64. p-*Sulphonamidobenzylaniline and Related Compounds of Pharmacological Interest.*

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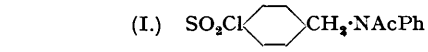
Chlorosulphonation of acetobenzylanilide affords aceto-*p*-chlorosulphonylbenzylanilide and its *m*-isomer in the approximate ratio 4 : 1. A number of compounds of the marfanil type have been prepared by condensing the *p*-sulphonyl chloride with ammonia, methylamine, guanidine, 2-aminopyridine and 2-aminothiazole and removing the acetyl group by hydrolysis.

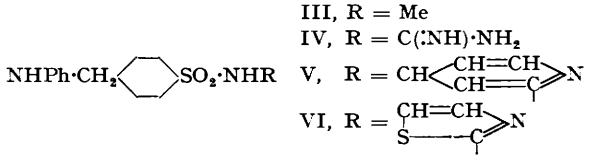
The discovery by Domagk (*Klin. Woch.*, 1942, **21**, 448; *Deutsch. med. Wschr.*, 1943, **69**, 379) that marfanil, which is *p*-sulphonamidobenzylamine hydrochloride (Miller, Sprague, Kissinger, and McBurney, *J. Amer. Chem. Soc.*, 1940, **62**, 2099; Klarer, *Klin. Woch.*, 1941, **20**, 1250), possesses considerable activity against

anaerobes both *in vitro* and *in vivo* has resulted in the investigation of a number of related compounds (Evans, Fuller, and Walker, *Lancet*, 1944, **247**, 523). The present communication records the preparation of a number of sulphonamides derived from *p*-sulphobenzylaniline. Access to compounds of this type could be obtained through aceto-*p*-chlorosulphonylbenzylanilide (I), which should be the main product of the chlorosulphonation of acetobenzylanilide. It is stated (Soc. des Usines Chimiques Rhône-Poulenc, B.P. 483,945) that the product of this reaction is N^4-benzylacetylsulphanilyl chloride (II), since by the action of aqueous ammonia it is converted into N^4-benzylsulphanilamide, m. p. 175°, identical with that obtained by benzylating sulphanilamide or by the reduction of N^4-benzylidenesulphanilamide (B.P. 465,914). Repetition of the



chlorosulphonation as described in the patent resulted in a 43% yield of a *sulphonyl chloride*, m. p. 107°, and an oil which on solution in ether and precipitation with light petroleum deposited an isomeric *sulphonyl chloride*, m. p. 80—83°. Amidation of the sulphonyl chloride of lower m. p. afforded *aceto*-m-*sulphonamidobenzylanilide*, m. p. 145°, which was oxidised by alkaline potassium permanganate to *m*-sulphonamidobenzoic acid. The higher-melting sulphonyl chloride does not suffer hydrolysis during amidation as stated in the patent, but yields a sulphonamide, m. p. 177°, which depresses the melting point of N^4-benzylsulphanilamide and must be aceto-*p*-sulphonamidobenzylanilide, since by successive oxidation with alkaline potassium permanganate and esterification it affords ethyl *p*-sulphonamidobenzoate. Amidation of the liquid mixture of sulphonyl chlorides and separation of the resulting isomeric sulphonamides by fractional crystallisation from methyl alcohol indicated that the chlorosulphonation of aceto-*p*-chlorosulphonylbenzylanilide results in the production of aceto-*p*-sulphonamidobenzylanilide and its *m*-isomer in the ratio 4 : 1, but owing to the ease with which the *m*-chloride is hydrolysed the estimate of the proportion of the *m*-isomeride must be regarded as a conservative one. The yield of the two sulphonyl chlorides was approximately 69% and if isomers sulphonated in the aniline nucleus were produced, they must have suffered hydrolysis when the sulphonation mixture was quenched in ice-water. Blangey, Fierz-David, and Stamm (*Helv. Chim. Acta*, 1942, **25**, 1162) have shown that benzylethylaniline undergoes predominant *m*-substitution in the benzyl nucleus with excess of chlorosulphonic acid and we attribute the formation of a smaller proportion of the *m*-isomeride in the chlorosulphonation of acetobenzylanilide to inhibition of salt formation by the acetyl radical.

Condensation of aceto-*p*-chlorosulphonylbenzylanilide with methylamine, guanidine, 2-aminopyridine and 2-aminothiazole respectively, followed by hydrolysis, afforded p-*sulphonmethylamidobenzylaniline* (III), m. p. 92—93°, p-*sulphonguanylamidobenzylaniline* (IV), m. p. 206°, p-*sulphon*-2′-*pyridylamidobenzylaniline* (V), m. p. 206°, and p *sulphon*-2′-*thiazolylamidobenzylaniline* (VI), m. p. 188—190°.



