90. *Substances Allied to Benzylamine-*p*-sulphonamide.*

By T. Dewing.

Homologues of di-(*p*-aminophenyl) sulphone have been made incorporating benzylamine groups. These are much less active against *Cl. Welchii* than is benzylamine-*p*-sulphonamide, and furnish additional evidence that the mode of action of this series is different from that of the sulphanilamides.

The recent revival of interest in benzylamine-*p*-sulphonamide, owing to its effectiveness against gas gangrene infections when applied locally, has led to the preparation of a number of compounds of the general type $NR'R''\cdot CH_2\cdot C_6H_4\cdot SO_2R$, many of which show activity against *Cl. Welchii*. The evidence available suggests that the mode of action of this series of drugs is different from that of the sulphanilamide series. Thus the N^1-thiazole and N^1-pyrimidine derivatives of benzylamine-*p*-sulphonamide (Bergeim and Braker, *J. Amer. Chem. Soc.*, 1944, **66**, 1458) were found by Hamré (*Proc. Soc. Exp. Biol. Med.*, 1944, **55**, 110) to be practically inactive and, whilst *p*-aminomethylphenyl methyl sulphone, $NH_2\cdot CH_2\cdot C_6H_4\cdot SO_2\cdot Me$, and *p*-guanylphenyl methyl sulphone, $NH_2\cdot(NH{:})C\cdot C_6H_4\cdot SO_2\cdot Me$, are effective drugs (Evans, Fuller, and Walker, *Lancet*, 1944, II, 523), *p*-aminophenyl methyl sulphone in the sulphanilamide series is inactive (Buttle, Dewing, *et al.*, *Biochem. J.*, 1938, **32**, 1101). Moreover the action of benzylamine-*p*-sulphonamide is not inhibited by *p*-aminobenzoic acid or by *p*-aminomethylbenzoic acid (Goldacre, *Nature*, 1944, **154**, 796).

In view of the higher activity shown by di-(*p*-aminophenyl) sulphone against streptococci compared with sulphanilamide, it was decided to prepare homologues of the former compound. Of these, *di*-(p-*aminomethylphenyl*) *sulphone* is of very feeble activity against *Strep. Pyogenes* and against *Cl. Welchii*, being much inferior to benzylamine-*p*-sulphonamide against the latter organism, but its activity is not inhibited by *p*-aminobenzoic acid or by *p*-aminomethylbenzoic acid. p-*Aminophenyl* p-*aminomethylphenyl sulphone* has no activity against *Cl. Welchii*, but shows good activity against streptococci which is inhibited by *p*-aminobenzoic acid. This compound is therefore a typical member of the sulphanilamide series and the introduction of a *p*-aminomethyl group has had no qualitative effect on its activity. Confirming the results of Goldacre (*loc. cit.*) it was found that *p*-aminomethylbenzoic acid had no inhibitory effect on the action of benzylamine-*p*-sulphonamide, although it had quite a definite inhibitory effect on the action of the sulphanilamides.

Experimental.

p-*Aminomethylbenzoic Acid*, $NH_2 \cdot CH_2 \cdot C_6H_4 \cdot CO_2H$.—This was originally prepared by Gunther (*Ber.*, 1890, **23**, 1060) by a rather lengthy method and more recently a simpler preparation has been described (Albert and Magrath, *J.*, 1944, 678). The following method was used by the author:

p-Tolyl cyanide was readily obtained in excellent yield from *p*-toluidine by the Sandmeyer method using sodium nickel cyanide, and on bromination *p*-bromomethylphenyl cyanide (Bense, *Ber.*, 1894, **27**, 2169) was obtained. This compound was lachrymatory and irritant to the skin. *p*-Bromomethylphenyl cyanide (5 g.) was boiled with concentrated hydrochloric acid (35 ml.) and water (15 ml.) for 30 hours. The material at first became oily and later resolidified. The solid was dissolved in 5% sodium carbonate solution (60 ml.), decolorised with charcoal, and the acid, m. p. 220°, precipitated with hydrochloric acid. Salkind (*Centr.*, 1914, II, 1271) gives m. p. 223° for the acid prepared by direct bromination of *p*-toluic acid. The acid (12·5 g.) was dissolved in concentrated ammonia (200 ml.) and after 48 hours the solution was concentrated under reduced pressure and the product precipitated with acetic acid. After four recrystallisations from water (30 parts), *p*-aminomethylbenzoic acid was obtained as flattened tetrahedra, m. p. 343° (Found: N, 9·20. Calc. for $C_8H_9O_2N$: N, 9·27%).

