3. *The Condensation of Halogeno-pyridines, -quinolines, and -isoquinolines with Sulphanilamide.*

By MONTAGUE A. PHILLIPS.

When halogeno-pyridines, -quinolines, and *-iso*quinolines are condensed with *p*-aminobenzenesulphonamide in the presence of potassium carbonate and copper, condensation generally occurs at the sulphonamide end of the molecule, owing probably to the intermediate formation of the potassium salt of the amide. In the absence of alkali-metal carbonate, condensation occurs exclusively at the amino-end of the sulphonamide molecule in all the cases investigated. 2-Chloro-5-nitropyridine, however, in the presence of potassium carbonate and copper gives a mixture of 5-*nitro*-2-(p-*aminobenzenesulphonamido*)*pyridine* and p-(5′-*nitro*-2′-*pyridylamino*)*benzenesulphonamide*, the former predominating. This is probably due to the exceedingly great reactivity of the chlorine atom in this particular pyridine derivative.

BOBRANSKI (*Arch. Pharm.*, 1939, **277**, 75) has shown that condensation of 2- and 4-chloroquinoline with sulphanilamide gives *p*-(2′- and 4′-quinolylamino)benzenesulphonamide respectively. Gray (J., 1939, 1202) has obtained *p*-(2′-pyridylamino)benzenesulphonamide by condensation of 2-chloropyridine and sulphanilamide. In connection with the scheme of chemotherapeutic study proceeding in these laboratories it has now been shown that when 2-halogeno-pyridines and -quinolines are condensed with sulphanilamide in the presence of potassium carbonate and a trace of copper powder, condensation generally occurs at the sulphonamide end of the second component, thus :

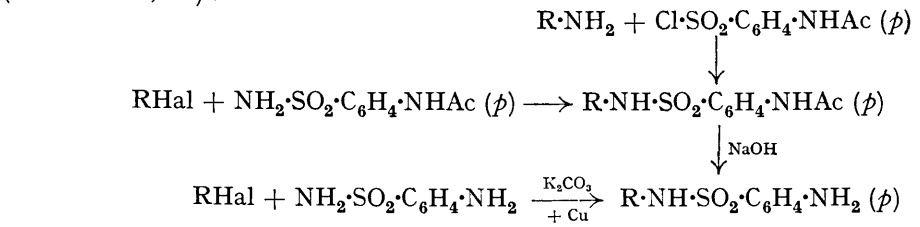
$$NH_2{\cdot}C_6H_4{\cdot}SO_2{\cdot}NH_2 + HalR \longrightarrow NH_2{\cdot}C_6H_4{\cdot}SO_2{\cdot}NHR$$

However, by fusion of the two components in the absence of alkali-metal carbonate, condensation occurs, as shown by Bobranski (*loc. cit.*), exclusively at the amino-end of the sulphonamide molecule in all the cases investigated.

$$NH_2{\cdot}SO_2{\cdot}C_6H_4{\cdot}NH_2 + HalR \longrightarrow NH_2{\cdot}SO_2{\cdot}C_6H_4{\cdot}NHR$$

Thus, 2-bromo- and 2-iodo-pyridine with sulphanilamide give *p*-(2′-pyridylamino)benzenesulphonamide and 2-(*p*-aminobenzenesulphonamido)pyridine by the Bobranski and the Ullmann method respectively, and from 2-bromoquinoline are obtained (2′-quinolylamino)-benzenesulphonamide and 2-(p-*aminobenzenesulphonamido*)*quinoline* by these two methods. 1-Chloro*iso*quinoline, when fused with *p*-aminobenzenesulphonamide, gives exclusively p-(1′-iso*quinolylamino*)*benzenesulphonamide*, which was identified by the absence of a free amino-group and by synthesis of the isomeric 1-(p-*aminobenzenesulphonamido*)iso*quinoline*, from *p*-acetamidobenzenesulphonyl chloride and 1-amino*iso*quinoline, followed by hydrolysis of the resulting 1-(p-*acetamidobenzenesulphonamido*)iso*quinoline*. The products of condensation of the 2-halogenopyridines and of 2-bromoquinoline with *p*-aminobenzenesulphonamide by the Ullmann method were also identified by this method of synthesis and also by condensation of the halogeno-pyridine or -quinoline with *p*-acetamidobenzene-

sulphonamide, followed by alkaline hydrolysis of the intermediate acetyl derivatives (see E.P. 512,145) :



To account for these results it is suggested that use of potassium carbonate causes the formation of the potassium salt of the sulphonamide, which then condenses with the halogen derivative. In the absence of alkali-metal carbonate, the amino-group appears to be more reactive than the sulphonamido-group and condensation in consequence proceeds at the basic end of the sulphonamide molecule.

