108. *New Therapeutic Agents of the Quinoline Series. Part III. Methoxy-, Hydroxy-, and Alkyl-pyridylquinolines.*

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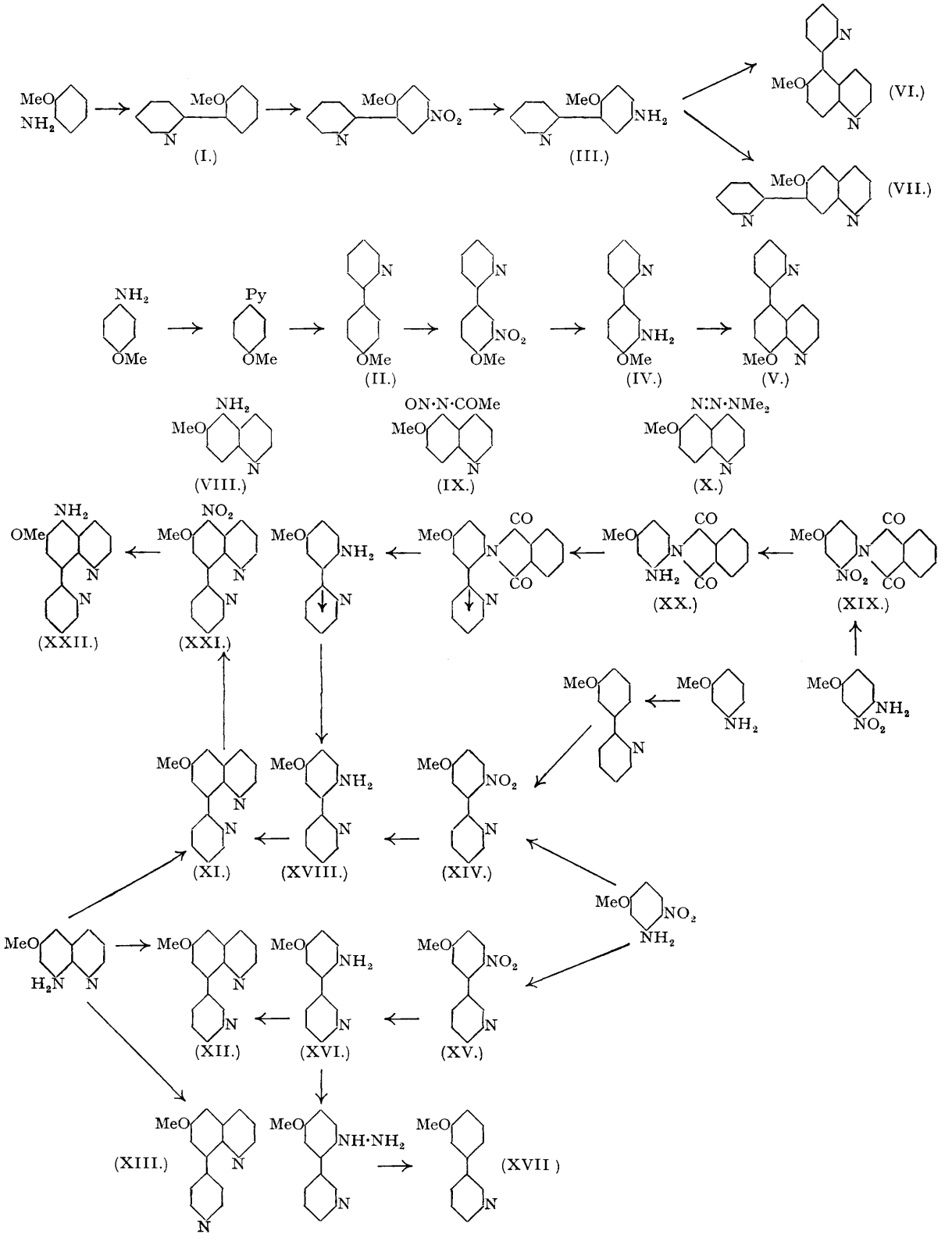
A representative series of methoxypyridylquinolines has been prepared by submitting pyridylanisidines of proved orientation to the Skraup reaction, as well as by directly introducing the pyridyl group into the quinoline system. A hydroxypyridylquinoline was similarly synthesised. By means of the Doebner–Miller reaction several aminophenylpyridines were converted into pyridylquinaldines, and a higher alkyl (*tert.*-butyl) pyridylquinoline was also synthesised. Preparations of pyridylacetoacetanilides and attempts to cyclise them to quinoline derivatives are also described.

As alkoxyl groups are a feature of most spasmolytic *iso*quinolines, the preparation and examination of representative methoxypyridylquinolines was desirable.

Both α-2- (I) and α-4-methoxyphenylpyridine (II) isolated from the reaction between the appropriate diazotised anisidine and pyridine (Haworth, Heilbron, and Hey, J., 1940, 358) have been separately nitrated (*loc. cit.*) and reduced to α-3-*amino*-6-*methoxyphenylpyridine* (III) and α-3-*amino*-4-*methoxyphenylpyridine* (IV) respectively. Each of these amino-compounds was converted into the quinoline by means of the Skraup reaction. The latter amine gave 8-*methoxy*-5-α-*pyridylquinoline* (V) exclusively. From the former, 6-*methoxy*-5- and -7-α-*pyridylquinoline* (VI) and (VII) were isolated by fractional crystallisation of the mixed picrates from acetone. With a view to proving the separate identities of these two isomerides, an attempt was made to synthesise 6-methoxy-5-α-pyridylquinoline by the following unambiguous method. 6-Methoxyquinoline, prepared from *p*-anisidine by Skraup's method, was nitrated as described by Jacobs and Heidelberger (*J. Amer. Chem. Soc.*, 1920, **42**, 2285; cf. Decker and Engler, *Ber.*, 1909, **42**, 1740), and the constitution of the resulting 5-nitro-6-methoxyquinoline proved by demethylation to the known 5-nitro-6-hydroxyquinoline. Reduction with iron filings and a dilute solution of hydrochloric acid in alcohol then gave 5-amino-6-methoxyquinoline (VIII). The use of stannous chloride and hydrochloric acid for this reduction (cf. Jacobs and Heidelberger, *loc. cit.*) gave a product containing chlorine. Although it has been established by Heilbron, Hey, and their

collaborators (J., 1940, 349, 355, 358, 1279) that in general a mixture of α-, β-, and γ-arylpyridines is obtained when an aqueous solution of a diazotised arylamine is added to excess of pyridine, the reaction of diazotised

