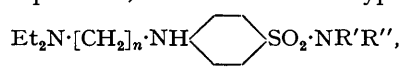
129. *Some* N^4-*Diethylaminoalkyl*-N^1-*dialkylsulphanilamides* * *and Related Compounds.*

By JAMES WALKER.

Sulphanilamide derivatives have a marked action on *Pl. knowlesi* infection of monkeys, a doubtful action on human malaria and no action on avian malaria. Since plasmochin and atebrin were developed through bird malaria tests, a number of sulphanilamide derivatives with basic side chains, resembling those of plasmochin and rhodoquine, were prepared in the hope that activity against bird malarial infection might be developed; the products, which were of the type



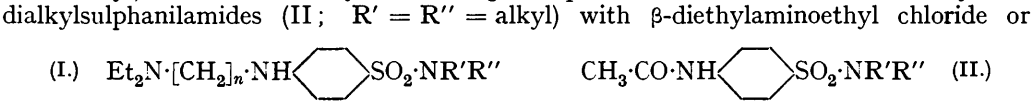
were inactive in *Pl. relictum* infection of canaries.

THE dramatic success which attended the introduction of the sulphonamide drugs into chemotherapy prompted trials of these agents in many infections other than those due to hæmolytic streptococci against which the compounds were, in the first instance, applied

* The nomenclature of substituted sulphanilamides is that of Crossley, Northey, and Hultquist (*J. Amer. Chem. Soc.*, 1938, **60**, 2217), which is receiving wide adoption in the American sulphanilamide literature. " In sulphanilamide the sulphonamide group, being the principal functional group, occupies the 1-position in the ring. The nitrogens are differentiated by superscripts: N^1 referring to substituents on the amide nitrogen and N^4 to substituents on the amino-nitrogen."

by Domagk (*Deut. med. Woch.*, 1935, **61**, 250). In 1937, encouraging clinical reports raised hopes that members of the sulphonamide group might be effective in human malaria but subsequent study has tempered the early promise with caution and, from a growing malaria-sulphonamide literature, it now appears that, of all forms of malaria, only *Pl. knowlesi* infection of monkeys is consistently controlled by sulphanilamide and its hitherto applied derivatives (cf. especially, Coggeshall, *J. Exp. Med.*, 1940, **71**, 13). Antimalarial drugs such as plasmochin and atebrin were developed with the aid of tests on bird infections (Roehl, *Arch. Schiffs- u. Tropen-Hygiene*, 1926, **30**, Beih. 3, 11; Kikuth, *Deut. med. Woch.*, 1932, **58**, 530) and these drugs are also active to some extent in monkey malaria. On the other hand, drugs of the sulphanilamide class have not so far been found to be active in bird malaria and the object of the present investigation was to see whether the antimalarial action of sulphanilamide, as shown by its effect on *Pl. knowlesi* in monkeys, could be further developed by the incorporation of basic side chains reminiscent of those of plasmochin and rhodoquine (Fourneau 710) to give drugs effective in bird malaria and thus facilitate further search for new human antimalarials.

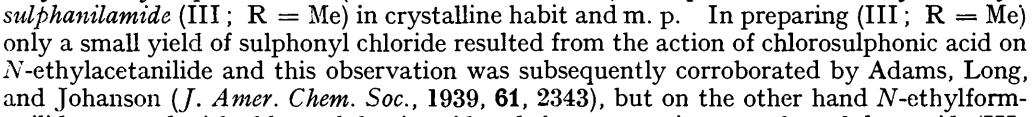
Such side chains could be attached either to the N^4- or the N^1-nitrogen atom or to the nucleus of sulphanilamide and the type selected was (I) in which the basic side chain is attached to the N^4-nitrogen atom. Access to compounds of the desired type (I; R′ = R″ = alkyl) was obtained by condensing the potassium derivatives of N^4-acetyl-N^1-dialkylsulphanilamides (II; R′ = R″ = alkyl) with β-diethylaminoethyl chloride or



(I.) (II.)