In accordance with this hypothesis, 2-chloro-5-nitropyridine gave by the Bobranski method exclusively p-(5′-*nitro*-2′-*pyridylamino*)*benzenesulphonamide*. When the condensation was done under the Ullmann conditions, a mixture of this compound with the isomeric 5-*nitro*-2-(p-*aminobenzenesulphonamido*)*pyridine* was obtained in which the latter predominated. No difficulty was experienced in isolating the latter compound in a practically pure condition, but its isomeride was only identified after considerable trouble. Both isomerides were subsequently identified by synthesis.

Reduction of 5-nitro-2-(*p*-aminobenzenesulphonamido)pyridine obtained by either method gave the corresponding *amino*-compound; similarly p-(5′-*amino*-2′-*pyridylamino*)-*benzenesulphonamide* was obtained from the isomeric compound made by either of the above alternative methods. Just as 2-(*p*-aminobenzenesulphonamido)pyridine is obtained from 2-bromopyridine and *p*-aminobenzenesulphonamide by the Ullmann method, so p-(2′-*pyridylamino*)*benzenesulphon*-2′-*pyridylamide* is obtained from *p*-(2′-pyridylamino)-benzenesulphonamide and 2-bromopyridine. This compound could not be obtained by the Bobranski method from 2-(*p*-aminobenzenesulphonamido)pyridine and 2-halogeno-pyridines. Attempts to obtain it from *p*-halogenobenzenesulphon-2′-pyridylamide and 2-aminopyridine also failed, presumably on account of the low order of reactivity of the halogen atom. This failure is paralleled by the failure to obtain *p*-(2′-pyridylamino)-benzenesulphonamide from *p*-bromobenzenesulphonamide and 2-aminopyridine; here also the bromine atom is relatively non-reactive.

Experimental.

2-(p-*Aminobenzenesulphonamido*)*pyridine*.—(1) A mixture of 2-bromopyridine (Craig, *J. Amer. Chem. Soc.*, 1934, **56**, 231) (4·0 g.), *p*-aminobenzenesulphonamide (4·3 g.), anhydrous potassium carbonate (3·6 g.), and copper powder (0·05 g.) was refluxed at 180° for 3 hours. The melt was dissolved in water (40 c.c.), filtered from copper, and extracted with chloroform in order to remove unchanged bromopyridine (0·9 g.). Addition of dilute acetic acid gave 2-(*p*-aminobenzenesulphonamido)pyridine, m. p. 190—191° after repeated crystallisation from 50% acetic acid.

(2) 2-Iodopyridine (Wibaut and La Bastide, *Rec. Trav. chim.*, 1933, **52**, 493) (5·2 g.) was substituted for the 2-bromopyridine in (1), and the mixture refluxed for 1 hour at 150°. The subsequent treatment gave the pyridylamide, m. p. 190—191° after recrystallisation from 50% acetic acid or aqueous acetone. Prolonged drying at 100° of the product from acetic acid is necessary in order to decompose the acetate of the base which is partially formed during crystallisation from this solvent.

(3) A mixture of 2-bromopyridine (7·9 g.), *p*-acetamidobenzenesulphonamide (10·7 g.), potassium carbonate (6·5 g.), and copper powder (0·5 g.) was refluxed for 1 hour at 220°. The mixture was dissolved in hot water (200 c.c.), filtered from copper, and acidified with dilute acetic acid, giving 2-(*p*-acetamidobenzenesulphonamido)pyridine, m. p. 224° after crystallisation from 50% acetic acid (Found : N, 14·5. Calc. for $C_{13}H_{13}O_3N_3S$: N, 14·4%). Hydrolysis by boiling with 10 parts of 2N-sodium hydroxide for 1 hour gave a 90% yield of the amino-

compound, m. p. 190° when crystallised as above. 2-Chloropyridine could not be substituted for the corresponding bromo-derivative in the above experiment.