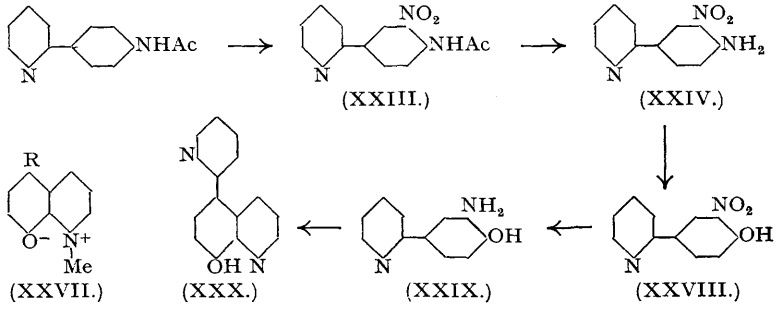


5-amino-6-methoxyquinoline with pyridine gave a solid tarry product, soluble in both acid and alkali, from which none of the required pyridylmethoxyquinoline could be isolated. A similar product also resulted from the action of the zinc chloride stabilised diazonium salt on pyridine (cf. Hodgson and Marsden, J., 1940, 208). Further attempts to effect the union of the quinoline and pyridine nuclei were made through the nitrosoacetamido-derivative (IX) (cf. Haworth, Heilbron, and Hey, J., 1940, 372) and also through the *triazen* (X) obtained by the action of the diazotised 5-amino-6-methoxyquinoline on dimethylamine (cf. B.P. 513,846), but none of the required product was obtained in either case.

From the reaction between aqueous diazotised 8-amino-6-methoxyquinoline and pyridine a mixture of isomerides has been obtained from which 6-*methoxy*-8-α- (XI), 6-*methoxy*-8-β- (XII) and 6-*methoxy*-8-γ-*pyridylquinoline* (XIII) were isolated by fractional crystallisation of the mixed *picrates* from acetone. With a view to placing the constitutions of these compounds beyond doubt, the possibility of synthesising them from the three isomeric 3-methoxyphenylpyridines by successive nitration, reduction and application of the Skraup reaction was investigated. Nitration of α-3-methoxyphenylpyridine (Haworth, Heilbron, and Hey, J., 1940, 358) gave a liquid product fom which two *mononitro*-compounds of unknown constitution, as well as α-2-*nitro*-5-*methoxyphenylpyridine* (XIV), were isolated in the form of *picrates*, but the low yield of these compounds rendered this method of synthesis impracticable. A second synthetic route was therefore examined and 6-methoxy-8-α-pyridylquinoline (XI) and 6-methoxy-8-β-pyridylquinoline (XII) were finally obtained by unambiguous methods. A mixture of 4- and 6-nitro-*m*-acetanisidide, prepared by the nitration of *m*-acetanisidide, was separated into its components as described by Reverdin and Widmer (*Ber.*, 1913, **46**, 4071) and hydrolysed. Addition of aqueous diazotised 4-nitro-*m*-anisidine to pyridine gave a mixture of 2-nitro-5-methoxyphenylpyridines in 22% yield. This comparatively low yield was due to the simultaneous formation of a considerable quantity of *p*-nitroanisole by elimination of the amino-group. From this mixture, α- (XIV) and β-2-amino-5-methoxyphenylpyridine (XV) were isolated by fractional crystallisation of the mixed picrates, but, although γ-2-nitro-5-methoxyphenylpyridine was probably present in small quantity, it was not found possible to isolate it owing to lack of material. The identity of α-2-nitro-5-methoxyphenylpyridine picrate with the corresponding compound isolated from the product obtained by the direct nitration of α-3-methoxyphenylpyridine placed the constitution of the compound beyond doubt. The constitution of β-2-nitro-5-methoxyphenylpyridine was proved by reduction to β-2-*amino*-5-*methoxyphenylpyridine* (XVI), followed by diazotisation, reduction to the hydrazine, and treatment with copper acetate to give β-3-*methoxyphenylpyridine* (XVII), the constitution of which was established by elimination following the synthesis of γ-3-methoxyphenylpyridine by an unambiguous method. Thus γ-3-nitrophenylpyridine, isolated from the product of the reaction between aqueous diazotised *m*-nitroaniline and pyridine (Haworth, Heilbron, and Hey, J., 1940, 1279), was converted into γ-3-*hydroxyphenylpyridine* through the diazonium salt. Treatment with diazomethane then gave γ-3-methoxyphenylpyridine, the picrate of which was identical with the compound of similar m. p. obtained by Haworth, Heilbron, and Hey (J., 1940, 361) from the product of the reaction between diazotised *m*-anisidine and pyridine. Reduction of α-2-nitro-5-methoxyphenylpyridine gave α-2-amino-5-methoxyphenylpyridine (XVIII), which was converted into 6-methoxy-8-α-pyridylquinoline (XI) by means of the Skraup reaction. In similar manner β-2-amino-5-methoxyphenylpyridine yielded 6-methoxy-8-β-pyridylquinoline (XII). Both these quinoline derivatives were shown to be identical with the corresponding compounds obtained by the reaction between aqueous diazotised 8-amino-6-methoxyquinoline and pyridine and the constitution of 6-methoxy-8-γ-pyridylquinoline (XIII) is thus established by elimination. An alternative route to the 2-amino-5-methoxyphenylpyridines, in which a somewhat better " over-all " yield (10%) was obtained and which involved the use of an amine more readily obtainable than *m*-anisidine, was also investigated. *Phthalo*-3-*nitro*-p-*anisidide* (XIX), obtained by heating 3-nitro-*p*-anisidine with phthalic anhydride at 160—170°, was reduced to the corresponding *amine* (XX) by means of iron filings and a dilute solution of hydrochloric acid in alcohol. Diazotisation of this amine, followed by reaction with pyridine and hydrolysis of the product, yielded a mixture of 2-amino-5-methoxyphenylpyridines, from which α-2-amino-5-methoxyphenylpyridine (XVIII) was isolated by fractional crystallisation of the mixed picrates from acetone.

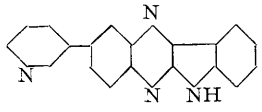
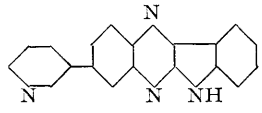
Nitration of 6-methoxy-8-α-pyridylquinoline gave a compound regarded as 5-*nitro*-6-*methoxy*-8-α-*pyridylquinoline* (XXI), which was reduced to the corresponding *amine* (XXII).

