38. *Attempts to find New Antimalarials. Part XVIII. Derivatives of* m-*Phenanthroline.*

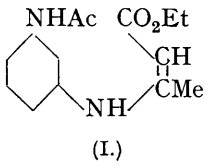
By William O. Kermack and William Webster.

Evidence is adduced that the compound formed by cyclisation of ethyl β-3-acetamidophenylaminocrotonate is 5-*acetamido*-4-*hydroxy*-2-*methylquinoline* and not 7-acetamido-4-hydroxy-2-methylquinoline. *m*-Phenylenediamine condenses with ethyl oxaloacetate as with ethyl acetoacetate to yield the 7- and not the 5-aminoquinoline derivative. Various 2- and 4-hydroxy- and -chloro-derivatives of 5 : 6 : 2′ : 3′- and 7 : 8 : 2′ : 3′-pyridoquinoline have been prepared, and the latter condensed with β-diethylaminoethylamine and δ-diethylamino-α-methylbutylamine to yield the following bases: 4-(β-diethylaminoethylamino)- and 4-(δ-diethylamino-α-methylbutylamino)-2-methyl-5 : 6 : 2′ : 3′-pyridoquinoline; 4-(β-*diethylaminoethylamino*)-2-*methyl*-7 : 8 : 2′ : 3′-*pyridoquinoline* and 4-(δ-diethylamino-α-methylbutylamino)-2-methyl-7 : 8 : 2′ : 3′-pyridoquinoline; 2-(β-*diethylaminoethylamino*)-4-*methyl*-7 : 8 : 2′ : 3′-*pyridoquinoline* and 2-(δ-diethylamino-α-methylbutylamino)-4-methyl-7 : 8 : 2′ : 3′-pyridoquinoline; 2-(β-diethylaminoethylamino)- and 2-(δ-diethylamino-α-methylbutylamino)-5 : 6 : 2′ : 3′-pyridoquinoline.

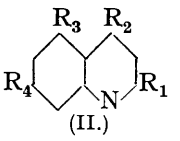
It is shown that the chloro-derivative formed by oxidation of *m*-phenanthroline methosulphate to *N*-methylphenanthrolone, followed by treatment of the latter with phosphorus oxychloride and pentachloride, is 2-chloro-5 : 6 : 2′ : 3′ -pyridoquinoline.

Backeberg (J., 1935, 1568) prepared ethyl β-3-acetamidophenylaminocrotonate (I) by the condensation of *m*-aminoacetanilide and ethyl acetoacetate, but he states that he was unable to effect its cyclisation by the method of Conrad and Limpach to 5- or 7-acetamido-4-hydroxy-2-methylquinoline. It has now been found possible to isolate from the product obtained by introducing the above compound into paraffin at 260°, a small yield of a crystalline product which in all probability is 5-*acetamido*-4-*hydroxy*-2-*methylquinoline* (II; R_1 = Me, R_2 = OH, R_3 = NHAc, R_4 = H). The reason for attributing to it this structure and not that of the isomeric 7-acetamido-derivative (II; R_1 = Me, R_2 = OH, R_3 = H, R_4 = NHAc), is the following. On hydrolysis, the compound yields an amino-4-hydroxy-2-methylquinoline, which when subjected to the Skraup synthesis is converted into **4**-*hydroxy*-2-*methyl*-5 : 6 : 2′ : 3′-*pyridoquinoline* (III; R_1 = Me, R_2 = OH) or 4-hydroxy-2-methyl-7 : 8 : 2′ : 3′-pyridoquinoline (IV; R_1 = Me, R_2 =

OH). The latter of these two compounds has been prepared by Hazlewood, Hughes, and Lions (*J. Proc. Roy. Soc. N.S. Wales*, 1937—38, **71**, 472) from 5-aminoquinoline and acetoacetic ester, and is



(I.)