(4) To 2-aminopyridine (9·4 g.), dissolved in dry pyridine (20 c.c.) at room temperature, was added *p*-acetamidobenzenesulphonyl chloride (24·0 g.). The temperature rose to 70°; after cooling, the mixture was treated with water, and the precipitated 2-(*p*-acetamidobenzenesulphonamido)pyridine crystallised from 50% acetic acid; m. p. 224° (Found: N, 14·4%). Its hydrolysis as in (3) gave a 90% yield of 2-(*p*-aminobenzenesulphonamido)pyridine in colourless plates or prisms, m. p. 190° (Found: C, 53·3; H, 4·5; N, 16·8; S, 12·9. Calc. for $C_{11}H_{11}O_2N_3S$: C, 53·2; H, 4·55; N, 16·8; S, 12·85%), readily soluble in dilute sodium hydroxide solution (1 mol.). From concentrated aqueous solutions alcohol precipitated the *sodium* salt in colourless plates, readily soluble in cold and slightly hydrolysed by boiling water. Aqueous solutions of the sodium salt are alkaline to phenolphthalein (Found: Na, 8·4. $C_{11}H_{10}O_2N_3SNa$ requires Na, 8·5%). The pyridylamide is soluble about 1 part in 1,000 in cold water. It is readily soluble in 2N-hydrochloric acid. The diazo-solution has a deep yellow colour; concentrated diazo-solutions deposit the diazo-compound in yellow needles, which couple normally with the usual reagents.

Action of Mineral Acids on 2-(p-*Aminobenzenesulphonamido*)*pyridine.*—The base (49·8 g.) was refluxed with 2N-hydrochloric acid for 1½ hours. On cooling, sulphanilic acid separated (34·6 g.; 75% of the calculated amount). The filtrate from this, on basification with excess of 50% sodium hydroxide solution and extraction with chloroform, gave 2-aminopyridine, m. p. 58° after washing with light petroleum, the slightly basic odour of which was devoid of the sharp smell characteristic of the distilled product obtained by amination of pyridine (Tschitschibabin and Seide, *J. Russ. Phys. Chem. Soc.*, 1915, **46**, 1216). Quantitative experiments on the acid fission of the above sulphonamide showed that about 80% was decomposed after 15 minutes' boiling with 2N-hydrochloric acid and 90% in about 30 minutes.

p-(2′-*Pyridylamino*)*benzenesulphonamide.*—A mixture of 2-bromopyridine (4·0 g.) and sulphanilamide (4·3 g.; 1 equiv.) was heated at 175° for 45 minutes. The product was dissolved in 2N-sodium hydroxide and reprecipitated, after filtration, with 2N-acetic acid. The base, crystallised from aqueous acetone, had m. p. 223—224° (Gray, *loc. cit.*, gives m. p. 235°). It was soluble in dilute sodium hydroxide solution and in dilute mineral acids, and was shown by diazo-coupling tests to be free from amino-group even in the crude material (Found: N, 16·8; S, 12·9. Calc. for $C_{11}H_{11}O_2N_3S$: N, 16·8; S, 12·85%). The same yield was obtained when 2 equivs. of either component were used in the condensation, but the time of reaction was considerably lessened.

2-(p-*Aminobenzenesulphonamido*)*quinoline.*—(1) 2-Bromoquinoline (5·2 g.), sulphanilamide (4·3 g.), potassium carbonate (3·5 g.), and copper powder (0·05 g.) were refluxed at 180° for 1½ hours. The product was dissolved in boiling water (40 c.c.) containing 5 c.c. of 2N-sodium hydroxide and, after filtration from copper, acidified with dilute acetic acid. The gum which formed slowly hardened and was boiled with 2N-sodium hydroxide (80 c.c.) for some minutes. On cooling, the sodium salt separated; this was collected and dissolved in boiling water (40 c.c.); treatment with 50% acetic acid gave a crystalline solid (3·0 g.), m. p. 194° (Found: N, 14·0. $C_{15}H_{13}O_2N_3S$ requires N, 14·05%). Diazo-tests showed the presence of a free amino-group.