In order to prepare a representative pyridylhydroxyquinoline, the following series of reactions has been examined :



α-3-*Nitro*-4-*aminophenylpyridine* (XXIV) was obtained *via* (XXIII). The amino-group of (XXIV) was replaced by hydroxyl by boiling with caustic potash to give (XXVIII); the structure of this was also confirmed by methylation, α-3-nitro-4-methoxyphenylpyridine being obtained identical with that obtained by Haworth, Heilbron, and Hey (J., 1940, 361). (XXVIII) was reduced to the corresponding *o-aminophenol* (XXIX), which on submission to the Skraup reaction afforded 8-*hydroxy*-5-α-*pyridylquinoline* (XXX). In attempting to methylate (XXX) with ethereal diazomethane, a dark red solid, freely soluble in hydroxylic solvents but sparingly soluble in hydrocarbons or chloroform, was obtained instead of the colourless methyl ether anticipated. This behaviour was simulated exactly by 8-hydroxyquinoline, which gave a scarlet solid probably identical with the product described by Lippman and Fleissner (*Monatsh.*, 1889, **10**, 665; cf. also Claus and Howitz, *J. pr. Chem.*, 1890, **42**, 222; 1892, **45**, 256). Having regard to the properties and the disappearance of the colour with acids, betaine structures (XXVII) are suggested for these compounds. When methyl sulphate and alkali were used, the normal methyl ether was formed; it was identified with 8-methoxy-5-α-pyridylquinoline prepared above.

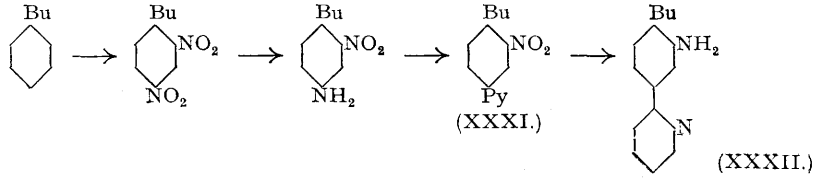
β-4-Acetamidophenylpyridine was nitrated, and the *o*-nitro-compound (cf. XXIII) hydrolysed to β-3-*nitro*-4-*aminophenylpyridine* (cf. XXIV). This constitution was established by reducing (XXIV) to an o-*diamine* which gave *quinoxalines* on condensing with glyoxal, benzil, and isatin, two products (XXV) and (XXVI) being obtained from the last-named dicarbonyl compound :

(XXV.)   (XXVI.)

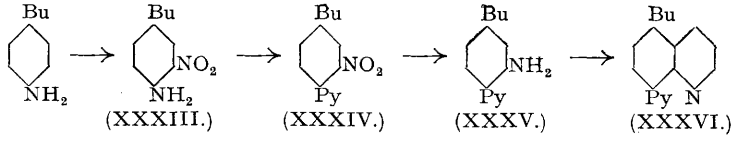
Pyridylalkylquinolines.—The three isomeric 4-aminophenylpyridines were converted by the Doebner–Miller reaction into 6-α-, 6-β-, and 6-γ-*pyridylquinaldine*. Further, condensation of 4-α- and 4-β-aminophenylpyridine with benzaldehyde and pyruvic acid gave 6-α- and 6-β-pyridylatophan (cf. Doebner and Gieseke, *Ber.*, 1887, **20**, 280). The spasmolytic activity of most of these substituted compounds was disappointing and we therefore proceeded to prepare pyridylquinolines carrying an alkyl substituent in the *Bz*-ring of the quinoline residue.

2 : 4-Dinitro-*tert.*-butylbenzene was reduced to 2-nitro-4-amino-*tert.*-butylbenzene; the free amino-group was diazotised and treated with pyridine in the usual manner to give a surprisingly good yield of 3-nitro-4-*tert.*-butylpyridylbenzenes (XXXI). The product was converted into a mixture of picrates and separated by fractional crystallisation into three components. It was only possible to assign provisional orientations to these picrates by comparing relative melting points with those of other series. That assumed to be of β-3-*nitro*-4-tert.-*butylphenylpyridine* was converted into the free base, which was reduced to β-3-*amino*-4-tert.-*butylphenylpyridine* (XXXII), but poor yields at this point compelled us to abandon this series.

4-*tert.*-Butylacetanilide was nitrated, and the acetamido-compound hydrolysed to 2-nitro-4-*tert.*-butylaniline (XXXIII). This base on diazotisation and treatment with pyridine gave 2-nitro-4-*tert.*-butylpyridylbenzene (XXXIV). Reduction and submission of the resulting 2-amino-4-*tert.*-butylpyridylbenzene (XXXV) to the Skraup reaction gave 8-*pyridyl*-5-tert.-*butylquinoline* (XXXVI). As preliminary pharmacological results showed the introduction of the butyl group to have had an unfavourable influence, no attempt was made to separate individual isomerides in this series. These reactions are summarised below :



(XXXI.) (XXXII.)



(XXXIII.) (XXXIV.) (XXXV.) (XXXVI.)

The reaction between aromatic bases and ethyl acetoacetate in many cases leads to good yields of acetoacetanilide or its derivatives; these in turn have frequently been cyclised to methylhydroxyquinolines. We therefore examined the reaction occurring between ethyl acetoacetate and the more readily available pyridylanilides.

4-α-Pyridylaniline failed to react to any useful extent with ethyl acetoacetate when the mixture was heated at 180° for 4 hours. A small yield of *acetoacet*-4-α-*pyridylanilide* was obtained by condensation in boiling xylene solution in presence of phosphorus oxychloride (cf. Coffey, Thompson, and Wilson, J., 1936, 856) or pyridine, but more satisfactory was condensation in presence of excess of acetoacetic ester at 160—170° (Fierz-David and Ziegler, *Helv. Chim. Acta*, 1928, **11**, 779). The β- and the γ-isomeride were obtained similarly. These acetoacetanilides, however, failed to cyclise on heating with sulphuric acid or thionyl chloride. On

heating in absence of condensing agent, s.-*bispyridylphenylureas* and unidentified products were formed; no evidence of the formation of pyridylmethylhydroxyquinolines was found and the investigation was discontinued.

Experimental.

α-3-*Amino*-4-*methoxyphenylpyridine*.—α-3-Nitro-4-methoxyphenylpyridine (27 g.) (Haworth, Heilbron, and Hey, J., 1940, 361) in ethanol (200 c.c.) was reduced with stannous chloride (150 g.) and hydrochloric acid (180 c.c.), a large excess of 30% caustic soda solution added, and the base extracted with ether; distillation at 210—215°/3 mm. gave a pale yellow, viscous liquid (20 g.) which gradually solidified. Crystallisation from light petroleum (b. p. 60—80°) gave α-3-*amino*-4-*methoxyphenylpyridine* in long needles, m. p. 98° (Found: C, 71·8; H, 6·2. $C_{12}H_{12}ON_2$ requires C, 72·0; H, 6·0%). Warming a portion on the steam-bath with acetic anhydride gave α-3-*acetamido*-4-*methoxyphenylpyridine*, which crystallised from benzene–light petroleum (b. p. 60—80°) in needle clusters, m. p. 171—172° (Found: C, 69·3; H, 5·8. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 5·8%).