γ-diethylaminopropyl chloride in xylene, followed by acid hydrolysis to remove the acetyl groups. In this way N⁴-β-*diethylaminoethyl*-N¹-*dimethylsulphanilamide* (I; $n = 2$, R′ = R″ = Me), -N¹-*diethylsulphanilamide* (I; $n = 2$, R′ = R″ = Et), -N¹-*pentamethylenesulphanilamide* (I; $n = 2$, R′R″ = C_5H_{10}), and N⁴-*γ-diethylaminopropyl*-N¹-*diethylsulphanilamide* (I; $n = 3$, R′ = R″ = Et) were prepared from the appropriate starting materials and isolated as the crystalline *hydrochlorides*; the last-named compound, in which the basic centres were separated by three methylene groups, gave a stable *dihydrochloride* under conditions where the other three analogues ($n = 2$) formed only *monohydrochlorides*. The compound (I; $n = 2$, R′ = R″ = Me) was also obtained in small yield by heating β-diethylaminoethyl chloride hydrochloride and N^1-dimethylsulphanilamide together without a solvent.

As the alkylation of N^4-acetylsulphanilamide (II; R′ = R″ = H) had not been reported at the time these investigations were undertaken, it was thought desirable to see whether alkylation would take place at N¹ or at N⁴. The alkylation of arylsulphonamides is, of course, a familiar process and proceeds with greater ease than that of acetanilide, but in the particular case of (II; R′ = R″ = H) it might have been anticipated that the electron-attracting group para to the acetamido-group might have reinforced the effect of the acetyl group on the imino-hydrogen atom and assisted towards preferential alkylation on N⁴. This was not the case, as ethylation gave a product consisting essentially of N⁴-*acetyl*-N¹-*ethylsulphanilamide* (II; R′ = Et, R″ = H) and quite unlike N⁴-*acetyl*-N⁴-*ethylsulphanilamide* (III; R = Me) in crystalline habit and m. p. In preparing (III; R = Me) only a small yield of sulphonyl chloride resulted from the action of chlorosulphonic acid on *N*-ethylacetanilide and this observation was subsequently corroborated by Adams, Long, and Johanson (*J. Amer. Chem. Soc.*, 1939, **61**, 2343), but on the other hand *N*-ethylformanilide, treated with chlorosulphonic acid and then ammonia, gave the *sulphonamide* (III; R = H) in an overall yield of 64%.



(III.) (IV.) (V.)

A probable route to compounds of type (I) appeared to be by the introduction of the sulphonamide group into *N*-diethylaminoalkylanilides, but neither *N*-β-diethylaminoethyl-

formanilide nor *N*-β-diethylaminoethylacetanilide underwent smooth sulphonation with chlorosulphonic acid and this route to compounds of the desired type appeared to be barred. Similarly N-*γ-phthalimidopropylformanilide* gave no sulphonyl chloride on treatment with chlorosulphonic acid, but from the water-soluble portion of the reaction mixture a sparingly soluble substance was obtained having the composition and anticipated properties of *γ*-(o-*carboxybenzamido*)*propylaminobenzene*-p(?)-*sulphonic acid* (IV); it slowly separated from the strongly acid aqueous medium and obviously resulted from a primary product of the reaction, probably *N*-*γ*-phthalimidopropylformanilide-*p*-sulphonic acid, by hydrolysis.

Tests for antimalarial activity were kindly supervised by Prof. D. Keilin, F.R.S.; the four compounds of type (I), sulphanilamide, sulphapyridine (M. and B. 693), N^4-*formyl*-N^4-*ethylsulphanilamide* (III; R = H), N^4-*ethylsulphanilamide* and 2-*aminonaphthalene*-6-*sulphonamide* (V) had no influence on the relapse rates in canaries infected with *Pl. relictum*. Drosdov and Stavrovskaya (*Compt. rend. Acad. Sci. U.R.S.S.*, 1939, **23**, 61) state without details that they have prepared several compounds analogous to (I) and that these also were inactive in bird malaria. Compound (V) was kindly tested by Dr. L. Colebrook for protective action in mice infected with hæmolytic streptococci with negative results.

Experimental.

