109. *New Therapeutic Agents of the Quinoline Series. Part IV. Lutidylquinolines.*

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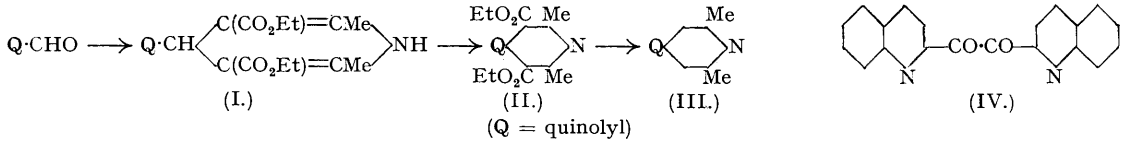
This work comprises further syntheses of compounds of the type of γ-pyridylquinoline. Six quinoline aldehydes, some prepared for the first time by indirect reduction of the corresponding acids, have been converted by the Hantzsch method eventually into γ-2′ : 6′-dimethylpyridylquinolines. By carrying out the Hantzsch reactions on benzaldehyde with subsequent introduction of an amino-group, or on nitrobenzaldehydes, followed by reduction, aminophenyl-lutidines were obtained; these were submitted to the Skraup reaction. The seven possible γ-2′ : 6′-dimethylpyridylquinolines were thus prepared.

Earlier results showed that, of pyridylquinolines isomeric with respect to the orientation of the pyridine nucleus, the γ-compounds were outstanding as spasmolytics. As the preparation of these involved the separation of the α-, β-, and γ-pyridyl compounds as picrates with consequent loss in yield, it was somewhat tedious. We have therefore synthesised the seven possible lutidyl compounds of type (III) by independent methods.

The two main routes were (*a*) subjection of quinoline aldehydes to the Hantzsch synthesis :



and (*b*) the preparation of lutidylanilines and their conversion into lutidylquinolines by the Skraup reaction.

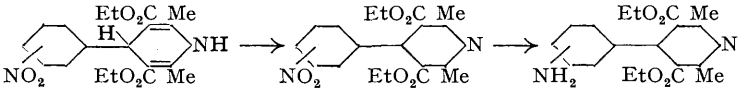
Quinoline-2- and -4-aldehyde, prepared best by oxidising quinaldine and lepidine respectively with fresh selenium dioxide (Kaplan, *J. Amer. Chem. Soc.*, 1941, **63**, 2654), were condensed with ethyl β-aminocrotonate to give the dihydro-esters (I); the product from the 2-aldehyde was accompanied by a yellow fluorescent compound, probably the diketone (IV). Difficulty was experienced in preparing quinoline-6-aldehyde in quantity by the method of Howitz and Philipp (*Annalen*, 1913, **396**, 28) and the rather similar conversion of 8-methylquinoline into quinoline-8-aldehyde by bromination, hydrolysis, and oxidation of 8-hydroxymethylquinoline eventually obtained, was found to be impracticable. Oxidation of methylquinolines with chromyl chloride, of methylquinolines (other than the 2- and the 4-isomeride) with selenium dioxide, or interaction of quinoline with methylformanilide and phosphorus oxychloride all failed to yield quinoline aldehydes. We also attempted to

couple diazotised aminoquinolines with cinnamic acid (cf. Meerwein, *J. pr. Chem.*, 1939, **159**, 256) whereby phenylquinolylethylenes which could be oxidised to aldehydes might have resulted; coupling in the expected manner did not take place and, from 8-amino-6-methoxyquinoline, for example, a good yield of 8-chloro-6-methoxyquinoline was obtained by a remarkably facile Sandmeyer reaction.

Eventually the difficulty was overcome by preparing quinoline-6- and -8-, as well as the hitherto unknown -3- and -5-aldehydes, by reducing the appropriate carboxylic acid by way of the hydrazide and its toluenesulphonyl compound (cf. McFayden and Stevens, J., 1936, 584; Pannizzon, *Helv. Chim. Acta*, 1941, **24**, 24).