(2) A mixture of 2-chloroquinoline (8·2 g.), *p*-acetamidobenzenesulphonamide (10·7 g.), potassium carbonate (6·5 g.), and copper powder (0·5 g.) was heated at 250° for 3½ hours. The product was dissolved in boiling water (100 c.c.) and filtered. Acidification of the hot filtrate (from which a potassium salt separated on cooling) with dilute acetic acid gave 5·5 g. of a solid, presumably the acetyl derivative of the above base, which was refluxed with 55 c.c. of 2N-sodium hydroxide for 1 hour. On cooling, the sodium salt of 2-(p-*aminobenzenesulphonamido*)-*quinoline* separated. This was collected and treated as in (1), giving the base (4·0 g.), m. p. 195° (Found: N, 14·1%).

(3) Coal-tar quinoline was aminated by sodamide in xylene (Tschitschibabin and Seide, *loc. cit.*; Tschitschibabin, Witkowsky, and Lapschin, *Ber.*, 1925, **58**, 805) and from the mixture of aminoquinolines and 1-amino*iso*quinoline so obtained, 2-aminoquinoline, m. p. 129°, was isolated by the method of Morgan and Stewart (J., 1938, 1302). To a solution of 2-aminoquinoline (2·0 g.) in pyridine (4 c.c.) was added *p*-acetamidobenzenesulphonyl chloride (3·2 g.). The temperature rose to 50°; after standing and dilution with water (60 c.c.) the precipitated 2-(p-*acetamidobenzenesulphonamido*)*quinoline* (3·3 g.) was crystallised from 50% acetic acid; m. p. 216° (Found for material dried at 100°: C, 59·6; H, 4·4; N, 12·3. $C_{17}H_{13}O_3N_3S$ requires C, 59·6; H, 4·5; N, 12·2%). Its hydrolysis as in (2) gave 2-(*p*-aminobenzenesulphonamido)-

quinoline, m. p. 195° (Found: C, 60·5; H, 4·4; N, 14·0; S, 10·6. $C_{15}H_{13}O_2N_3S$ requires C, 60·2; H, 4·4; N, 14·05; S, 10·7%).

2-(*p*-Aminobenzenesulphonamido)quinoline obtained by any of the above methods forms colourless plates giving a sparingly soluble, crystalline sodium salt with dilute caustic soda; with 2N-hydrochloric acid in excess it forms an insoluble hydrochloride. It is sparingly soluble in ordinary organic solvents. The diazo-solution is yellow and couples normally.

p-(2′-*Quinolylamino*)*benzenesulphonamide*.—A mixture of 2-bromoquinoline (4·2 g.) and sulphanilamide (3·4 g.; 1 equiv.) was heated at 170°. After melting, the mixture resolidified within 5 minutes; after 10 minutes' heating, the mixture was boiled with 15% hydrochloric acid (80 c.c.) for 10 minutes, and the suspension of the hydrochloride treated with excess of saturated sodium acetate solution. The base obtained (4·2 g.) was dissolved in a mixture of boiling alcohol (100 c.c.) with the requisite amount of 2N-sodium hydroxide, and the hot filtered solution treated with boiling 50% acetic acid (25 c.c.). The sulphonamide so obtained formed colourless plates, m. p. 251° (Found: C, 60·2; H, 4·3; N, 14·1. Calc. for $C_{15}H_{13}O_2N_3S$: C, 60·2; H, 4·4; N, 14·05%). Bobranski (*loc. cit.*) gives the m. p. as 251°, but Gray (*loc. cit.*) gives 261°. Repeated crystallisations, however, of the above product failed to raise the m. p. It was soluble in dilute caustic alkali solution, but gave an insoluble hydrochloride with 2N-hydrochloric acid. Diazo-coupling tests for free amino-group were negative.