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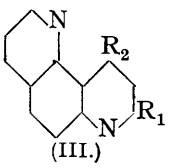

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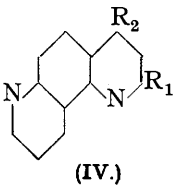

(IV.)

unmelted at 345°. We have repeated this synthesis and find that the m. p. is 395°, with previous darkening and sublimation at 300°. Furthermore, the *4-chloro-2-methyl-7 : 8 : 2′ : 3′-pyridoquinoline* (IV; R_1 = Me, R_2 = Cl) prepared from this compound by the action of phosphorus oxychloride and phosphorus pentachloride melts at 190°, and that from the new compound at 140°. It follows that the latter must be derived from *5-amino-4-hydroxy-2-methylquinoline* (II; R_1 = Me, R_2 = OH, R_3 = NH_2, R_4 = H). The possibility that the new compound produced by the Skraup reaction is 4-hydroxy-2-methyl-7 : 6 : 2′ : 3′-pyridoquinoline, formed from the 7-aminoquinoline derivative by addition of a pyridine ring so as to form a linear instead of an angular structure, may be neglected in view of the large mass of evidence which shows that an angular structure is formed in preference to a linear one when both are possible products of reaction.

Various workers have shown (cf. Besthorn and Byvanck, *Ber.*, 1898, **31**, 796; Capps and Hamilton, *J. Amer. Chem. Soc.*, 1938, **60**, 2104) that, when *m*-phenylenediamine is heated with ethyl acetoacetate in a sealed tube or an autoclave, 7-amino-2-hydroxy-4-methylquinoline (II; R_1 = OH, R_2 = Me, R_3 = H, R_4 = NH_2) is formed. Here ring closure takes place in a direction different from that found above. The fact that one amino-group remains free throughout the reaction and is not acetylated may account for the difference, though the different orientation of the methyl and the hydroxyl group in the resulting compound may also play some part. It is unnecessary to use a closed vessel; if the components are gently refluxed on a sand-bath until the mixture solidifies, a 60% yield of the product is obtained. The application of the Skraup synthesis to 7-amino-2-hydroxy-4-methylquinoline yields *2-hydroxy-4-methyl-7 : 8 : 2′ : 3′-pyridoquinoline* (IV; R_1 = OH, R_2 = Me), from which *2-chloro-4-methyl-7 : 8 : 2′ : 3′-pyridoquinoline* (IV; R_1 = Cl, R_2 = Me) is readily obtained by treatment with phosphorus oxychloride and pentachloride in a sealed tube at 120°.

When *m*-phenylenediamine is heated with ethyl oxaloacetate, ethyl 5 (or 7)-amino-2-hydroxyquinoline-4-carboxylate (II; R_1 = OH, R_2 = CO_2Et, R_3 = NH_2 or H, R_4 = H or NH_2) is obtained. On the analogy of the reaction with ethyl acetoacetate, the second of these two possible formulæ is the more probable. This view is confirmed in the following manner. The ester is hydrolysed to yield an amino-2-hydroxyquinoline-4-carboxylic acid, from which, on decarboxylation, an amino-2-hydroxyquinoline is obtained. That this is definitely 7-amino-2-hydroxyquinoline is shown by the fact that it is also obtained by oxidising 7-nitroquinoline with sodium hypochlorite according to the method of Capps and Hamilton (*loc. cit.*) to 7-nitro-2-hydroxyquinoline and reducing the latter. The amino-group must therefore be in the 7-position in the above compounds.

When the Skraup reaction is carried out on 7-amino-2-hydroxyquinoline, 2-hydroxy-7 : 8 : 2′ : 3′-pyridoquinoline (IV; R_1 = OH, R_2 = H) is obtained, from which 2-chloro-7 : 8 : 2′ : 3′-pyridoquinoline (IV; R_1 = Cl, R_2 = H) is formed by the action of phosphorus oxychloride and pentachloride.

By a similar series of reactions, 5-nitroquinoline may be converted into 5-nitro- and 5-amino-2-hydroxyquinoline (cf. Capps and Hamilton, *loc. cit.*). The application of the Skraup reaction to the latter compound results in the formation of *2-hydroxy-5 : 6 : 2′ : 3′-pyridoquinoline* (III; R_1 = OH, R_2 = H), from which the corresponding *2-chloro-5 : 6 : 2′ : 3′-pyridoquinoline* (III; R_1 = Cl, R_2 = H) is obtained by the action of phosphorus oxychloride and pentachloride.