8-*Methoxy*-5-α-*pyridylquinolines*.—α-3-Amino-4-methoxyphenylpyridine (19 g.) was heated with anhydrous glycerol (30 g.), concentrated sulphuric acid (28 g.), and anhydrous arsenic acid (14 g.) at 160—170° for 6 hours, the mass treated as described (preceding paper) for the preparation of 6-α-pyridylquinoline, and the base extracted with benzene. After removal of benzene, distillation at 130—160° in a high vacuum gave a very viscous, brown liquid (16 g.), which was treated with a solution of picric acid (2 mols.) in alcohol. Crystallisation of the product from methyl ethyl ketone gave the pure *picrate* (26 g.) in long prismatic needles, m. p. 196—198° (decomp.) (Found: N, 15·2. $C_{15}H_{12}ON_2,C_6H_3O_7N_3$ requires N, 15·0%). Dilute caustic soda solution liberated 8-*methoxy*-5-α-*pyridylquinoline*, which separated from light petroleum (b. p. 60—80°) in small prisms, m. p. 115—116° (Found: C, 76·4; H, 5·1. $C_{15}H_{12}ON_2$ requires C, 76·3; H, 5·1%).

α-3-*Amino*-6-*methoxyphenylpyridine*.—α-5-Nitro-2-methoxyphenylpyridine (8·8 g.) (Haworth, Heilbron, and Hey, J., 1940, 359) in ethanol (80 c.c.) was reduced with stannous chloride (50 g.) and hydrochloric acid (50 c.c.), 30% caustic soda solution added, and the base extracted with ether. After removal of ether, α-3-amino-6-methoxyphenylpyridine remained as a viscous liquid (7·0 g.), which became semi-solid after 24 hours. Warming a portion with acetic anhydride gave α-3-*acetamido*-6-*methoxyphenylpyridine*, which separated from benzene–light petroleum (b. p. 40—60°) in silky needles, m. p. 168—169° (Found: C, 69·7; H, 5·9. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 5·8%).

6-*Methoxy*-5(and 7)-α-*pyridylquinoline*.—α-3-Amino-6-methoxyphenylpyridine (7·0 g.) was heated with anhydrous glycerol (14 g.), concentrated sulphuric acid (13 g.), and anhydrous arsenic acid (7·0 g.). After boiling for 4 hours, the mixture was cooled, diluted with water (2 vols.), filtered after 12 hours, and made alkaline. The precipitated tarry oil was extracted with benzene. After removal of benzene, distillation at 167—180°/0·04 mm. gave a yellowish-brown viscous liquid (4·9 g.). It was treated with picric acid (2 mols.) in ethanol, and the resulting picrates crystallised from acetone. Numerous crystallisations gave a pure *picrate* (3·4 g.) in small prisms, decomp. 222° (Found: N, 15·3. $C_{15}H_{12}ON_2,C_6H_3O_7N_3$ requires N, 15·0%), from which dilute caustic soda solution liberated 6-*methoxy*-5(or 7)-α-*pyridylquinoline*; this crystallised from light petroleum (b. p. 40—60°) in small needles, m. p. 100—101° (Found: C, 76·6; H, 5·2. $C_{15}H_{12}ON_2$ requires C, 76·3; H, 5·1%). From the mother-liquors, a second pure picrate was obtained in hard needles (3·1 g.), m. p. 215—216° (decomp.). 6-*Methoxy*-7(or 5)-α-*pyridylquinoline* separated from light petroleum (b. p. 40—60°) in long prismatic needles, m. p. 95° (after drying at 45° in a high vacuum) (Found: C, 76·4; H, 5·3%).

5-*Amino*-6-*methoxyquinoline*.—6-Methoxyquinoline (38 g.; b. p. 166—167°/22 mm.), prepared from *p*-anisidine (50 g.) by means of the Skraup reaction, was converted into 5-nitro-6-methoxyquinoline (36 g.; m. p. 104—105°) by treatment with fuming nitric acid at 0° (Jacobs and Heidelberger, *loc. cit.*). Reduction with iron filings and alcoholic hydrochloric acid gave 5-amino-6-methoxyquinoline (27 g.; m. p. 153—154°). The constitution of the 5-nitro-6-methoxyquinoline was proved by heating with concentrated hydrochloric acid in a sealed tube for 5 hours at 180°, 5-nitro-6-hydroxyquinoline, m. p. 136—137° (lit., m. p. 136°, 138—139°, 139—140°), being obtained.

Preparation of a Triazen from 5-*Amino*-6-*methoxyquinoline*.—A diazonium solution prepared from 5-amino-6-methoxyquinoline (5 g.) was added slowly with stirring to an aqueous solution of dimethylamine (5 c.c.; 33%) and sodium carbonate (cf. B.P. 513,846). The separated brown solid was purified by passing its benzene solution through a column of alumina. After removal of most of the benzene and addition of light petroleum, the *triazen* separated in pale yellow needles (3·5 g.), m. p. 82—83° (Found: C, 63·0; H, 6·1. $C_{12}H_{14}ON_4$ requires C, 62·6; H, 6·1%).

6-*Methoxy*-8-α(β and γ)-*pyridylquinoline*.—8-Amino-6-methoxyquinoline (20 g.) was dissolved in concentrated hydrochloric acid (25 c.c.) and water (75 c.c.) at 90°, hydrochloric acid (25 c.c.) added, and the whole cooled in a freezing mixture; the paste formed was diazotised at 0—5° with sodium nitrite (8·4 g.). The diazonium solution was stirred during 1½ hours into pyridine (350 g.) at 40—50°, after a further hour's stirring at 40—50° a concentrated solution of caustic soda added, and the pyridine layer separated. Excess of pyridine was removed in steam, and the tarry residue extracted with benzene. After removal of the benzene, distillation at 150—180°/0·002 mm. gave a very viscous, red-brown oil (10·0 g.). This was treated with a hot solution of picric acid (2 mols.) in alcohol, and the resulting mixed picrates crystallised from glacial acetic acid. After several crystallisations, a pure *picrate*, separating in long orange needles (2·8 g.), m. p. 247—248°, was obtained (Found: C, 54·3; H, 3·5; N, 14·7. $C_{15}H_{12}ON_2,C_6H_3O_7N_3$ requires C, 54·2; H, 3·2; N, 15·0%), from which dilute caustic soda solution liberated 6-*methoxy*-8-α-*pyridylquinoline*; this separated from benzene–light petroleum (b. p. 40—60°) in prisms, m. p. 106—107° (Found: C, 76·1; H, 5·1. $C_{15}H_{12}ON_2$ requires C, 76·3; H, 5·1%). The mixed picrates obtained from the mother-liquors were extracted with acetone and from the acetone solution a pure *picrate*, crystallising in needle clusters, m. p. 260° (decomp.), was obtained (Found: C, 54·4; H, 3·2%). Treatment with dilute caustic soda solution liberated 6-*methoxy*-8-γ-*pyridylquinoline*, which separated from benzene–light petroleum (b. p. 60—80°) in small prisms, m. p. 146° (Found: C, 76·2; H, 5·1%). Fractional crystallisation from methyl ethyl ketone of the material remaining after the acetone extraction gave a third pure *picrate* in needle clusters, m. p. 243—244° (Found: N, 14·8%), from which 6-*methoxy*-8-β-*pyridylquinoline* was isolated; it separated from benzene–light petroleum (b. p. 60—80°) in prisms, m. p. 100° (Found: C, 76·5; H, 5·1%). The identity of 8-α- and 8-β-pyridyl-6-methoxyquinoline with the corresponding compounds prepared as described below was shown by means of mixed melting-points.