p-(1′-iso*Quinolylamino*)*benzenesulphonamide*.—A mixture of 1-chloro*iso*quinoline (4·0 g.) and sulphanilamide (4·3 g.; 1 equiv.) was refluxed at 165° for 30 minutes. The mixture was dissolved in hot 2N-sodium hydroxide (70 c.c.) and, after filtration, was acidified with 50% acetic acid. The gum formed rapidly solidified; it weighed 7·3 g. (97%) and was crystallised by solution in alcohol (70 c.c.) mixed with 2N-hydrochloric acid (11 c.c.) at 70°, followed by addition of saturated sodium acetate solution to the filtered solution, p-(1′-iso*quinolylamino*)-*benzenesulphonamide* being obtained in colourless plates, m. p. 275° (sintering at 265°), soluble in 2N-sodium hydroxide and in 2N-hydrochloric acid but sparingly soluble in the usual organic solvents. Diazo-coupling tests showed absence of a free amino-group (Found: N, 14·0. $C_{15}H_{13}O_2N_3S$ requires N, 14·05%).

1-(p-*Aminobenzenesulphonamido*)iso*quinoline*.—This could not be obtained from 1-chloro-*iso*quinoline and sulphanilamide in the presence of potassium carbonate and copper. It was obtained by addition of *p*-acetamidobenzenesulphonyl chloride (16·0 g.) to a solution of 1-amino*iso*quinoline (9·7 g.) in pyridine (20 c.c.), the temperature being kept below 50°. Addition of water (350 c.c.) caused precipitation of a gum, which was induced to solidify with difficulty. Purified by solution in a mixture of alcohol (250 c.c.) and the required amount of 2N-sodium hydroxide at 70° and precipitation of the filtered solution at the b. p. with 2N-acetic acid, 1-(p-*acetamidobenzenesulphonamido*)iso*quinoline* (7·7 g.) was obtained in colourless prisms, m. p. 225° (Found: N, 12·2. $C_{17}H_{15}O_3N_3S$ requires N, 12·3%). When it was boiled with 2N-sodium hydroxide (10 c.c. per g.) for 1 hour and the mixture acidified with dilute acetic acid, 1-(p-*aminobenzenesulphonamido*)iso*quinoline* was obtained in tiny prismatic crystals, m. p. 263° (yield, 84%) (Found: N, 14·0. $C_{15}H_{13}O_2N_3S$ requires N, 14·05%). It was soluble in caustic alkalis and gave an insoluble crystalline hydrochloride with 2N-hydrochloric acid. It was practically insoluble in the ordinary solvents and gave an insoluble yellow diazo-compound, which coupled normally.

2-*Chloro*-5-*nitropyridine*.—Since the original work on the nitration of 2-aminopyridine is published by Tschitschibabin and his co-workers in Russian (*J. Russ. Phys. Chem. Soc.*, 1914, **46**, 1236; 1915, **47**, 1386; 1923, **55**, 471), the following details are given. 2-Aminopyridine (54 g.) was added with stirring to sulphuric acid (*d* 1·84, 240 c.c.) below 90°. The solution was cooled to 0°, and a cooled mixture of nitric acid (*d* 1·42, 39 c.c.) and sulphuric acid (*d* 1·84, 42 c.c.) added with stirring between 10° and 20°. The mixture was stirred for 1 hour further at 15° [if it is treated at this stage with ice, 2-nitroaminopyridine, m. p. 190° (decomp.), is obtained in 70% yield] and then warmed to 35°; the temperature rose spontaneously to about 65°. On addition of ice and water and basification with sodium carbonate (anhydrous) a mixture of 5- and 3-nitro-2-aminopyridines was formed, from which the two isomerides could be separated by a tedious fractionation from alcohol and acetone.* It is not necessary, however, to separate them in order to proceed to 2-chloro-5-nitropyridine. The wet mixture was estimated for water content; the nitration yield was usually about 70%. The equivalent of 59 g. of the dry mixture was dissolved in water (915 c.c.) by means of sulphuric acid (*d* 1·84, 63·6 c.c.), ice (250 g.) added,

* It is not prudent to isomerise larger batches of nitroaminopyridine; if larger nitrations are done, it is advisable to divide them into lots approximately equal to the above, to isomerise them separately, and to recombine them before working up.