2-Hydroxy-5 : 6 : 2′ : 3′-pyridoquinoline is mentioned in the literature as being obtained as a by-product when *m*-nitroaniline is subjected to the Skraup reaction (La Coste, *Ber.*, 1883, **16**, 674). Later work (cf. Matsumura, *J. Amer. Chem. Soc.*, 1930, **52**, 3974; Sucharda and Mazonski, *Ber.*, 1936, **69**, 2719) has, however, shown that the compound in question is almost certainly 8-hydroxy-5 : 6 : 2′ : 3′-pyridoquinoline. It melts at 159—160° and so is different from 2-hydroxy-5 : 6 : 2′ : 3′-pyridoquinoline now synthesised. This is in keeping with the view that the hydroxy-group is in the 8-position.

According to D.R.-P. 654,444 the oxidation of *m*-phenanthroline (5 : 6 : 2′ : 3′- or 7 : 8 : 2′ : 3′-pyridoquinoline) methosulphate by alkaline potassium ferricyanide yields a *N*-methylphenanthrolone, from which by treatment with a mixture of phosphorus oxychloride and pentachloride, a 2-chlorophenanthroline

is obtained, the m. p. of which is given as 151°. The precise constitutions of these two compounds do not seem so far to have been determined; it is clear that the first might be either 2-keto-1-methyl-1 : 2-dihydro-5 : 6 : 2′ : 3′-pyridoquinoline or 2-keto-1-methyl-1 : 2-dihydro-7 : 8 : 2′ : 3′-pyridoquinoline, and the second might be the 2-chloro-derivative of either 5 : 6 : 2′ : 3′- or 7 : 8 : 2′ : 3′-pyridoquinoline, according to which of the two nitrogen atoms of *m*-phenanthroline reacts with methyl sulphate. It is now shown that the chloropyridoquinoline obtained by this series of reactions is identical with 2-chloro-5 : 6 : 2′ : 3′-pyridoquinoline synthesised by the method described in the last paragraph, and distinct from the isomeric 2-chloro-7 : 8 : 2′ : 3′-pyridoquinoline. The methosulphate is therefore 1-methyl-5 : 6 : 2′ : 3′-pyridoquinolinium methyl sulphate, and the intermediate product is 2-keto-1-methyl-1 : 2-dihydro-5 : 6 : 2′ : 3′-pyridoquinoline.

In preparing the methosulphate, it was found that freshly distilled *m*-phenanthroline and methyl sulphate, refluxed in methyl-alcoholic solution, yielded a crystalline salt of the original base, $C_{12}H_8N_2$,$MeHSO_4$. When the freshly distilled base and methyl sulphate were warmed together, the product was not homogeneous, but fractional crystallisation gave the true methosulphate, m. p. 168—169° (the patent gives 171°). It seems that in presence of *m*-phenanthroline, methyl sulphate undergoes hydrolysis with peculiar ease, unless special precautions are taken to exclude all traces of water.

The bases listed in the summary were prepared by heating the appropriate chloro-compounds with β-diethylaminoethylamine or δ-diethylamino-α-methylbutylamine in presence of a trace of copper bronze.

Experimental.

5-Acetamido-4-hydroxy-2-methylquinoline.—Ethyl β-3-acetamidophenylaminocrotonate (10 g.), prepared by heating on a boiling water-bath an equimolecular mixture of ethyl acetoacetate and *m*-aminoacetanilide containing a drop of concentrated hydrochloric acid (cf. Coffey, Thomson, and Wilson, J., 1936, 856) and scratching the cooled product with light petroleum, was added to medicinal paraffin (400 c.c.) preheated to 270°. Ethyl alcohol was evolved and a heavy brown oil separated. When this had cooled, light petroleum was added, and a small quantity of a yellow crystalline product removed by filtration. The bulk of the product, however, remained in the flask as a sticky brown oil; this was washed with light petroleum and extracted several times with boiling water, from which, on cooling, *5-acetamido-4-hydroxy-2-methylquinoline* separated; recrystallised from hot water, it formed yellow needles (2·5 g.), m. p. 236°, soluble in alcohol and methyl alcohol, but insoluble in light petroleum and benzene (Found: C, 66·6; H, 5·8. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·6%). The compound is soluble in cold dilute sodium hydroxide solution, but only slightly soluble in cold dilute mineral acid.

5-Amino-4-hydroxy-2-methylquinoline.—5-Acetamido-4-hydroxy-2-methylquinoline (5 g.) was boiled with 33% hydrochloric acid (100 c.c.) for 30 minutes. *5-Amino-4-hydroxy-2-methylquinoline*, precipitated when the cooled filtered solution was basified, crystallised from hot water in pale yellow needles (3·8 g.), m. p. 210° (Found: N, 16·2. $C_{10}H_{10}ON_2$ requires N, 16·1%). This compound is soluble in alcohol and methyl alcohol, slightly soluble in benzene, and insoluble in light petroleum. It is soluble in dilute mineral acid but only slightly soluble in dilute sodium hydroxide solution.