Di-(p-aminomethylphenyl) Sulphone, $(NH_2 \cdot CH_2 \cdot C_6H_4)_2SO_2$.—(*a*) A suspension of di-(*p*-aminophenyl) sulphone (30 g.) in water (150 ml.) and concentrated hydrochloric acid (100 ml.) was diazotised at 0° with sodium nitrite (17 g.) in water (41 ml.) and added to a solution of sodium cyanide (58 g.) and nickel chloride hexahydrate (56 g.) in water (370 ml.) at 90°. The precipitated solid was collected and extracted with acetone. On evaporation to about 200 ml., di-(*p*-cyanophenyl) sulphone separated as a cream coloured crystalline powder, m. p. 237° after recrystallisation from acetone (Found: N, 10·05; S, 11·8. Calc. for $C_{14}H_8O_2N_2S$: N, 10·45; S, 12·0%). A suspension of the cyanide (1 g.) in alcohol (50 ml.) and concentrated hydrochloric acid (10 ml.) was hydrogenated at 21°/1205 mm. in the presence of palladised charcoal (2 g.) (total absorption, 220 ml. Calc., 225 ml.). After removal of the catalyst and concentration of the filtrate, *di-(p-aminomethylphenyl) sulphone dihydrochloride* was obtained as white needles, sparingly soluble in water, having m. p. *ca.* 340° (decomp.) (Found: N, 7·8; S, 9·6; Cl, 20·0. $C_{14}H_{16}O_2N_2S,2HCl$ requires N, 8·0; S, 9·2; Cl, 20·3%).

(*b*) This method is based on that of Delépine (*Compt. rend.*, 1897, **124**, 292). A solution of di-(*p*-bromomethylphenyl) sulphone (15 g.) in chloroform (30 ml.) was added to a warm solution of hexamine (11 g.) in chloroform (140 ml.). The addition compound began to separate rapidly and after 30 minutes' refluxing it was obtained quantitatively as white crystals, m. p. 142°. This material (10 g.) was refluxed with alcohol (20 ml.) and concentrated hydrochloric acid (10 ml.). At first a clear solution was formed, but crystallisation rapidly took place. After 30 minutes' boiling the alcoholic hydrochloric acid was evaporated and the process was repeated three times. After recrystallisation from water the product was identical with that obtained by method (*a*).

By the addition of sodium hydroxide solution to a warm concentrated aqueous solution of the salt, *di-(p-aminomethylphenyl) sulphone*, was precipitated as an oil which rapidly hardened. After thrice recrystallising it from water (30 parts) it was obtained as white needles, m. p. 114° (Found: N, 9·9; S, 11·5. $C_{14}H_{16}O_2N_2S$ requires N, 10·1; S, 11·6%).

p-Chlorobenzylamine, $C_6H_4Cl \cdot CH_2 \cdot NH_2$.—This compound has been prepared by the action of alcoholic ammonia on *p*-chlorobenzyl chloride (Berlin, *Annalen*, 1869, **151**, 137; Jackson and Field, *Amer. Chem. J.*, 1880, **2**, 92) together with the corresponding secondary and tertiary amines and by hydrolysis of *NN'*-di-(*p*-chlorobenzyl)urea (Curtius, *J. pr. Chem.*, 1914, **89**, 533). These methods are tedious, and the following simple procedure gave good results. By the Sandmeyer method *p*-chloroaniline was converted into *p*-chlorophenyl cyanide which was isolated by steam distillation and was obtained after recrystallisation from alcohol (2 parts) as white crystals, m. p. 95°. The cyanide (5 g.) was dissolved in alcohol (50 ml.) and concentrated hydrochloric acid (6 ml.), and hydrogenated in the presence of palladised charcoal (5 g.) at 20°/1369 mm. (absorption, 880 ml. Calc., 920 ml.). After dilution with water (100 ml.) and filtration the solution was concentrated until the hydrochloride crystallised. It was obtained as flat white needles, m. p. 254° (Jackson and Field found m. p. 239—241°, Curtius, 250°). Treatment of an aqueous solution of the salt with excess of sodium hydroxide followed by extraction with ether gave the corresponding base, and this, by treatment with acetic anhydride, gave *p*-chlorobenzylacetamide, m. p. 109° after recrystallisation from alcohol (2 parts).