followed by a solution of sodium nitrite (32·8 g.) in water (118 c.c.) with stirring. The stem of the dropping-funnel carrying the nitrite solution was arranged to dip below the surface of the reaction mixture and to feed near the point of maximum agitation. After the addition the mixture was stirred for 30 minutes, and the precipitated solid collected and washed with water. This proved to be nearly pure 5-nitro-2-hydroxypyridine, m. p. 180°. It did not depress the m. p. (184°) of a pure specimen made similarly from pure 5-nitro-2-aminopyridine (Tschitschibabin and Bylinkin, *J. Russ. Phys. Chem. Soc.*, **1914**, **46**, 1236). The yield was 30 g.; a further 10 g. were obtained by concentration of the filtrate to about half bulk. The total yield was thus 66%. The fate of the isomeric 3-nitro-derivative has not yet been determined. The dry 5-nitro-2-hydroxypyridine (41·4 g.) was refluxed with phosphorus pentachloride (69·1 g.) and phosphorus oxychloride (4·1 c.c.) at 110° for 3 hours, the volatile phosphorus chlorides removed by distillation under reduced pressure, and the residue treated with ice. The mixture was ground, and the solid washed with water and dried at 90°, giving 2-chloro-5-nitropyridine (44·3 g.), m. p. 106° alone or mixed with an authentic specimen.

p-(5′-*Nitro*-2′-*pyridylamino*)*benzenesulphonamide*.—(1) A mixture of 2-chloro-5-nitropyridine (15·8 g.) with sulphanilamide (17·2 g.; 1 equiv.) was heated at 170° for 15 minutes. The solid cake was extracted with boiling 2N-sodium hydroxide, and the deep red solution acidified with dilute hydrochloric acid. Excess of saturated sodium acetate was then added, and the amorphous precipitate collected, washed with water, and boiled for a short time with alcohol (160 c.c.). The crystalline solid was collected, washed with 50% spirit, and dried (7·7 g., m. p. 204—206°). From the alcoholic filtrate a further crop (7·0 g.), m. p. 200—202°, was obtained after several days. The total yield of the *sulphonamide* was about 51%. Crystallised from 50% acetic acid, both fractions melted at 209—210° and were identical with the synthetic product described below (Found: N, 19·0. $C_{11}H_{10}O_4N_4S$ requires N, 9·0%).

(2) (a) *Sodium* p-(5′-*nitro*-2′-*pyridylamino*)*benzenesulphonate*. Anhydrous sulphanilic acid (35 g. or an equivalent amount of the hydrated acid) was dissolved in a solution of sodium hydroxide (8·0 g.) in water (100 c.c.). One equiv. (32 g.) of 2-chloro-5-nitropyridine was added, and the mixture refluxed for several hours, during which period a further amount of sodium hydroxide solution (8·0 g. in 50 c.c. of water) was added. The final reaction was alkaline to litmus but not to phenolphthalein. On cooling, the above sodium salt separated; it was drained on a porous tile, washed with alcohol and ether, and dried (36 g. Found for material crystallised from 2 parts of boiling water: Na, 7·5; N, 13·0. $C_{11}H_8O_5N_3SNa$ requires Na, 7·3; N, 13·1%). The procedure is based upon that given in E.P. 152,406 for the preparation of sodium 2 : 4-dinitrodiphenylamine-4-sulphonate. (b) p-(5′-*Nitro*-2′-*pyridylamino*)*benzenesulphonamide*. A mixture of the sodium salt from (a) (26 g.) with phosphorus pentachloride (17·3 g.) and phosphorus oxychloride (7·5 c.c.) was heated on a steam-bath for 45 minutes. The volatile phosphorus compounds were removed by distillation under reduced pressure, and the residue treated with ice. The moist sulphonyl chloride obtained was treated with aqueous ammonia (*d* 0·880, 70 c.c.), and the mixture heated on a steam-bath to remove the excess of ammonia. Dilution with water and addition of a little 2N-acetic acid gave the above sulphonamide (8·0 g.), m. p. 209—210° after crystallisation from 50% acetic acid (Found: N, 19·0%). The sulphonamide formed characteristic yellow rhombs, which gave a deep red solution in dilute aqueous sodium hydroxide. A faint pink colour with this reagent was discernible in dilutions as high as 1 in 10,000. It was insoluble in 2N-hydrochloric acid and incompletely soluble in 2N-ammonia (1 g. in 2 c.c.). Owing to the intense colour given in dilute sodium hydroxide solution, the diazo-coupling tests for free amino-group were indecisive.