Nitration of α-3-*Methoxyphenylpyridine*.—To a solution of α-3-methoxyphenylpyridine (4·0 g.) (Haworth, Heilbron, and Hey, J., 1940, 361) in glacial acetic acid (20 c.c.), nitric acid (*d* 1·5; 8 c.c.) was added in small portions. After refluxing for 1 hour, the mixture was cooled and poured into dilute caustic soda solution, and the liquid product extracted with benzene. After removal of solvent the residual oil was treated with alcoholic picric acid, and the resulting picrates crystallised from acetone. Numerous crystallisations gave α-2-*nitro*-5-*methoxyphenylpyridine picrate* in small rectangular prisms, m. p. and mixed m. p. with the corresponding compound prepared as described below, 190—191° (Found: N, 15·0. $C_{12}H_{10}O_3N_2,C_6H_3O_7N_3$ requires N, 15·2%). Fractionation of the more soluble portion of the mixed picrates from benzene gave a second *isomeride* in needle clusters, m. p. 155—156° (Found: N, 15·0%); a third *isomeride*, m. p. 273°, was obtained in orange needles (alcohol) by passing a solution of the remaining material in benzene through a column of alumina and washing with alcohol–benzene (1 : 1) (Found: N, 15·2%).

*Action of Diazotised 4-Nitro-*m*-anisidine on Pyridine.*—4-Nitro-*m*-anisidine (16·5 g.) (Reverdin and Widmer, *Ber.*, 1913, **46**, 4071) was suspended in hydrochloric acid (29 c.c.) and water (24 c.c.) and diazotised with a solution of sodium nitrite (7·1 g.) in water (24 c.c.) at 15°. After removal of insoluble matter, the diazonium solution was added during 1 hour to pyridine (250 c.c.) at 50—55°. Stirring was continued for a further hour at 50—60°. Excess of a concentrated solution of caustic soda was added, the pyridine layer distilled in steam, and the residue extracted with benzene. After removal of benzene, distillation under reduced pressure gave a pale yellow solid (5 g.), b. p. 90—135°/1 mm., and a reddish-brown oil (5 g.), b. p. 135—175°/1 mm. The first fraction crystallised from dilute alcohol in needles, m. p. and mixed m. p. with *p*-nitroanisole 52—53°. The second fraction was treated with alcoholic picric acid and by fractional crystallisation of the resulting mixed picrates from acetone, two pure isomerides were obtained. The less soluble *β-2-nitro-5-methoxyphenylpyridine picrate* separated in fine needles (1·2 g.), m. p. 202—204° (Found: N, 15·0. $C_{12}H_{10}O_3N_2,C_6H_3O_7N_3$ requires N, 15·2%), whereas the more soluble *α*-2-nitro-5-methoxyphenylpyridine picrate separated in small prisms (1·0 g.), m. p. and mixed m. p. with the corresponding compound prepared as described above 190—191°. On treatment with dilute caustic soda solution the former gave *β-2-nitro-5-methoxypyridine*, which separated from light petroleum (b. p. 60—80°) in needles, m. p. 91—92° (Found: C, 62·6; H, 4·6. $C_{12}H_{10}O_3N_2$ requires C, 62·6; H, 4·3%), and the latter gave *α-2-nitro-5-methoxyphenylpyridine*, which crystallised from benzene–light petroleum (b. p. 60—80°) in long needles, m. p. 76° (Found: C, 62·8; H, 4·5%).

β-2-Nitro-5-methoxyphenylpyridine (0·5 g.) in ethanol (5 c.c.) was reduced with stannous chloride (2·0 g.) and concentrated hydrochloric acid (3 c.c.), excess of 30% caustic soda solution added, and the base extracted with benzene. After removal of solvent, the residue was crystallised from benzene–light petroleum (b. p. 60—80°), *β-2-amino-5-methoxyphenylpyridine* being obtained in small needle clusters, m. p. 131—132° (Found: C, 72·2; H, 6·2, $C_{13}H_{12}ON_2$ requires C, 72·0; H, 6·0%). A solution of this base (0·2 g.) in concentrated hydrochloric acid (0·5 c.c.) and water (0·5 c.c.) was diazotised at 0·5° with a solution of sodium nitrite (0·07 g.) in water (0·5 c.c.). A cold solution of stannous chloride (1 g.) in hydrochloric acid (2 c.c.) was then added and after 1 hour the *β*-2-hydrazino-5-methoxyphenylpyridine was liberated with aqueous sodium hydroxide and extracted with benzene. The product obtained on removal of solvent was dissolved in glacial acetic acid (1 c.c.), and powdered copper acetate (0·4 g.) added. After removal of copper as sulphide, the filtrate was made alkaline and extracted with ether. Removal of the ether from the dried extract left *β*-3-methoxyphenylpyridine as an oil, which was treated with alcoholic picric acid. Crystallisation of the resulting picrates from alcohol yielded *β-3-methoxyphenylpyridine picrate* in needles, m. p. 160—162° (Found: N, 13·5. $C_{12}H_{11}ON,C_6H_3O_7N_3$ requires N, 13·6%).

γ-3-Nitrophenylpyridine, prepared from diazotised *m*-nitroaniline and pyridine (Haworth, Heilbron, and Hey, J., 1940, 353), was reduced to *γ*-3-aminophenylpyridine with stannous chloride and hydrochloric acid (Heilbron, Hey, and Lambert, J., 1940, 1279). The base (0·75 g.) in concentrated sulphuric acid (3 c.c.) and water (30 c.c.) was diazotised at 0—5° with an aqueous solution of sodium nitrite (0·32 g.) and added in a thin stream to a boiling mixture of concentrated sulphuric acid (8 c.c.) and water (10 c.c.). When evolution of nitrogen had ceased, the solution was diluted, neutralised with aqueous caustic soda, and acidified with glacial acetic acid. Crystallisation of the resultant precipitate from alcohol gave *γ-3-hydroxyphenylpyridine* in colourless prisms, m. p. 227—228° (Found: C, 77·0; H, 5·4. $C_{11}H_9ON$ requires C, 77·2; H, 5·3%). The hydroxy-compound (0·2 g.) in ether (50 c.c.) was treated with a large excess of diazomethane in the same solvent and kept overnight. After filtration and evaporation the residual oil was treated with alcoholic picric acid (1 mol.). Crystallisation of the resulting picrate from acetone gave *γ*-3-methoxyphenylpyridine picrate in long prisms, m. p. 202—203°, both alone and mixed with the compound of similar m. p. isolated from the product of the reaction between diazotised *m*-anisidine and pyridine (Haworth, Heilbron, and Hey, J., 1940, 361).