N^4-*Acetyl*-N^1-*dimethylsulphanilamide* (II; R′ = R″ = Me).—Acetylsulphanilyl chloride (23 g.; 1 mol.) (Stewart, J., 1922, **121**, 2558; "Organic Syntheses," **5**, 3) in a mixture (200 c.c.) of equal parts of acetone and ether was treated with a chilled solution of dimethylamine (10 g.; 2 mols.) in ether (50 c.c.). There was a vigorous reaction and after a few minutes no basic odour was perceptible. The solvent was removed under reduced pressure at 60° and the solid residue was recrystallised from aqueous alcohol (yield, 22·9 g.; m. p. 102—103°). Colourless rhombs were obtained from 30% aqueous ethyl alcohol, m. p. after drying over calcium chloride in a vacuum, 106—107°; this material was obviously solvated, because drying in a vacuum at 100° caused the m. p. to rise to 145—146°. Recrystallisation from aqueous methyl alcohol gave thin hexagonal plates of the non-solvated compound, m. p. 145—146° (Found: C, 49·5; H, 6·1. Calc. for $C_{10}H_{14}O_3N_2S$: C, 49·6; H, 5·8%). Ganapati (*J. Indian Chem. Soc.*, 1938, **15**, 525) records m. p. 143° and Sakai and Yamamoto (*J. Pharm. Soc. Japan*, 1938, **58**, 683; *Chem. Abst.*, 1940, **34**, 86) found m. p. 103—130° for a product obtained by the methylation of N^4-acetylsulphanilamide (II; R′ = R″ = H) with methyl sulphate.

N^1-*Dimethylsulphanilamide*.—The acetyl derivative (4·65 g.) was refluxed for ½ hour with 16% hydrochloric acid (30 c.c.), and the crude product (3·6 g.) isolated by neutralisation with sodium bicarbonate. Recrystallisation from water afforded small colourless cubes with truncated corners, m. p. 169—170° (Found: N, 13·6; S, 16·1. Calc. for $C_8H_{12}O_2N_2S$: N, 14·0; S, 16·0%). F.P. 816,988 and Ganapati (*loc. cit.*) record m. p. 168° and 172° respectively.

N^4-β-*Diethylaminoethyl*-N^4-*acetyl*-N^1-*dimethylsulphanilamide*.—N^4-Acetyl-N^1-dimethylsulphanilamide (II; R′ = R″ = Me) (12·1 g.), partly dissolved and partly suspended in xylene (100 c.c.), was added to powdered potassium (1·95 g.) under xylene (50 c.c.) and the mixture was heated for 2 hours on the water-bath and then at 140—150° (oil-bath) until all the potassium had reacted (3—4 hours). The amber-coloured potassium derivative was a viscous gum when hot and a brittle resin when cold and appeared to be insoluble in xylene; these disadvantageous physical properties were shared by the analogous potassium derivatives to be described later and, by precluding intimate contact with the basic halides, were responsible for variations in the yields of condensation products obtained. When cold, the potassium derivative was broken up and treated with β-diethylaminoethyl chloride (12·8 g.; excess) (Gough and King, J., 1928, 2437). The mixture was refluxed for 5 hours and darkened considerably towards the end of the operation. The cooled reaction mixture was treated with water and benzene and filtered from traces of tarry material. The separated benzene–xylene solution was washed twice with dilute hydrochloric acid (*ca.* 2N), once with water, and evaporated, yielding impure unchanged acetyldimethylsulphanilamide (1 g.). The acid washings were basified with sodium hydroxide solution, and the precipitated oil extracted with benzene, which, dried and evaporated, yielded a clear reddish-brown viscous syrup (12·7 g.) showing no tendency towards crystallisation. On fractional distillation in a vacuum there were obtained: (i) a fairly mobile, golden-yellow oil (1·53 g.), b. p. over a range but mainly *ca.* 195°/0·05 mm.; (ii) a golden-yellow viscous *syrup* (10·23 g.) distilling fairly steadily at 210°/0·05 mm. (Found: C, 57·1; H, 8·1; N, 12·0; S, 9·8. $C_{16}H_{27}O_3N_3S$ requires C, 56·3; H, 7·9; N, 12·3; S, 9·4%). The distilled product crystallised in plates on standing, but a satisfactory means of recrystallisation was not found.

N^4-β-*Diethylaminoethyl*-N^1-*dimethylsulphanilamide* (I; $n = 2$, $R' = R'' = Me$).—(A) The above acetyl derivative (8·17 g.) was refluxed for 70 minutes with 16% hydrochloric acid (50 c.c.) and the cooled solution was then diluted with a little water and rendered strongly alkaline with sodium hydroxide solution. The precipitated oil was extracted with benzene and recovered as a light brown, viscous syrup (6·3 g.) distilling as a golden-yellow viscous *syrup* (5·9 g.) at approximately 195°/0·08 mm. (Found: C, 56·5; H, 8·5; N, 13·8; S, 10·5. $C_{14}H_{25}O_2N_3S$ requires C, 56·2; H, 8·4; N, 14·0; S, 10·7%).