4-Hydroxy-2-methyl-5 : 6 : 2′ : 3′-pyridoquinoline.—5-Amino-4-hydroxy-2-methylquinoline (4·1 g.), arsenic acid (3·4 g.), glycerol (7·1 g.), and concentrated sulphuric acid (6·4 g.) were refluxed for 5—6 hours; the dark brown solution then no longer gave the diazo-reaction. The cooled product was diluted with water, filtered, and basified with sodium hydroxide solution. The brown precipitate was collected and dissolved in dilute hydrochloric acid; the solution was almost neutralised with sodium hydroxide solution and filtered from the tarry precipitate. On basification *4-hydroxy-2-methyl-5 : 6 : 2′ : 3′-pyridoquinoline* (30 g.) separated; recrystallised from aqueous alcohol, it formed colourless needles, m. p. 142° (Found: N, 13·6. $C_{13}H_{10}ON_2$ requires N, 13·3%), insoluble in cold but slightly soluble in hot water, slightly soluble in alcohol, methyl alcohol and benzene, but insoluble in light petroleum. It was soluble in dilute acid and to a less extent in dilute sodium hydroxide solution.

4-Chloro-2-methyl-5 : 6 : 2′ : 3′-pyridoquinoline.—4-Hydroxy-2-methyl-5 : 6 : 2′ : 3′-pyridoquinoline (1 g.), phosphorus pentachloride (1 g.), and phosphorus oxychloride (8 c.c.) were refluxed for 3 hours. The excess of phosphorus oxychloride was removed in a vacuum, and the residue extracted with hot water. On basification of the filtered aqueous solution a cream-coloured precipitate of *4-chloro-2-methyl-5 : 6 : 2′ : 3′-pyridoquinoline* was obtained; recrystallised from aqueous alcohol, it formed long colourless needles (0·8 g.), m. p. 140° (Found: C, 67·9; H, 3·6. $C_{13}H_9N_2Cl$ requires C, 68·3; H, 3·9%), soluble in light petroleum, benzene and alcohol, insoluble in cold but slightly soluble in boiling water, from which, on cooling, it separated in colourless needles. It was soluble in dilute mineral acid but insoluble in dilute alkali solution.

4-Chloro-2-methyl-7 : 8 : 2′ : 3′-pyridoquinoline, similarly obtained (5 hours' heating) from 4-hydroxy-2-methyl-7 : 8 : 2′ : 3′-pyridoquinoline (1 g.), crystallised from alcohol in long colourless needles (0·85 g.), m. p. 190° (Found: C, 68·0; H, 3·9%), insoluble in cold and very slightly soluble in hot water, moderately soluble

in benzene and light petroleum, but insoluble in acetone. It was soluble in dilute mineral acid but insoluble in dilute sodium hydroxide solution.

2-Hydroxy-4-methyl-7 : 8 : 2′ : 3′-pyridoquinoline.—7-Amino-2-hydroxy-4-methylquinoline (5 g.), arsenic acid (4·15 g.), glycerol (8·5 g.), and concentrated sulphuric acid (7·8 g.) were refluxed for 6 hours, and the cooled solution diluted with water (2 vols.), filtered, and exactly neutralised with sodium hydroxide solution; a light brown precipitate then separated. This was dissolved in warm 50% acetic acid, and the filtered solution made alkaline with sodium hydroxide solution. The insoluble tar was removed and when the filtrate was exactly neutralised with hydrochloric acid, *2-hydroxy-4-methyl-7 : 8 : 2′ : 3′-pyridoquinoline* separated (3·5 g.); it crystallised from alcohol in small, light yellow plates, m. p. 318° with previous sublimation and darkening at about 300° (Found : N, 13·4. $C_{13}H_{10}ON_2$ requires N, 13·3%). This compound is insoluble in water and most of the common organic solvents, soluble to a small extent in hot alcohol and methyl alcohol. The alcoholic solution of the base exhibits a bluish-purple fluorescence which changes to green on the addition of hydrochloric acid but disappears on the addition of sodium hydroxide. No fluorescence was observed in either acid or alkaline aqueous solution. A small sample of compound in a very pure condition may be obtained by sublimation, but this method entails considerable loss by decomposition.