A solution of *α*-2-nitro-5-methoxyphenylpyridine (0·3 g.) in ethanol (5 c.c.) was reduced with stannous chloride (1·5 g.) and concentrated hydrochloric acid (2 c.c.), excess of 30% sodium hydroxide solution added, and the base extracted with ether. A portion of the semi-solid product obtained on removal of the solvent was treated with alcoholic picric acid, and the resulting picrate crystallised from ethanol. *α-2-Amino-5-methoxyphenylpyridine picrate* separated in fine needles, m. p. and mixed m. p. with the corresponding compound prepared as above, 193—194° (Found: N, 16·2. $C_{13}H_{12}ON_2,C_6H_3O_7N_3$ requires N, 16·3%).

6-Methoxy-8-α- and *-β-pyridylquinoline.*—*α*-2-Amino-5-methoxyphenylpyridine (0·2 g.) was refluxed with sulphuric acid (66%, 2·4 g.), glycerol (0·5 g.), and sodium *m*-nitrobenzenesulphonate (0·5 g.) for 6 hours. The mixture was cooled, diluted, filtered, and made alkaline. After 12 hours, the tarry precipitate was extracted with benzene. The viscous oil left on removal of solvent was treated with alcoholic picric acid, and the resulting picrate crystallised from glacial acetic acid. 6-Methoxy-8-*α*-pyridylquinoline picrate was obtained in orange-yellow needles, m. p. and mixed m. p. with the corresponding compound prepared as described above, 247—248°. Treatment of this picrate with dilute sodium hydroxide solution liberated the free base, m. p. 106—107° alone and on admixture with the base of the same m. p. obtained as described above. *β*-2-Amino-5-methoxyphenylpyridine was also submitted to the Skraup reaction. 6-Methoxy-8-*β*-pyridylquinoline yielded a picrate, m. p. 243—244°, both alone and on admixture with the picrate of the same m. p. already described.

2-Amino-5-methoxyphenylpyridine via *3-Nitro*-p-*anisidine.*—Phthalic anhydride (100 g.) and 3-nitro-*p*-anisidine (88 g.) were fused together at 170° for 6 hours. After cooling, the solid cake was powdered and crystallised from glacial acetic acid. *Phthalo-3-nitro*-p-*anisidide* separated in yellow plates (130 g.), m. p. 150° (Found: C, 60·4; H, 3·4. $C_{15}H_{10}O_5N_2$ requires C, 60·4; H, 3·4%). To a solution of the phthaloyl compound (130 g.) in alcohol (1960 c.c.), water (22 c.c.), hydrochloric acid (9 c.c.), and iron filings (130 g.) were added and the whole was refluxed for 24 hours. After being made alkaline, the liquid was filtered, and the sludge extracted with alcohol. *4-Phthalo-3-amino*-p-*anisidide* crystallised from the combined alcoholic filtrate and extracts in yellow needles (88 g.), m. p. 188° (Found: C, 67·0; H, 4·6. $C_{15}H_{12}O_3N_2$ requires C, 67·2; H, 4·5%). Finely powdered 4-phthalo-3-amino-*p*-anisidide (88 g.), suspended in hydrochloric acid (102 c.c.) and water (75 c.c.), was diazotised with sodium nitrite (23 g.) in water (60 c.c.) at 10°. After filtering from a little insoluble matter, the diazonium solution was added during 1½ hours with stirring to pyridine (750 c.c.) at 50—55°. After being stirred for a further hour at 50—55°, the solution was poured into water, and the precipitated oil extracted with benzene. The residue, after removal of benzene, was refluxed for 1 hour with excess of hydrochloric acid. The acid solution was basified, and the precipitated oil extracted with benzene. After removal of the benzene, distillation at 160—170°/<1 mm. gave a red-brown oil (10 g.) which solidified on cooling. This solid was treated with alcoholic picric acid; crystallisation of the resulting mixed picrates from acetone gave *α-2-amino-5-methoxyphenylpyridine* picrate in fine needles, m. p. 193—194° both alone and mixed with the picrate of same m. p. prepared as described above.

5-Nitro-6-methoxy-8-α-pyridylquinoline.—6-Methoxy-8-*α*-pyridylquinoline (2·1 g.) was added in small portions to nitric acid (*d* 1·5; 10 c.c.) at 0°. After a further ½ hour's stirring at 0° the solution was diluted with ice-water and made alkaline. Repeated crystallisation of the precipitate from acetone gave the *nitro*-compound in fine, pale yellow needles, m. p. 192—193° (Found: C, 64·3; H, 3·9. $C_{15}H_{11}O_3N_3$ requires C, 64·1; H, 3·9%).

5-Amino-6-methoxy-8-α-pyridylquinoline.—To a solution of 5-nitro-6-methoxy-8-*α*-pyridylquinoline (1·4 g.) in alcohol (50 c.c.), water (0·3 c.c.), hydrochloric acid (0·2 c.c.), and iron filings (1·7 g.) were added and the whole stirred under

reflux on the steam-bath for 24 hours. After being made alkaline with caustic soda solution, the liquid was filtered, the sludge extracted with alcohol, and the combined extracts and filtrate evaporated to dryness. Crystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave the *base* in small orange-yellow prisms (0·8 g.), m. p. 124—125° (Found : C, 71·6; H, 5·0. $C_{15}H_{13}ON_3$ requires C, 71·7; H, 5·2%).

6-*Pyridylquinaldine*.—α-4-Aminophenylpyridine (5 g.) was heated with concentrated hydrochloric acid (150 c.c.) and paraldehyde (5 g.) on the steam-bath for several hours and the product was diluted with water (2 vols.), kept overnight, and filtered. The filtrate was made alkaline with dilute caustic soda solution, and the precipitated base extracted with benzene. After removal of benzene, distillation at 160° in a high vacuum gave 6-*α-pyridylquinaldine* as a greenish-yellow solid, which crystallised from light petroleum (b. p. 40—60°) in colourless needles (1·7 g.), m. p. 106—107° (Found : C, 81·9; H, 5·4. $C_{15}H_{12}N_2$ requires C, 81·8; H, 5·4%). β-4-Aminophenylpyridine (15 g.) was similarly treated; after removal of the benzene, distillation at 150°/0·001 mm. gave a viscous brown oil (5 g.), which separated from light petroleum (b. p. 40—60°) in colourless prismatic needles of 6-*β-pyridylquinaldine*, m. p. 65—66° (Found : C, 81·8; H, 5·3%). From γ-4-aminophenylpyridine (3·2 g.), after similar treatment (concentrated hydrochloric acid, 50 c.c.; paraldehyde, 4 g.; distillation of the benzene residue at 150—180° in a high vacuum), a brown-yellow solid was obtained, which was purified by passage of its solution in benzene through a column of alumina. Partial removal of the solvent deposited 6-*γ-pyridylquinaldine* in colourless needles, m. p. 186° (Found : C, 81·8; H, 5·4%).