The *hydrochloride* was quantitatively precipitated from a benzene solution of the base with dry hydrogen chloride as a greenish-brown gelatinous mass which rapidly crystallised. Recrystallisation from absolute alcohol afforded small radiating clusters of prisms, m. p. 159—160° (Found: C, 50·2; H, 7·7; N, 12·8; S, 9·8; Cl, 10·4. $C_{14}H_{25}O_2N_3S$,HCl requires C, 50·1; H, 7·8; N, 12·5; S, 9·5; Cl, 10·6%).

(B) The compound was obtained in small yield when N^1-dimethylsulphanilamide (1 g.) was heated at 145—150° for 5 hours with β-diethylaminoethyl chloride hydrochloride (0·86 g.). The reaction mixture was worked up for strongly basic material and the resulting brown gum (0·14 g.) was converted into the hydrochloride as in (A) above. Recrystallisation yielded a product (50 mg.), m. p. 153—154°, raised to 155—156° by one further recrystallisation and not depressed on admixture with the authentic substance prepared in (A).

N^4-*Acetyl*-N^1-*pentamethylenesulphanilamide* (II; $R'R'' = C_5H_{10}$).—Acetylsulphanilyl chloride (23·4 g.; 1 mol.) in acetone (300 c.c.) was treated with a solution of piperidine (20 c.c.; 2 mols.) in acetone (50 c.c.); a vigorous exothermic reaction took place. After a few hours (room temperature) water (*ca.* 300 c.c.) was added, and the acetone distilled off under reduced pressure. The heavy oil left behind with the water rapidly solidified. It (27·6 g.) was collected and recrystallised from 60% aqueous alcohol, forming colourless leaflets, m. p. 149—150° (Found: N, 9·3; S, 11·2. Calc. for $C_{13}H_{18}O_3N_2S$: N, 9·9; S, 11·3%). Goldyrev and Postovskiĭ (*J. Appl. Chem. Russia*, 1938, **11**, 316; *Chem. Abst.*, 1938, **32**, 5800) record m. p. 156°.

N^4-β-*Diethylaminoethyl*-N^1-*pentamethylenesulphanilamide* (I; $n = 2$, $R'R'' = C_5H_{10}$) *Hydrochloride.*—N^4-Acetyl-N^1-pentamethylenesulphanilamide (15·5 g.) was converted into the potassium derivative with powdered potassium (2·14 g.) in xylene similarly to the example already given. β-Diethylaminoethyl chloride (10 g.; excess) was added to the mixture, which was then refluxed for 2 hours (bath 150°) until the solution began to darken appreciably. The mixture was worked up as in the previous example, and the product separated into neutral (6 g.; unchanged starting material) and basic (13·8 g.) portions. The crude reddish-brown viscous basic syrup (N^4-diethylaminoethyl-N^4-acetyl-N^1-pentamethylenesulphanilamide) was at once hydrolysed with 16% hydrochloric acid (80 c.c.) under reflux for 80 minutes, and the free base (10·75 g.) recovered by addition of sodium hydroxide solution and extraction with benzene. The *hydrochloride* was quantitatively precipitated from a benzene solution of the base (10·2 g.) as a gelatinous mass which crystallised on standing. It was much more soluble than the dimethyl analogue described above and successive crops (total, 5·2 g.) were obtained from alcohol by concentration and cooling in the ice-chest. Recrystallisation from absolute alcohol afforded clusters of colourless radiating prisms, m. p. 201—203° (Found: C, 54·8; H, 7·7; N, 11·1; S, 7·9; Cl, 9·3. $C_{17}H_{29}O_2N_3S$,HCl requires C, 54·3; H, 8·0; N, 11·2; S, 8·5; Cl, 9·5%).