p-*Acetamidomethylbenzenesulphinic Acid*, $NHAc \cdot CH_2 \cdot C_6H_4 \cdot SO_2H$.—This was satisfactorily prepared by the method described for *p*-acetamidobenzenesulphinic acid (Bere and Smiles, *J.*, 1924, 2361). Damp *p*-acetamidomethylbenzenesulphonyl chloride (300 g. = 150 g. approx. of dry material) was added to a solution of anhydrous sodium sulphite (300 g.) in water (900 ml.) in three portions, 40% sodium hydroxide solution (total of 170 ml.) being added so as to keep the mixture just alkaline. When solution was complete the crude acid was precipitated with 60% sulphuric acid (200 ml.); after recrystallisation from water (500 ml.) and drying in a vacuum the *compound* was obtained as irregular plates, m. p. 148° (Found: N, 6·8; S, 15·2. $C_9H_{11}O_3NS$ requires N, 6·6; S, 15·0%).

p-*Aminophenyl* p-*Aminomethylphenyl Sulphone*, $NH_2 \cdot CH_2 \cdot C_6H_4 \cdot SO_2 \cdot C_6H_4 \cdot NH_2$.—Attempts to prepare *p*-acetamidophenyl *p*-cyanophenyl sulphone and *p*-nitrophenyl *p*-cyanophenyl sulphone from the corresponding amines were unsuccessful as also were attempts to condense *p*-chlorobenzylamine or *p*-chlorobenzylacetamide with sodium *p*-acetamidobenzenesulphinate. The following method gave good results. To a solution of *p*-acetamidomethylbenzenesulphinic acid (10 g.) and sodium carbonate (2·5 g.) in warm ethylene glycol (100 ml.) was added *p*-chloronitrobenzene (7·4 g.) and the mixture was refluxed for six hours. On cooling, crude p-*nitrophenyl* p-*acetamidomethylphenyl sulphone* separated (5·3 g.); after recrystallising from alcohol (150 ml.) it was obtained as pale cream coloured needles, m. p. 214° (Found: N, 8·6; S, 9·25. $C_{15}H_{14}O_5N_2S$ requires N, 8·3; S, 9·5%). This substance (2·5 g.) was suspended in concentrated hydrochloric acid (50 ml.) and water (30 ml.) and boiled for one hour. The solid rapidly dissolved and then the sparingly soluble *p*-nitrophenyl *p*-aminomethylphenyl sulphone hydrochloride began to separate. On cooling a total yield of 2·4 g., m. p. 256°, was obtained. This material (2·3 g.) was suspended in 10% hydrochloric acid (30 ml.) and hydrogenated in the presence of palladised charcoal (2·0 g.) at 20° and 1388 mm. (total absorption, 305 ml. Calc., 274 ml.). The sparingly soluble product which separated during the reaction was dissolved by heating, and the catalyst was filtered off. On cooling, p-*aminophenyl* p-*aminomethylphenyl sulphone dihydrochloride* was obtained, m. p. 285° (Found: N, 8·7; S, 9·4; Cl, 21·4. $C_{13}H_{14}O_2N_2S,2HCl$ requires N, 8·4; S, 9·6; Cl, 21·7%). The last two steps can be reversed; *i.e.*, reduction can precede hydrolysis. By adding sodium hydroxide to a concentrated aqueous solution of the dihydrochloride and recrystallising the precipitate from water (50 parts) p-*aminophenyl* p-*aminomethylphenyl sulphone* was obtained as white needles, m. p. 159° (Found: N, 10·6; S, 11·9. $C_{13}H_{14}O_2N_2S$ requires N, 10·7; S, 12·2%).

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