2-Chloro-4-methyl-7 : 8 : 2′ : 3′-pyridoquinoline, prepared by heating 2-hydroxy-4-methyl-7 : 8 : 2′ : 3′-pyridoquinoline (3·9 g.) with phosphorus pentachloride (3·9 g.) and oxychloride (16 c.c.) in a sealed tube for 3 hours at 120°, and isolated in the same way as the two preceding chloro-compounds, crystallised from aqueous alcohol in colourless needles (3·4 g.), m. p. 161° (Found : C, 68·3; H, 3·7. $C_{13}H_9N_2Cl$ requires C, 68·3; H, 3·9%), soluble in dilute mineral acid but insoluble in dilute sodium hydroxide solution, slightly soluble in alcohol and methyl alcohol, moderately easily soluble in hot light petroleum, from which it crystallised on cooling, soluble in benzene but insoluble in acetone. Its alcoholic solution exhibited a bluish-violet fluorescence.

Ethyl 7-Amino-2-hydroxyquinoline-4-carboxylate.—*m*-Phenylenediamine (10·8 g.), freshly distilled in a vacuum, and ethyl oxaloacetate (18·8 g.), freshly prepared from its sodium salt, were refluxed on the sand-bath. After 1 hour the crystalline mass of *ethyl 7-amino-2-hydroxyquinoline-4-carboxylate* was cooled, washed with methyl alcohol, and recrystallised from alcohol, forming long yellow needles (8 g.), m. p. 262° (Found : C, 61·8; H, 4·9. $C_{12}H_{12}O_3N_2$ requires C, 62·1; H, 5·2%), slightly soluble in water, methyl alcohol, benzene, and light petroleum. It dissolved in hot dilute aqueous sodium hydroxide and in dilute acid, giving a colourless and a yellow solution respectively.

7-Amino-2-hydroxyquinoline-4-carboxylic Acid.—The ethyl ester (6·0 g.) and an alcoholic solution of potassium hydroxide (60 c.c. of 5%) were refluxed for 20 minutes. Potassium 7-amino-2-hydroxyquinoline-4-carboxylate separated in light brown crystals; a further quantity was obtained by the addition of acetone. Recrystallised from aqueous acetone, the salt formed long colourless needles, m. p. 394° (decomp.), the yield being almost theoretical. It was readily soluble in cold water (green fluorescence), slightly soluble in hot alcohol (blue fluorescence) and soluble in methyl alcohol. When an aqueous solution of the salt was made very slightly acid, *7-amino-2-hydroxyquinoline-4-carboxylic acid* separated as a light brown precipitate (soluble in excess of the mineral acid); it crystallised from alcohol in small light needles, which began to decompose at 345° but were unmelted at 400° (Found : C, 58·5; H, 3·8. $C_{10}H_8O_3N_2$ requires C, 58·8; H, 3·9%). This acid was only sparingly soluble in hot alcohol and very sparingly soluble in most of the usual organic solvents. Its alcoholic solution exhibited a strong green fluorescence; no fluorescence was observed in hydrochloric acid.

7-Amino-2-hydroxyquinoline.—The preceding acid (2 g.), copper powder (1·0 g.), and quinoline (20 c.c.) were refluxed for 3 hours. Water was added to the hot filtered solution, and the quinoline removed by steam-distillation. 7-Amino-2-hydroxyquinoline, which separated from the concentrated, cooled aqueous solution, crystallised from hot water in white needles (0·5 g.), m. p. 292—293°, not depressed by a sample prepared by the reduction of 7-nitro-2-hydroxyquinoline (Capps and Hamilton, *loc. cit.*).

2-Chloro-7 : 8 : 2′ : 3′-pyridoquinoline.—7-Amino-2-hydroxyquinoline (1 g.), arsenic acid (0·8 g.), glycerol (1·8 g.), and concentrated sulphuric acid (1·6 g.) were refluxed for 3 hours, and the product diluted with water, filtered, and neutralised with sodium carbonate solution. The 2-hydroxy-7 : 8 : 2′ : 3′-pyridoquinoline was recrystallised from alcohol, forming pale yellow needles, m. p. 290° after decomposition and sublimation at 275°. This slightly impure compound (0·5 g.) was refluxed with phosphorus oxychloride (4 c.c.) and pentachloride (0·5 g.) for 3 hours, and the product treated in the usual way. *2-Chloro-7 : 8 : 2′ : 3′-pyridoquinoline* separated from aqueous alcohol in small colourless needles (0·35 g.), m. p. 160° (Found : C, 66·6; H, 3·1. $C_{12}H_7N_2Cl$ requires C, 67·1; H, 3·3%), very slightly soluble in water, soluble in alcohol, insoluble in light petroleum, soluble in dilute mineral acids but insoluble in sodium hydroxide solution.