The activity of these compounds against a number of bacteria has been determined by Mr. C. E. Coulthard, M.P.S., whose results will be reported elsewhere.

Experimental.

Acetochlorosulphonylbenzylanilides.—Acetobenzylanilide (112 c.c.) was slowly added with mechanical stirring, so that the temperature did not exceed 25°, to chlorosulphonic acid (164 c.c.; 5·0 mols.). After being kept overnight, the mixture was maintained at 65° for 2—3 hours, cooled, and poured into ice-water. The sulphonyl chlorides were extracted with benzene, and the washed and dried solution was concentrated, diluted with light petroleum (b. p. 60—80°), and kept at 0° until crystallisation was complete. After washing with light petroleum the solid (69 g.) melted at 85—97° and recrystallisation from light petroleum–benzene afforded *aceto*-p-*chlorosulphonylbenzylanilide*, m. p. 107° (Found : Cl, 11·0. $C_{15}H_{14}O_3NClS$ requires Cl, 11·0%). The liquid portion of the sulphonyl chlorides was dissolved in ether and precipitated with light petroleum, giving first a precipitate (9 g.), m. p. *ca.* 75°, and then a further yield of the *p*-sulphonyl chloride. Recrystallisation from xylene–light petroleum afforded *aceto*-m-*chlorosulphonylbenzylanilide*, m. p. 80—83° (Found : Cl, 11·1%).

Sulphonamidobenzylanilides.—*Aceto*-p-*sulphonamidobenzylanilide*, m. p. 178° (Found : N, 9·0. $C_{15}H_{16}O_3N_2S$ requires N, 9·2%), and *aceto*-m-*sulphonamidobenzylanilide*, m. p. 145° (Found : N, 9·1%), were obtained in 96% yield by shaking the afore-mentioned sulphonyl chlorides (15 g.) with 19% aqueous ammonia (162 c.c.; 36 mols.) for 50 minutes and crystallising the products from alcohol. Admixture of the *p*-isomer with N^4-benzylsulphanilamide, m. p. 178—179° (Found : N, 10·7. $C_{13}H_{14}O_2N_2S$ requires N, 10·7%), prepared by the benzylation of sulphanilamide (B.P. 465,914), depressed the m. p. to 145—155°. Hydrolysis of aceto-*p*-sulphonamidobenzylanilide by heating on the steam-bath for 24 hours with 2·5N-sodium hydroxide (8·0 mols.) afforded a quantitative yield of p-*sulphonamidobenzylaniline*, m. p. 144—145° (Found : C, 60·0; H, 5·6. $C_{13}H_{14}O_2N_2S$ requires C, 59·2; H, 5·3%). Aceto-*p*-sulphonamidobenzylanilide (5 g.) was dissolved in 5N-sodium hydroxide and stirred mechanically during the slow addition of a solution of potassium permanganate (7·5 g., equivalent to 4·3 atoms of oxygen) in water (150 c.c.). After being stirred for 24 hours, the mixture was heated on the steam-bath for an hour and afforded *p*-sulphonamidobenzoic acid (2·6 g.), m. p. 280° (decomp.) (Found : N, 7·3. Calc. for $C_7H_7O_4NS$: N, 7·0%), which was esterified by solution in 10% ethyl-alcoholic hydrogen chloride. The ethyl *p*-sulphonamidobenzoate so obtained has m. p. 112°, undepressed on admixture with an authentic specimen (Remsen, *Annalen*, 1875, **178**, 300). Oxidation of aceto-*m*-sulphonamidobenzylanilide

similarly afforded *m*-sulphonamidobenzoic acid (Found: N, 7·1%), m. p. and mixed m. p. 248—249°, which was converted into its ethyl ester, m. p. and mixed m. p. 129°. *Ethyl* m-*sulphonamidobenzoate*, prepared by refluxing *m*-sulphonamidobenzoic acid (10 g.), ethyl alcohol (25 c.c.), and concentrated sulphuric acid (2 c.c.) for 80 minutes, separated from 50% aqueous alcohol in flat needles, m. p. 129° (Found: N, 6·25. $C_9H_{11}O_4NS$ requires N, 6·1%). Yield, 10·2 g. (89%).