Pyridylatophans.—α-4-Aminophenylpyridine (5 g.), benzaldehyde (3·1 g.), and pyruvic acid (2·6 g.) were refluxed in ethanol (80 c.c.) for 4 hours. 2-*Phenyl*-6-*α-pyridylquinoline*-4-*carboxylic acid* (1·2 g.) separated from the hot solution. It crystallised from ethanol in needles, m. p. 287—288° (decomp.) (Found : C, 77·0; H, 4·6. $C_{21}H_{14}O_2N_2$ requires C, 77·3; H, 4·3%). 2-*Phenyl*-6-*β-pyridylquinoline*-4-*carboxylic acid*, obtained similarly, crystallised from acetic acid or much ethanol in plates, m. p. 301° (decomp.) (Found : C, 77·8; H, 4·3%).

3-*Nitro*-4-tert.-*butylpyridylbenzenes*.—2-Nitro-4-amino-*tert*.-butylbenzene (48 g.) was suspended in concentrated hydrochloric acid (90 c.c.) and water (60 c.c.) and diazotised at 0° with sodium nitrite (17 g.). The filtered solution was added gradually to pyridine (300 c.c.) at 40—50°. After standing, the upper layer was decanted and a further quantity of pyridine solution was obtained by basifying the lower layer with ammonia. The mixed pyridine solution was treated with sodium hydroxide, and pyridine distilled in steam. The oily residue was extracted with benzene, and the extract distilled, eventually in a vacuum. The nitrobutylpyridylbenzene was obtained as an oil (37 g.), b. p. 190—210°/0·01 mm., and the mixture was converted into a mixture of picrates, which were fractionally crystallised first from acetone and then from methyl ethyl ketone. Three apparently pure *picrates* were obtained (given here in order of increasing solubility) : A, probably the β-isomeride, m. p. 217—218° (Found : N, 14·6. $C_{15}H_{16}O_2N_2,C_6H_3O_7N_3$ requires N, 14·4%); B, probably the γ-isomeride, m. p. 231° (decomp.) (Found : N, 14·3%); C, probably the α-isomeride, m. p. 160° (Found : N, 14·5%).

Picrate A (3 g.) was heated on the steam-bath for 2 hours with 5% aqueous sodium hydroxide (25 c.c.). On dilution, extraction with benzene, and distillation of the extract in a vacuum a pure *β(?)-isomeride* of 3-nitro-4-*tert*.-butylpyridylbenzene was obtained as a faintly yellow oil distilling at 130° in a high vacuum (yield, 2 g.) (Found : C, 70·7; H, 6·3. $C_{15}H_{16}O_2N_2$ requires C, 70·3; H, 6·3%). The preceding nitro-compound (2 g.) in ethanol (25 c.c.) was added slowly to stannous chloride (10 g.) in concentrated hydrochloric acid (10 c.c.), and the whole refluxed for 2 hours. Ethanol was removed, and the residue suspended in water (10 c.c.) and basified with 50% aqueous sodium hydroxide. 3-Amino-4-*tert*.-butylpyridylbenzene was extracted with benzene and was obtained, after removal of solvent, as a colourless solid crystallising from benzene.

2-*Nitro*-4-tert.-*butylpyridylbenzene*.—4-Nitro-, 4-amino-, 4-acetamido-, 3-nitro-4-acetamido-, and 3-nitro-4-amino-*tert*.-butylbenzene were prepared according to Gelzer's methods (*Ber*., 1887, **20**, 3257). The nitroamine (78 g.) in a mixture of concentrated hydrochloric acid (200 c.c.) and water (150 c.c.) was diazotised at 0° with sodium nitrite (27·5 g.) in a little water. The filtered diazo-solution was added slowly to pyridine (490 c.c.), stirring being maintained at 40—50° for 1 hour afterwards. The product was worked up as in the case of the isomeride above to give 2-*nitro*-4-tert.-*butylpyridylbenzene* as an oil, b. p. 170—190°/0·05 mm. (31 g.) (Found : C, 70·4; H, 6·3%).

The preceding nitro-compound (31 g.) in ethanol (250 c.c.) was added slowly to stannous chloride (135 g.) in concentrated hydrochloric acid (100 c.c.), the whole refluxed for 2 hours, the ethanol distilled off, the residue made alkaline with 50% aqueous sodium hydroxide, and the organic base extracted with benzene. The extract was distilled in a vacuum and collected at 136—141°/0·02 mm. to give 2-*amino*-4-tert.-*butylpyridylbenzene* (22 g.) (Found : C, 79·4; H, 8·3. $C_{15}H_{18}N_2$ requires C, 79·5; H, 8·0%). This base (22 g.), 64% aqueous sulphuric acid (146 g.), glycerol (33·5 g.), and sodium *m*-nitrobenzenesulphonate (39 g.) were refluxed with stirring at 160° (bath temperature) for 6·5 hours. The cold solution was filtered, made alkaline with ammonia, and, after standing, the tarry deposit was extracted with benzene. Solvent was removed from the extract, and the residue distilled in a vacuum. 8-*Pyridyl*-5-tert.-*butylquinoline*, distilled repeatedly at 120° in a high vacuum, was a pale yellow oil (Found : C, 82·8; H, 7·0. $C_{18}H_{18}N_2$ requires C, 82·5; H, 6·9%).

A mixture of α-3-nitro-4-aminophenylpyridine (preceding paper) (16 g.), caustic potash (50 g.), and water (100 c.c.) was refluxed for 24 hours, the solution made faintly acid with acetic acid, and the precipitate recrystallised from benzene–light petroleum (b. p. 40—60°). α-3-*Nitro*-4-*hydroxyphenylpyridine* was obtained in yellow needles (11·5 g.), m. p. 125° (Found : C, 61·5; H, 3·6. $C_{11}H_8O_3N_2$ requires C, 61·1; H, 3·7%). Methylation with diazomethane in ether gave α-3-nitro-4-methoxyphenylpyridine, m. p. 85—86°, identical with that prepared by Haworth, Heilbron, and Hey (J., 1940, 361).

α-3-Nitro-4-hydroxyphenylpyridine (11 g.) was dissolved in 5% caustic soda solution (165 c.c.), and sodium hydrosulphite (44 g.) added gradually until no further change in colour took place. The solution was then made slightly acid with glacial acetic acid and thoroughly extracted with ether. After washing and removal of ether, the residue was distilled at 195—197°/0·02 mm. Yield, 6 g. Recrystallisation from alcohol–light petroleum (b. p. 40—60°) gave colourless prisms of solvated material melting constantly at 144°. Recrystallisation from benzene gave silky needles of unsolvated α-3-*amino*-4-*hydroxyphenylpyridine*, m. p. 166—167° (Found : C, 71·2; H, 5·3; N, 15·1. $C_{11}H_{10}ON_2$ requires C, 71·0; H, 5·4; N, 15·1%).