2-Hydroxy-5 : 6 : 2′ : 3′-pyridoquinoline (3·0 g.), prepared from 5-amino-2-hydroxyquinoline (4·0 g.), arsenic acid (3·5 g.), glycerol (7·2 g.), and concentrated sulphuric acid (6·6 g.) (3 hours' refluxing) and isolated as in the case of 4-hydroxy-2-methyl-5 : 6 : 2′ : 3′-pyridoquinoline, was sublimed at 290° and then recrystallised from alcohol, forming colourless needles, m. p. 315° after decomposition and sublimation at 290° (Found : C, 72·9; H, 4·3. $C_{12}H_8ON_2$ requires C, 73·4; H, 4·1%), insoluble in water, slightly soluble in most organic solvents, soluble in dilute mineral acids and in dilute sodium hydroxide solution.

2-Chloro-5 : 6 : 2′ : 3′-pyridoquinoline (0·85 g.), prepared from 2-hydroxy-5 : 6 : 2′ : 3′-pyridoquinoline (1·0 g.), phosphorus pentachloride (1·0 g.), and oxychloride (8 c.c.), crystallised from aqueous alcohol in colour-

less needles, m. p. 147—148° (Found : C, 66·8; H, 3·3. $C_{12}H_7N_2Cl$ requires C, 67·1; H, 3·3%), very slightly soluble in water, soluble in alcohol, moderately easily soluble in methyl alcohol, insoluble in light petroleum, soluble in dilute mineral acids but insoluble in dilute sodium hydroxide solution.

5 : 6 : 2′ : 3′-*Pyridoquinolinium Methyl Sulphate.*—5 : 6 : 2′ : 3′-Pyridoquinoline (*m*-phenanthroline) (0·9 g.) and methyl sulphate (0·46 c.c.) were refluxed in methyl alcohol (15—20 c.c.) for 1 hour and the methyl alcohol was then removed by distillation; a reddish-yellow crystalline mass remained which, recrystallised from methyl alcohol, yielded pale yellow, rectangular prisms, m. p. 192°, of 5 : 6 : 2′ : 3′-*pyridoquinolinium methyl sulphate* (Found : C, 53·4; H, 3·7. $C_{12}H_8N_2,HMeSO_4$ requires C, 53·4; H, 4·1%). This somewhat hygroscopic salt readily dissolved in water and when the solution was basified 5 : 6 : 2′ : 3′-pyridoquinoline was precipitated. This showed that the quaternary salt had not been formed.

1-*Methyl*-5 : 6 : 2′ : 3′-*pyridoquinolinium Methyl Sulphate* (N-*Methyl*-m-*phenanthrolinium Methyl Sulphate*).—Freshly distilled 5 : 6 : 2′ : 3′-pyridoquinoline (3·6 g.) and methyl sulphate (1·84 c.c.), dried over potassium carbonate, were warmed on the water-bath for 1 hour. When acetone was added to the reddish-brown liquid, the latter changed to a sticky solid, which became crystalline on repeated washing with acetone. This very hygroscopic material, dried in a desiccator over sulphuric acid, melted at about 145°. When a concentrated solution in alcohol was cooled, crystals separated which melted at about 130°. Part of the alcohol was removed from the mother-liquor, and acetone added; on cooling, a further crop of crystals was obtained, m. p. 162—164°, 168—169° after recrystallisation, and was evidently identical with the methylpyridoquinolinium methyl sulphate, m. p. 171°, mentioned in D.R.-P. 654,444.

