the product was steam-distilled to remove unchanged *m*-chlorotoluene and extracted with boiling methanol (150 c.c.). Evaporation of the solvent gave the *sulphoxide* (6·5 g., 57%), m. p. 102—103° (from acetone–water) (Found, after drying at 56° under reduced pressure : C, 53·2; H, 4·6. $C_{14}H_{12}OCl_2S,H_2O$ requires C, 53·0; H, 4·4%).

Oxidation of the sulphoxide with potassium permanganate in acetic acid yielded di-(4-chloro-2-methylphenyl) sulphone in 87% yield.

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