N^4-β-*Diethylaminoethyl*-N^1-*diethylsulphanilamide* (I; $n = 2$, $R' = R'' = Et$) *Hydrochloride.*—N^4-Acetyl-N^1-diethylsulphanilamide monohydrate (11 g.) (Gray, Buttle, and Stephenson, *Biochem. J.*, 1937, **31**, 727) was heated in a vacuum at 100° for ¾ hour to drive off the water of crystallisation. The resulting gum was emulsified with warm xylene (*ca.* 100 c.c.) and added to powdered potassium (1·49 g.) under xylene and after 4 hours' refluxing the mixture was cooled, and the resinous insoluble potassium derivative broken up. β-Diethylaminoethyl chloride (7·8 g.; excess) was added to the mixture, which was again refluxed for 4½ hours, darkening somewhat towards the end. As in the previous cases, the product was separated into crude neutral unchanged starting material (1·97 g.) and crude basic N^4-diethylaminoethyl-N^4-acetyl-N^1-diethylsulphanilamide (10·65 g.) in the form of a reddish-brown syrup. The crude acetyl derivative was at once hydrolysed with 16% hydrochloric acid (80 c.c.) by refluxing for an hour and basic material (8·6 g.) was recovered in the usual way. At this stage the hydrochloride could not be obtained in a crystalline condition until it was noticed that, though the basic material gave a clear solution with the calculated volume (1 equiv.) of N-hydrochloric acid, the solution was strongly acid in reaction and dilution with water produced a turbidity indicating contamination with a weak base. The entire basic material was dissolved in ether and fractionally extracted with N/10-sulphuric acid; this was effective in eliminating the weak basic impurity,

which was retained in the ether. The strong base was isolated (5·23 g.) from the acid washings and converted into the *hydrochloride*, which separated from alcohol–ether in colourless leaflets, m. p. 138—139° (Found: C, 52·8; H, 8·4; N, 11·3; S, 8·5; Cl, 9·9. $C_{16}H_{29}O_2N_3S$,HCl requires C, 52·8; H, 8·3; N, 11·6; S, 8·8; Cl, 9·8%). The weakly basic impurity (1·2 g.) recovered from the ether was recrystallised from 40% methyl alcohol; it had m. p. 104° alone and in admixture with authentic N^1-diethylsulphanilamide (Gray *et al.*, *loc. cit.*, record m. p. 105°) and obviously resulted from the starting material by deacetylation prior to the separation of the reaction mixture into neutral and basic portions.

N^4-*γ-Diethylaminopropyl*-N^1-*diethylsulphanilamide* (I; $n = 3$, $R' = R'' = Et$) *Dihydrochloride*.—γ-Diethylaminopropyl chloride was prepared from the alcohol following Gough and King's (*loc. cit.*) conditions rather than those of Magidson and Strukow (*Arch. Pharm.*, 1933, **271**, 572). The hydrochloride could be recrystallised from acetone, but this was unsatisfactory on account of the very soluble and hygroscopic nature of the salt and the free base was purified by distillation. Acetyldiethylsulphanilamide monohydrate (14·7 g.) was dehydrated as before and converted into the potassium derivative in the usual way. After the addition of γ-diethylaminopropyl chloride (10·8 g.; excess) to the xylene suspension of the potassium derivative the mixture was refluxed (bath, 160°) for 6 hours; the reaction mixture remained clear throughout and the darkening which took place in the experiments with diethylaminoethyl chloride was not observed in this case. The reaction mixture was worked up in the usual way, yielding neutral unchanged starting material (7 g.) and a rather viscous, brown basic gum (9·1 g.), which was immediately hydrolysed with 16% hydrochloric acid (70 c.c.) by refluxing for 70 minutes. The deacetylated base was isolated and converted into the *dihydrochloride*, which separated from absolute alcohol in clusters of fine colourless prisms, m. p. 180—181° (Found: C, 49·3; H, 8·1; N, 9·9; S, 7·5; Cl, 16·7. $C_{17}H_{31}O_2N_3S$,2HCl requires C, 49·3; H, 8·0; N, 10·1; S, 7·7; Cl, 17·1%).

N^4-*Acetyl*-N^4-*ethylsulphanilamide* (III; R = Me).—*N*-Ethylacetanilide (27 g.) was treated with chlorosulphonic acid (55 c.c.) at 65—70° for 2¼ hours and the cooled reaction mixture was poured into ice-water in the usual way. The bulk of the precipitated sulphonyl chloride was much less than anticipated and several months after this observation was made Adams *et al.* (*loc. cit.*) stated that the yield of sulphonyl chloride obtained in this particular case is only of the order of 15—20%. The damp sulphonyl chloride was at once shaken with 20% aqueous ammonia (40 c.c.); the resulting *sulphonamide* (III; R = Me) separated from water in stout colourless prisms (2·7 g.), m. p. 126—127° with frothing. This m. p. was not raised on recrystallisation and water of crystallisation appeared to be lost at *ca.* 102° (Found: N, 10·8; S, 12·3; loss at 120°/16 mm., 6·9. $C_{10}H_{14}O_3N_2S,H_2O$ requires N, 10·8; S, 12·3; $1H_2O$, 6·9%).