Conversion of 2-*Keto*-1-*methyl*-1 : 2-*dihydro*-5 : 6 : 2′ : 3′-*pyridoquinoline into* 2-*Chloro*-5 : 6 : 2′ : 3′-*pyridoquinoline* (cf. D.R.-P. 654,444).—2-Keto-1-methyl-1 : 2-dihydro-5 : 6 : 2′ : 3′-pyridoquinoline (m. p. 194°) (0·5 g.), prepared from slightly impure 1-methyl-5 : 6 : 2′ : 3′-pyridoquinolinium methyl sulphate by oxidation with alkali ferricyanide, was refluxed with phosphorus oxychloride (1 c.c.) and pentachloride (1 g.) at 150—160° for 10 hours. The homogeneous solution was cooled, treated with water, filtered, and basified with sodium hydroxide solution; the brownish precipitate which separated, after recrystallisation from aqueous alcohol, had m. p. 148—149°, not depressed by 2-chloro-5 : 6 : 2′ : 3′-pyridoquinoline (m. p. 147—148°) prepared from 2-hydroxy-5 : 6 : 2′ : 3′-pyridoquinoline, but considerably depressed by 2-chloro-7 : 8 : 2′ : 3′-pyridoquinoline.

The following amines were obtained by refluxing the appropriate chloropyridoquinolines and bases in the presence of a trace of copper bronze for several hours. The excess of amine was removed in a vacuum, the product treated with dilute sodium hydroxide solution and extracted with ether, and the ether removed from the dried extract by distillation. The base obtained sometimes crystallised; otherwise it was converted into the hydrobromide by treatment with fuming alcoholic hydrogen bromide or into the picrate by addition of an ethereal or alcoholic solution of picric acid to a solution of the base in the same solvent. None of the first four bases or their salts showed fluorescence in solution. The last four bases showed a weak green fluorescence in ethereal solution but none in dilute mineral acid. All the bases, except the two described as crystalline, were recovered as oils from their picrates.

4-(β-Diethylaminoethylamino)-2-methyl-5 : 6 : 2′ : 3′-pyridoquinoline, from 4-chloro-2-methyl-5 : 6 : 2′ : 3′-pyridoquinoline (0·5 g.) and β-diethylaminoethylamine (1 c.c.), refluxed at 150° for 6 hours. The *dipicrate*, recrystallised from methyl ethyl ketone, formed small, bright yellow plates, m. p. 237°, in almost theoretical yield (Found : C, 48·6; H, 3·7. $C_{19}H_{24}N_4,2C_6H_3O_7N_3$ requires C, 48·6; H, 3·9%); it was very slightly soluble in water, methyl alcohol, alcohol and benzene, but somewhat more soluble in acetone.

4-(δ-Diethylamino-α-methylbutylamino)-2-methyl-5 : 6 : 2′ : 3′-pyridoquinoline, from 4-chloro-2-methyl-5 : 6 : 2′ : 3′-pyridoquinoline (0·5 g.) and δ-diethylamino-α-methylbutylamine (1 c.c.), refluxed for 8 hours at 200°. The *dipicrate*, recrystallised from methyl ethyl ketone, formed brownish-yellow plates, m. p. 195° (yield, almost theoretical) (Found : C, 50·4; H, 4·4. $C_{22}H_{30}N_4,2C_6H_3O_7N_3$ requires C, 50·5; H, 4·5%), very slightly soluble in water, methyl alcohol, alcohol and benzene and to a small extent in hot acetone.

4-(β-*Diethylaminoethylamino*)-2-*methyl*-7 : 8 : 2′ : 3′-*pyridoquinoline*, from 4-chloro-2-methyl-7 : 8 : 2′ : 3′-pyridoquinoline (1·0 g.) and β-diethylaminoethylamine (2 c.c.), refluxed at 150° for 8 hours, crystallised from light petroleum in pale yellow plates (1 g.), m. p. 115—116° (Found : C, 73·1; H, 8·0. $C_{19}H_{24}N_4$ requires C, 74·0; H, 7·8%), very soluble in alcohol, acetone, benzene and ether, insoluble in water and dilute sodium hydroxide solution, but readily soluble in dilute mineral acid. It readily absorbed carbon dioxide from the atmosphere and consequently was difficult to purify. The *trihydrobromide* crystallised from alcohol in colourless needles, m. p. 284—285° (Found : C, 41·8; H, 4·6. $C_{19}H_{24}N_4,3HBr$ requires C, 41·4; H, 3·9%). This salt is very hygroscopic and is readily soluble in water, but insoluble in benzene, ligroin and acetone.