p-(5′-*Amino*-2′-*pyridylamino*)*benzenesulphonamide*.—The nitro-compound (2·9 g., made by either of the above methods) was dissolved in 2N-sodium hydroxide (10 c.c.) and added at 60° to a suspension of ferrous hydroxide from crystallised ferrous sulphate (20·0 g.) in water (50 c.c.) and sodium hydroxide (5·6 g.) in water (15 c.c.). After filtration and neutralisation with dilute acetic acid the above *amine* was obtained. After solution in 2N-hydrochloric acid (charcoal) in the cold and neutralisation of the filtered solution with 25% aqueous sodium hydroxide, it formed pink needles, m. p. 221°, readily soluble in dilute caustic alkali solution and in dilute acetic and hydrochloric acids. Diazo-coupling tests were positive (Found: N, 21·1. $C_{11}H_{12}O_2N_4S$ requires N, 21·1%).

5-*Nitro*-2-(p-*aminobenzenesulphonamido*)*pyridine*.—(1) 2-Chloro-5-nitropyridine (15·8 g.) was mixed with *p*-acetamidobenzenesulphonamide (21·4 g.), potassium carbonate (anhydrous, 13·5 g.), and copper powder (1·0 g.) and heated at 180° for 1 hour. The mixture was extracted with hot water, and the filtered extract acidified with 2N-acetic acid. The 5-*nitro*-2-(p-*acetamidobenzenesulphonamido*)*pyridine* obtained (20·0 g.) was suspended in boiling alcohol (400 c.c.)

and dissolved by addition of 2N-sodium hydroxide; addition of boiling 50% acetic acid (100 c.c.) gave the acetyl derivative, m. p. 279° (Found : N, 16·4. $C_{13}H_{12}O_5N_4S$ requires N, 16·6%).

(2) The same compound (m. p. 277—279° when purified as above) was obtained by addition of *p*-acetamidobenzenesulphonyl chloride (5·6 g.) to a solution of 5-nitro-2-aminopyridine (3·2 g.) in pyridine (10 c.c.), followed by addition of cold N-hydrochloric acid when the somewhat vigorous reaction was over. It did not depress the m. p. of the product from (1) (Found : N, 16·5%).

The acetyl compound was boiled with 2N-sodium hydroxide (10 c.c. per g.) for 1 hour; acidification with acetic acid gave *5-nitro-2-(p-aminobenzenesulphonamido)pyridine*, m. p. 218—220° after crystallisation from 50% acetic acid (Found : N, 19·0. $C_{11}H_{10}O_4N_4S$ requires N, 19·0%).

(3) A mixture of 2-chloro-5-nitropyridine (8·0 g.), sulphanilamide (8·6 g.), potassium carbonate (7·0 g.), and copper powder (0·05 g.) was heated at 140° for 30 minutes. A vigorous reaction took place. The mixture was dissolved in boiling N-sodium hydroxide, filtered, and acidified with acetic acid, and the precipitate washed with water and dried (8·1 g., m. p. 190—200°. Found : N, 18·7%). This mixture was boiled for a few minutes with N-sodium hydroxide (11 c.c.) and, after cooling, the solution was filtered. The solid (A) weighed 9·6 g., melted at 214—215°, and did not depress the m. p. of genuine 5-nitro-2-(*p*-aminobenzenesulphonamido)-pyridine. It gave a pale red solution with dilute aqueous hydroxide. Mixed with *p*-(5′-nitro-2′-pyridylamino)benzenesulphonamide, it melted at 180—190°. After crystallisation from 50% acetic acid the m. p. rose to 218—220° and the substance appeared to be identical in all respects, including its characteristic crystalline form, with the synthetic product from (1) and (2), save that it gave a pale pink solution in dilute aqueous caustic soda (Found : N, 18·9%). Nesslerisation indicated this to contain 0·1—0·2% of the isomeric *p*-(5′-nitro-2′-pyridylamino)benzenesulphonamide, but further purification could not be effected.