N^4-*Formyl*-N^4-*ethylsulphanilamide* (III; R = H).—In strong contrast with the preceding experiment a good yield of the sulphonyl chloride was obtained from the formanilide derivative. *N*-Ethylformanilide (15 g.) (Pictet and Crépieux, *Ber.*, 1888, **21**, 1107) was added dropwise in the cold to chlorosulphonic acid (33 c.c.) and the clear, almost colourless solution was heated to 70—75° and kept at that temperature for 4 hours. The sulphonyl chloride was recovered in the usual way and treated while still moist with 16% aqueous ammonia (60 c.c.). After a short induction period an exothermic reaction took place. After 2 hours at room temperature the *solid* was collected, washed with water, and dried (yield, 16 g.; m. p. 187—188°). Recrystallisation from ethyl alcohol afforded colourless prisms, m. p. 188—189° (Found: C, 47·4; H, 5·0; N, 12·4; S, 14·5. $C_9H_{12}O_3N_2S$ requires C, 47·4; H, 5·2; N, 12·3; S, 14·0%).

N^4-*Ethylsulphanilamide*.—Hydrolysis of the formyl derivative (9 g.) with 16% hydrochloric acid (50 c.c.) under reflux for ¾ hour, followed by neutralisation with sodium bicarbonate, yielded a colourless *solid* (7·4 g.), which separated from aqueous alcohol in small stout prisms, m. p. 134—135·5° (Found: N, 13·9; S, 16·2. $C_8H_{12}O_2N_2S$ requires N, 14·0; S, 16·0%).

N^4-*Acetyl*-N^1-*ethylsulphanilamide* (II; $R' = H$, $R'' = Et$) was obtained in almost quantitative yield by treating an acetone solution of acetylsulphanilyl chloride with an ethereal solution of ethylamine (2 mols.). The compound separated from water in fine plates, m. p. 153—155° (Found: N, 11·6; S, 13·2. $C_{10}H_{14}O_3N_2S$ requires N, 11·5; S, 13·2%).

Ethylation of N^4-*Acetylsulphanilamide* (II; $R' = R'' = H$).—N^4-Acetylsulphanilamide (5·3 g.) was added to 95% alcohol (40 c.c.) containing potassium hydroxide (1·4 g.). Heat was evolved and 50% alcohol (20 c.c.) was added to assist in dissolving the rather sparingly soluble potassium derivative. An excess of ethyl iodide (10 c.c.) was added, and the mixture refluxed for 2¼ hours. The solution was then neutral to litmus and was evaporated to small bulk and treated with water. The precipitated oil (4·9 g.) crystallised rapidly and it was isolated and dried in the usual way; the substance softened at 135°, collapsed at 138°, and only cleared

completely at *ca.* 195°. Recrystallisation from water afforded shining white plates, m. p. 140—141°, raised to 141—143° but no further by further recrystallisations; mixed m. p. with N^4-acetyl-N^1-ethylsulphanilamide, 143—149°; mixed m. p. with N^4-acetyl-N^4-ethylsulphanilamide, 107—117°; mixed m. p. with N^4-acetylsulphanilamide (m. p. 219°), 138—195° (Found: C, 49·6; H, 6·0. $C_{10}H_{14}O_3N_2S$ requires C, 49·6; H, 5·8%).