4-(δ-Diethylamino-α-methylbutylamino)-2-methyl-7 : 8 : 2′ : 3′-pyridoquinoline, from 4-chloro-2-methyl-7 : 8 : 2′ : 3′-pyridoquinoline (1·0 g.) and δ-diethylamino-α-methylbutylamine (2 c.c.), refluxed for 8 hours at 200°, was obtained as an oil which yielded solid derivatives with picric acid, methylenedisalicylic acid and flavianic acid. The last two were amorphous and very sparingly soluble in most organic solvents. The bright yellow picrate was best purified by conversion into the base and precipitation with picric acid in ethereal solution. Analysis suggested that it was the *tripicrate* (Found : C, 46·9; H, 3·3. $C_{22}H_{30}N_4,3C_6H_3O_7N_3$ requires C, 46·3; H, 3·9%). It shrank at 85° and melted at 130° and was soluble in acetone but insoluble in most other common solvents.

2-(β-*Diethylaminoethylamino*)-4-*methyl*-7 : 8 : 2′ : 3′-*pyridoquinoline*, from 2-chloro-4-methyl-7 : 8 : 2′ : 3′-pyridoquinoline (0·7 g.) and β-diethylaminoethylamine (1·4 c.c.), refluxed at 150° for 6 hours, crystallised from

light petroleum in clusters of pale yellow needles (0·7 g.), m. p. 113—114° (Found: C, 74·2; H, 8·3. $C_{19}H_{24}N_4$ requires C, 74·0; H, 7·8%), very soluble in alcohol, acetone and methyl alcohol, soluble in benzene, moderately easily soluble in light petroleum, insoluble in water and dilute sodium hydroxide solution but easily soluble in cold dilute mineral acid. It readily absorbed carbon dioxide from the atmosphere. The *dihydrobromide* crystallised from alcohol in long, pale yellow needles, m. p. 281—283° (decomp.) (Found: C, 47·8; H, 5·5. $C_{19}H_{24}N_4,2HBr$ requires C, 48·5; H, 5·5%), soluble in water and methyl alcohol but insoluble in benzene, ligroin and acetone.

2-(δ-Diethylamino-α-methylbutylamino)-4-methyl-7 : 8 : 2′ : 3′-pyridoquinoline, from 2-chloro-4-methyl-7 : 8 : 2′ : 3′-pyridoquinoline (0·7 g.) and δ-diethylamino-α-methylbutylamine (1·4 c.c.), refluxed at 200° for 8 hours. The *monopicrate*, recrystallised from methyl ethyl ketone, melted at 260° after decomposition at about 230° (Found: C, 57·6; H, 5·3. $C_{22}H_{30}N_4,C_6H_3O_7N_3$ requires C, 58·0; H, 5·7%); it was very slightly soluble in water, alcohol and benzene but somewhat more soluble in hot acetone.

2-(β-Diethylaminoethylamino)-5 : 6 : 2′ : 3′-pyridoquinoline, from 2-chloro-5 : 6 : 2′ : 3′-pyridoquinoline (0·5 g.) and β-diethylaminoethylamine (1 c.c.), refluxed at 150° for 5 hours. The *dipicrate* crystallised from methyl ethyl ketone in small, yellow, rectangular plates, m. p. 223—224° (Found: C, 47·9; H, 3·8. $C_{18}H_{22}N_4,2C_6H_3O_7N_3$ requires C, 47·9; H, 3·7%), very slightly soluble in water, methyl alcohol, alcohol and benzene, but more soluble in acetone, from which it crystallised.

2-(δ-Diethylamino-α-methylbutylamino)-5 : 6 : 2′ : 3′-pyridoquinoline, from 2-chloro-5 : 6 : 2′ : 3′-pyridoquinoline (0·8 g.) and δ-diethylamino-α-methylbutylamine (1·6 c.c.), refluxed at 200° for 8 hours. The *dipicrate* crystallised from methyl ethyl ketone in small yellow prisms (1·6 g.), m. p. 195° (Found: C, 50·0; H, 4·1. $C_{21}H_{28}N_4,2C_6H_3O_7N_3$ requires C, 49·9; H, 4·3%), slightly soluble in alcohol, methyl alcohol, water, and benzene and somewhat more soluble in acetone.

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RESEARCH LABORATORY, ROYAL COLLEGE OF PHYSICIANS, EDINBURGH. [*Received, October 7th*, 1941.]