p-*Sulphonmethylamidobenzylaniline*.—When aceto-*p*-chlorosulphonylbenzylanilide (20 g.) was shaken for ½ hr. with excess of 20% aqueous methylamine, *aceto*-p-*sulphonmethylamidobenzylanilide*, m. p. 138—139° (Found: N, 8·8. $C_{16}H_{18}O_3N_2S$ requires N, 8·8%), was obtained in 81·5% yield and hydrolysis by heating on the steam-bath with 2·5N-sodium hydroxide gave p-*sulphonmethylamidobenzylaniline*, m. p. 92—93° (Found: N, 10·35. $C_{14}H_{16}O_2N_2S$ requires N, 10·15%).

p-*Sulphonguanylamidobenzylaniline*.—A solution of aceto-*p*-chlorosulphonylbenzylanilide (32 g.) in acetone (80 c.c.) was added below 10° to an alkaline solution of guanidine prepared from guanidine nitrate (13 g.; 1·1 mols.), sodium hydroxide (10 g.; 2·5 mols.), water (20 c.c.), and acetone (40 c.c.). After being stirred for 2 hours at room temperature, the solution was made alkaline to litmus, and the solvent removed by distillation. The residue was diluted with water, made alkaline to brilliant-yellow and filtered (32 g. or 93%). Recrystallisation from 5N-acetic acid afforded *aceto*-p-*sulphonguanylamidobenzylanilide* as a white powder, m. p. 250—257° (decomp.) (Found: N, 15·9. $C_{16}H_{18}O_3N_4S$ requires N, 16·2%). Hydrolysis was effected by boiling the acetyl derivative (10 g.) with 6N-hydrochloric acid (20 c.c.) for 10 minutes, diluting the solution with water, removing unchanged material, and treating the filtrate with alkali. The recovered material was hydrolysed in the same way and the operations repeated until the whole of the acetyl derivative had been hydrolysed. Recrystallisation from aqueous alcohol afforded 4·3 g. (46%) of a *monohydrate*, m. p. 186—187° (Found: H_2O, 5·5. $C_{14}H_{18}O_2N_4S,H_2O$ requires H_2O, 5·6%), which on drying at 100° gave anhydrous p-*sulphonguanylamidobenzylaniline*, m. p. 206° (Found: C, 55·0; H, 5·3. $C_{14}H_{16}O_2N_4S$ requires C, 55·3; H, 5·3%).

p-*Sulphon-2′-pyridylamidobenzylaniline*.—Aceto-*p*-chlorosulphonylbenzylanilide (15 g.) was added in portions to a solution of 2-aminopyridine (6 g.; 1·4 mols.) in dry pyridine (40 c.c.; 10·7 mols.), and after keeping for 12 hours, the solution was diluted with water (400 c.c.). The solid was collected, washed with N-acetic acid and recrystallised from methyl alcohol. *Aceto*-p-*sulphon-2′-pyridylamidobenzylanilide* separated in white plates, m. p. 184—185° (Found: C, 63·3; H, 5·1; N, 11·0. $C_{20}H_{19}O_3N_3S$ requires C, 63·0; H, 5·0; N, 11·0%). Yield, 13·5 g. or 76·5%. The acetyl derivative (12 g.) was hydrolysed by heating on the steam-bath for 24 hours with 2·5N-sodium hydroxide (125 c.c.) and the solid, which separated after dilution with water and addition of ammonium chloride, was crystallised from aqueous dioxan (charcoal), yielding p-*sulphon-2′-pyridylamidobenzylaniline* (8·1 g.), m. p. 206° (Found: N, 12·3. $C_{18}H_{17}O_2N_3S$ required N, 12·4%).

p-*Sulphon-2′-thiazolylamidobenzylaniline*.—Aceto-*p*-chlorosulphonylbenzylanilide (16 g.), 2-aminothiazole (7 g.; 1·4 mols.), and the minimum quantity of dry pyridine, when kept for 24 hours and poured into water, afforded a buff solid, which, when washed with water and crystallised from alcohol, gave white plates (13 g. or 68%) of *aceto*-p-*sulphon-2′-thiazolylamidobenzylanilide*, m. p. 197—198° (Found: N, 10·95. $C_{18}H_{17}O_3N_3S_2$ requires N, 10·85%). The acetyl derivative (14·8 g.) was hydrolysed by heating with 2·5N-sodium hydroxide for 24 hours at 100° and precipitating with ammonium chloride. The product (13·8 g.) was recrystallised from aqueous dioxan, giving colourless needles (9·75 g. or 74%) of p-*sulphon-2′-thiazolylamidobenzylaniline*, m. p. 188—190° (Found: C, 55·5; H, 4·35. $C_{16}H_{15}O_2N_3S_2$ requires C, 55·7; H, 4·35%).

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