N-β-*Diethylaminoethylformanilide.*—Formanilide (12·1 g.; 1 mol.) was converted into the sodio-derivative by 3 hours' refluxing on the water-bath with powdered sodium (2·3 g.; 1 at.) in benzene (200 c.c.). To the cooled solution β-diethylaminoethyl chloride (13·5 g.; 1 mol.) was added, and the mixture left overnight at room temperature and then refluxed for 5 hours on the water-bath. After the addition of water to the mixture, the benzene layer was separated, washed thrice with 2N-hydrochloric acid, dried, and evaporated, yielding a small amount of unchanged formanilide (0·5 g.). Basic material was isolated from the acid washings by addition of sodium hydroxide solution and extraction with ether. The ethereal extract was dried by shaking for a few minutes with potassium hydroxide pellets, decanted, and evaporated, yielding a reddish-brown oil (22 g.), which, on vacuum distillation, gave a colourless limpid oil (19·5 g.; 88%) with a feeble basic odour, b. p. 143—144°/0·1 mm., $n_D^{18°}$ 1·5250 (Found: C, 71·2; H, 9·1. Calc. for $C_{13}H_{20}ON_2$: C, 70·9; H, 9·1%). The observed b. p. was higher than that (126—127°/1·5 mm.) recorded in D.R.-P. 547,108.

N-β-*Diethylaminoethylaniline.*—The above formyl derivative (33 g.) was boiled for a few hours with 22% hydrochloric acid (90 c.c.); the hydrolysis solution then assumed a succession of unexpected colours (initially colourless, then pink, violet and finally bright blue). The free base, isolated by the addition of aqueous potassium hydroxide and ether extraction, was distilled under reduced pressure, a colourless mobile oil (27·7 g.; 93%) with a feeble basic odour passing over at 152—153°/18 mm., $n_D^{17·5°}$ 1·5278 (Found: C, 75·1; H, 10·3. Calc. for $C_{12}H_{20}N_2$: C, 75·0; H, 10·4%). The observed b. p. was somewhat lower than that (163°/17 mm.) found by Clemo and Perkin (J., 1924, **125**, 1809); E.P. 267,169 and E.P. 433,625 record b. p.'s 121—123°/5 mm. and 145°/14 mm. respectively.

N-β-*Diethylaminoethylacetanilide.*—The foregoing base (10 g.) was refluxed for a short time with acetic anhydride (25 c.c.), and the reaction mixture fractionated directly, giving a quantitative yield of pure acetyl derivative as a colourless oil, b. p. 118—120°/0·01 mm., $n_D^{21°}$ 1·5118 (Found: C, 72·2; H, 9·5. Calc. for $C_{14}H_{22}ON_2$: C, 71·8; H, 9·4%). E.P. 267,169 records b. p. 134°/3 mm.

Attempted Preparation of Sulphonamides from the above Anilides.—Sulphonation of either of the above anilides did not proceed smoothly under the conditions used by Stewart (J., 1922, **121**, 2558; "Organic Syntheses," **5**, 3) for acetanilide, much of the material being recovered unchanged. Diethylaminoethylformanilide (18 g.) was treated with chlorosulphonic acid (27 c.c.) at first at 0° and then at 65—70° for 2½ hours. The resulting mixture was cooled and poured into ice-water, to the slightly turbid solution an equal volume of concentrated ammonia solution (*ca.* 300 c.c.) was at once added, and the mixture set aside overnight. The oil (12·2 g.) which was precipitated was extracted with benzene and, on vacuum distillation, yielded only unchanged starting material (9·7 g.). A similar result was obtained with diethylaminoethylacetanilide. An unsuccessful attempt was made to effect sulphonation of the formyl derivative in chloroform solution, followed by direct treatment of the reaction mixture with solid ammonium carbonate.

N-γ-*Phthalimidopropylformanilide.*—Formanilide (12·1 g.; 1 mol.) was converted into the sodio-derivative by heating on the water-bath for 5 hours with powdered sodium (2·3 g.; 1 at.) in a mixture (200 c.c.) of equal parts of benzene and toluene. γ-Bromopropylphthalimide (27 g.; 1 mol.) (kindly supplied by Dr. W. L. Glen) was added, and the mixture heated for 10 hours on the water-bath. The reaction mixture was washed with water, dried, and evaporated, yielding a light khaki, crystalline solid (32·3 g.); this was recrystallised with little loss from methyl alcohol, fine square-ended colourless prisms separating, m. p. 123—124°, which was not raised by further recrystallisation at this stage, and the presence of a trace of bromine (*i.e.*, unchanged bromopropylphthalimide) interfered with analysis (Found: C, 68·7; H, 5·2%). The entire product was refluxed in methyl alcohol (250 c.c.) with fused sodium acetate (12 g.) for 3½ hours. After evaporation of the solvent the halogen-free *product* was recovered in benzene and recrystallised as before, m. p. 126° (C, 70·0; H, 5·3. $C_{18}H_{16}O_3N_2$ requires C, 70·1; H, 5·2%).