A mixture of α-3-amino-4-hydroxyphenylpyridine (2 g.), 63% sulphuric acid (12 g.), glycerol (2·4 g.), and sodium *m*-nitrobenzenesulphonate (2 g.) was heated in an oil-bath at 160° for 5 hours, the solution cooled and diluted with water (10 c.c.), and 10% caustic soda solution added until no further precipitation took place. After 12 hours, the solid was collected, dried, and recrystallised from benzene–light petroleum, giving pale yellow needles of 8-*hydroxy*-5-*α-pyridylquinoline*. Sublimation at 80° in a high vacuum gave colourless needles (1 g.), m. p. 133·5—134° (Found : C, 76·0; H, 4·7. $C_{14}H_{10}ON_2$ requires C, 75·7; H, 4·5%). The hydroxy-compound (0·2 g.) was added to excess of diazomethane in ether and after 24 hours the deep red solid was collected and recrystallised from benzene, in which it gave a blue solution and was sparingly soluble. The *substance* blackened at 140° but did not melt below 250° (Found : N, 11·5. $C_{15}H_{12}ON_2$ requires N, 11·9%. $C_{15}H_{14}O_2N_2$ requires N, 11·3%). To a solution of the pyridylhydroxyquinoline (0·25 g.) and potassium hydroxide (0·125 g.) in water (3 c.c.), methyl sulphate (0·145 g.) was added. The solution was maintained at 70° for 20 mins., cooled, made strongly alkaline with more caustic potash, and extracted with benzene (charcoal).

The solvent was removed, and the residue converted into the picrate, which, recrystallised from acetone, had m. p. 194—196°, alone or mixed with authentic 8-methoxy-5-α-pyridylquinoline picrate.

Pyridylquinoxalines.—β-4-Acetamidophenylpyridine (11·5 g.), obtained from β-4-nitrophenylpyridine (Heilbron, Hey, and Lambert, J., 1940, 1279), was added gradually to nitric acid (47 c.c., *d* 1·5) at 0° as described for the α-isomer (preceding paper). The product was recrystallised from acetone, giving yellow micro-needles of *β-3-nitro-4-acetamidophenylpyridine* (11 g.), m. p. 169° (decomp.) (Found : N, 16·2. $C_{13}H_{11}O_3N_3$ requires N, 16·3%). This acetyl compound (10 g.) was boiled for 20 minutes with 20% caustic potash solution. The product was collected and recrystallised from methanol, giving orange-red needles of *β-3-nitro-4-aminophenylpyridine* (6·5 g.), m. p. 176—177° (Found : N, 19·65. $C_{11}H_9O_3N_3$ requires N, 19·5%). The preceding nitro-compound (6 g.) in a mixture of ethyl acetate (200 c.c.) and ethanol (24 c.c.) was reduced catalytically with hydrogen and Adams's catalyst (0·2 g.). The solution was filtered, solvent removed in a vacuum, and the residue crystallised from benzene–light petroleum (b. p. 40—60°), giving pale fawn leaflets of *β-3 : 4-diaminophenylpyridine* (4·6 g.), m. p. 122—123° (Found : C, 71·4; H, 6·0; N, 23·0. $C_{11}H_{11}N_3$ requires C, 71·4; H, 6·0; N, 22·7%). The diamine (1 g.) in water (12 c.c.) was treated with a suspension of glyoxal sodium bisulphite compound (3 g.) in water (5 c.c.), glacial acetic acid (3 c.c.) added, and the mixture heated for 1 hour at 70°. After standing for 1 hour at room temperature, the solution was made alkaline, and the resulting fawn precipitate crystallised from benzene–light petroleum (b. p. 40—60°), giving pale yellow needles of *6-β-pyridylquinoxaline* (0·65 g.), m. p. 144—145° (Found : N, 20·5. $C_{13}H_9N_3$ requires N, 20·3%). To the diamine (0·5 g.) in methanol (3 c.c.) and glacial acetic acid (0·5 c.c.), a solution of benzil (0·5 g.) in methanol (3 c.c.) was added. The mixture was heated at 100° for 10 mins., most of the alcohol removed, the solution made alkaline, and the product crystallised from benzene–light petroleum (b. p. 40—60°), giving colourless prisms of *6-β-pyridyl-2 : 3-diphenylquinoxaline* (0·4 g.), m. p. 194·5—196·5° (Found : N, 11·8. $C_{25}H_{17}N_3$ requires N, 11·7%). A solution of isatin (1·1 g.) in methanol (20 c.c.) and glacial acetic acid (3 c.c.) was added to a solution of the diamine (1·2 g.) in methanol (6 c.c.) and heated on the steam-bath for 5 hours, a yellow solid separating. The solution was kept overnight and then made alkaline with 10% caustic soda solution, and the product crystallised from *cyclo*hexanone, giving two fractions. These were sublimed in a high vacuum at 160° and recrystallised from aqueous pyridine. Two pure products, both crystallising in yellow needles, m. p. 275—276° (Found : N, 19·0. $C_{19}H_{12}N_4$ requires N, 18·9%), and m. p. 307—308° (decomp.) (Found : N, 18·7%), were obtained.

Pyridylacetoacetanilides.—4-Pyridylaniline (5 g.) was dissolved in xylene (50 c.c.) and heated to boiling. A mixture of ethyl acetoacetate (8 g.), pyridine (4 c.c.), and xylene (75 c.c.) was added during 1 hour, xylene being distilled as fast as the solution was added. Boiling was continued for 45 minutes; on cooling, the acetoacetanilide crystallised. The crude product was washed with ether and recrystallised from xylene. The following were prepared : *α-4-Pyridylaceto-acetanilide*, m. p. 136° (Found : N, 11·0. $C_{15}H_{14}O_2N_2$ requires N, 11·0%), *β-4-pyridylacetoacetanilide*, m. p. 154·5° (Found : N, 10·7%), *γ-4-pyridylacetoacetanilide*, m. p. 174° (Found : N, 11·0%). The α-acetoacetanilide (10 g.) was heated at 220° until effervescence ceased. When cold, the hard brown mass was warmed with 16% hydrochloric acid (15 c.c.), again cooled, and the bright yellow solid collected. After treatment with ammonia, *s.-bis-α-4-pyridylphenylurea* crystallised from ethanol in iridescent needles, m. p. 278° (decomp.) (Found : N, 15·3; *M*, cryoscopic in camphor, 364. $C_{23}H_{18}ON_4$ requires N, 15·3%; *M*, 366).

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