The filtrate from the solid (A) was acidified with acetic acid, giving 5·95 g. of amorphous substance (B). This was digested with cold 2N-ammonia (10 c.c.), and the liquid filtered. The insoluble solid was re-treated with cold N-ammonia (5 c.c.) and then, on repeated crystallisation from 50% acetic acid and finally from 95% alcohol, had m. p. 208—209°, gave a deep red solution in dilute aqueous sodium hydroxide, and did not depress the m. p. of synthetic *p*-(5′-nitro-2′-pyridylamino)benzenesulphonamide (Found : N, 19·1%). A mixture with its isomeride, however, melted at 180—190°. The ammoniacal filtrate from this on acidification with acetic acid gave 3·2 g. of crude 5-nitro-2-(*p*-aminobenzenesulphonamido)pyridine, identified as above. A similar mixture of the two isomerides was obtained from 2-chloro-5-nitropyridine, the sodium salt of sulphanilamide (1 equiv.), potassium carbonate (0·5 mol.), and a trace of copper under similar conditions.

5-Nitro-2-(*p*-aminobenzenesulphonamido)pyridine forms stout yellow polyhedra of characteristic shape, m. p. 218—220°, gives yellow solutions in dilute aqueous sodium hydroxide and ammonia, and is insoluble in dilute mineral acids and in the ordinary organic solvents. The diazo-coupling reactions show the presence of a free amino-group.

5-Amino-2-(p-aminobenzenesulphonamido)pyridine.—The nitro-compound obtained by any of the above methods (54 g.) was mixed with reduced iron powder (32 g.) and added to a boiling solution of acetic acid (32 c.c.) in water (800 c.c.). After boiling for 20 minutes, the mixture was neutralised with 2N-ammonia and the solution was filtered and acidified with 50% acetic acid. The crystalline solid obtained, presumably 5-amino-2-(*p*-acetamidobenzenesulphonamido)pyridine, was washed, dried (yield, 6 g.), and boiled with 60 c.c. of 2N-sodium hydroxide for 1 hour. Acidification with 50% acetic acid then gave a 50% yield of *5-amino-2-(p-aminobenzenesulphonamido)pyridine*. This crystallised from 50% alcohol in colourless needles, which turned pink on exposure to air; it was readily soluble in dilute caustic alkalis and in mineral acids. The diazo-solution was yellow and coupled normally. The amine had no definite m. p. but sintered at 140—150° and was not completely molten at 200° (Found : N, 21·1. $C_{11}H_{12}O_2N_4S$ requires N, 21·1%).

p-*(2′-Pyridylamino)benzenesulphon-2′-pyridylamide.*—A mixture of *p*-(2′-pyridylamino)-benzenesulphonamide (6·25 g.) with 2-bromopyridine (4·0 g.), potassium carbonate (3·5 g.), and copper powder (0·05 g.) was refluxed for 1 hour. The product was dissolved in boiling water (150 c.c.), filtered from copper, and acidified with dilute acetic acid, giving 5·5 g. of a product, m. p. 185—190°. This was dissolved in a mixture of boiling alcohol (37 c.c.) and 2N-sodium hydroxide (25 c.c.) and acidified with excess of boiling 2N-acetic acid. p-*(2′-Pyridylamino)benzenesulphon-2′-pyridylamide* so obtained formed colourless needles, m. p. 204°, soluble in dilute caustic alkalis and mineral acids and sparingly soluble in the ordinary organic solvents

(Found : N, 17·2. $C_{16}H_{14}O_2N_4S$ requires N, 17·1%). Attempts to prepare this compound from 2-(*p*-aminobenzenesulphonamido)pyridine and 2-bromo- or 2-iodo-pyridine by Bobranski's method (*loc. cit.*) failed, the unchanged pyridylamide being recovered in each case in good yield.

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RESEARCH LABORATORIES, MESSRS. MAY AND BAKER, LTD.,
DAGENHAM.

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