Sulphonation of Phthalimidopropylformanilide. N-γ-(o-*Carboxybenzamido*)*propylaniline*-p(?)-*sulphonic Acid* (IV).—When chlorosulphonic acid (5 c.c.; *ca.* 7 mols.) was added at 0° to phthalimidopropylformanilide (6 g.), partial liquefaction of the latter occurred. The mixture was warmed gently and then maintained at 65—70° for 4½ hours. Next day the golden-yellow

gum was warmed slightly to increase its mobility and added to melting ice with stirring. The precipitated gum showed no tendency to crystallise and so it was extracted with a considerable bulk of ether and a little chloroform; the aqueous acid layer was retained for examination (see below). The ether–chloroform solution, dried and evaporated, yielded a viscous amber gum (4·43 g.), which partly crystallised on standing; it was dissolved in alcohol (50 c.c.), treated with concentrated aqueous ammonia (6 c.c.), and set aside for 24 hours. Dilution with water precipitated an oil, which was isolated by extraction with benzene. The gum (2·4 g.) thus isolated crystallised on standing, m. p. 100—107°; recrystallisation from aqueous methyl alcohol raised the m. p. to 117—119°, not depressed on admixture with the starting material, m. p. 126°. As this portion of the product was free from sulphur, it was taken to be impure unchanged starting material.

The aqueous acid layer (see above) on standing for 24 hours deposited a white microcrystalline solid, which was collected (0·74 g.), and the filtrate on further standing deposited a second crop (0·66 g.); a third crop (0·27 g.) separated during the next 2 days (total, 1·67 g.). The m. p.'s of the three crops lay in the range 250—253°. The *substance* was sparingly or not soluble in the usual organic solvents and separated from hot water in colourless microscopic plates, m. p. 253° [Found: C, 54·2; H, 4·9; N, 7·4; S, 8·3; equiv., 188. $C_{17}H_{18}O_6N_2S$ requires C, 54·0; H, 4·8; N, 7·4; S, 8·4%; equiv. (dibasic acid), 189].

2-*Acetamidonaphthalene*-6-*sulphonamide*.—(A) Grinding the sodium salt of 2-acetamidonaphthalene-6-sulphonic acid (1 mol.) (Forster, Hanson, and Watson, *J. Soc. Chem. Ind.*, 1928, **47**, 155T) with phosphorus pentachloride (1 mol.) was an unsatisfactory procedure for the preparation of the acid chloride (cf. acetylsulphanilyl chloride; Schroeter, *Ber.*, 1906, **39**, 1563) owing to the difficulty of attaining intimate mixture. The reaction mixture was treated with water, and the insoluble sulphonyl chloride collected and treated with 20% aqueous ammonia at room temperature overnight. The *amide* separated from 25% aqueous methyl alcohol in minute needles which were greyish in bulk, m. p. 246—247° (Found: C, 54·2; H, 4·9; N, 10·4; S, 12·1. $C_{12}H_{12}O_3N_2S$ requires C, 54·5; H, 5·5; N, 10·6; S, 12·1%).

(B) A better result was achieved by a modification of Heumann and Köchlin's procedure (*Ber.*, 1882, **15**, 1114). The sodium salt (6·7 g.) was added to chlorosulphonic acid (18 c.c.) at room temperature and the violet solution was set aside for 2½ hours. The sulphonyl chloride, isolated on the centrifuge after pouring into water, was converted into the amide in the usual way (yield, 5 g.), m. p. 246—247° (Found: S, 12·4%). The analysis shows that further sulphonation had not taken place and a mixed m. p. with the product obtained in (A) showed no depression.

2-*Aminonaphthalene*-6-*sulphonamide* (V) (*Amide of Bronner's Acid*).—The acetyl derivative (4·4 g.) was refluxed for 40 minutes with 16% hydrochloric acid (80 c.c.), and the crude product (3·6 g.) precipitated by neutralisation with sodium bicarbonate. Recrystallisation from 40% aqueous methyl alcohol afforded slightly pink, long leaflets of irregular outline, m. p. 233·5—235° (Found: C, 54·0; H, 5·2; N, 12·3; S, 14·6. $C_{10}H_{10}O_2N_2S$ requires C, 54·0; H, 4·5; N, 12·6; S, 14·4%).

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