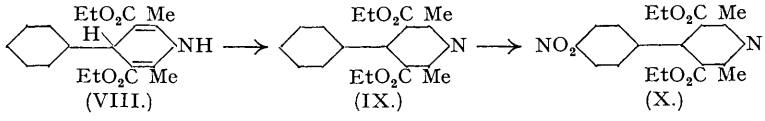
Each of these aldehydes was converted into the dihydro-esters (I) either with ethyl β-aminocrotonate or, in the case of the 3-, 5-, and 8-isomerides, preferably with ethyl acetoacetate and alcoholic ammonia. All these dihydro-esters were unaffected by nitrous acid or ethyl nitrite (cf. Lepetit, *Ber.*, 1887, **20**, 1340), but were smoothly oxidised by warm dilute nitric acid to the esters (II); with all except the 6-ester, 2N-nitric acid was sufficient; in this case 4N-nitric acid induced further reaction, probably hydrolysis, but oxidation was uncomplicated when 3N-acid was used. The lutidyldicarboxylic esters were hydrolysed with caustic alkali; the free acids were readily soluble in water and insoluble in organic extractants and so were not usually purified. Decarboxylation by heating the alkali salts with soda-lime could not be satisfactorily effected, nor was the action of heat on mixtures of the free acid with copper bronze successful. The lutidylquinolines were ultimately obtained in good yield by heating the moist silver salts of the carboxylic acids in a vacuum. All were highly crystalline compounds.

Whilst the above difficulties were being overcome, we investigated the preparation and usefulness of lutidylanilines. *o*-, *m*-, and *p*-Nitrobenzaldehyde had been condensed with ammonia and ethyl acetoacetate to give the esters (V) (cf. Lepetit, *Ber.*, 1887, **20**, 1338; Hinkel, Ayling, and Morgan, J., 1931, 1835). We obtained the *m*- and the *p*-nitro-ester (V) in much improved yield by condensing the aldehydes with ethyl β-aminocrotonate in absence of solvent. All three esters were smoothly oxidised to the lutidyl derivatives (VI) by dilute nitric acid. The *m*- and the *p*-ester were reduced with tin and hydrochloric acid to the corresponding amines (VII), but the *o*-nitro-ester was resistant to reduction; since the preparation of 8-lutidylquinoline had already



been accomplished, this second route to the same compound was then abandoned. The *m*- and the *p*-amino-ester were hydrolysed, and the acids decarboxylated, best by dry distillation with copper powder, the method of heating moist silver salts being unsuccessful in this series. In this way we obtained 4-m- and -p-*aminophenyl*-2 : 6-*lutidine*. The latter underwent the Skraup reaction to give 6-2′ : 6′-*lutidylquinoline* identical with that already prepared *via* quinoline-6-aldehyde, but *m*-aminophenyl-lutidine on being submitted to the same reaction afforded two isomerides; one, formed in preponderating amount, was identical with 5-2′ : 6′-lutidylquinoline and the second product must therefore have been the remaining 7-2′ : 6′-*lutidylquinoline*. There appears little doubt that the product, m. p. 109°, obtained by Lepetit (*Gazzetta*, 1887, **17**, 474) was a mixture of these two isomerides.

Inconvenience attached to the preparation of *p*-nitrobenzaldehyde led us to examine the nitration of phenyl-lutidinedicarboxylic ester (IX). Benzaldehyde and ethyl β-aminocrotonate afforded an extremely good yield of the ester (VIII); this was oxidised by warm dilute nitric acid to the lutidine derivative (IX), which was then treated with fuming nitric acid in concentrated sulphuric acid. The crude nitro-compounds



in alcoholic solution deposited the pure *p*-nitro-compound (X), identical with that prepared from *p*-nitrobenzaldehyde, in 33% yield on cooling; by nitrating at −20°, the yield of *p*-nitro-compound was raised to 60%.

Of the above lutidylquinolines, the most easily accessible was the 6-isomeride and in view of promising biological results, we attempted to obtain it by the interaction of 6-nitrosoacetamidoquinoline with 2 : 6-lutidine. Reaction was normal, though only a small yield of 6-lutidylquinoline was isolated; fractionation of the picrate of this product gave only one pure compound and since it was isomeric with the base previously obtained, it was formulated as 6-β-2′ : 6′-dimethylpyridylquinoline.

Experimental.

2-γ-2′ : 6′-*Dimethylpyridylquinoline*.—Quinoline-2-aldehyde (3 g.) or an equivalent quantity of the monohydrate and ethyl β-aminocrotonate (5 g.) were heated on the steam-bath for 3 hours. The viscous oil was washed with a little ether to cause it to solidify, and the crystalline product collected. The *ethyl* 4-2′-*quinolyl*-2 : 6-*dimethyldihydropyridine*-3 : 5-*dicarboxylate* (2·36 g.) was crystallised from ethanol and later from benzene to yield almost colourless plates, m. p. 190° (Found: N, 7·4; *M*, cryoscopic in camphor, 355. $C_{22}H_{24}O_4N_2$ requires N, 7·3%; *M*, 366). When heating was prolonged in the original preparation, a more soluble yellow compound with a green fluorescence was formed. This crystallised from ethanol in yellow plates, m. p. 159°, and was probably 2 : 2′-diquinolylglyoxal. The dihydro-compound (5 g.) was treated with 2N-nitric acid (40 c.c.), and the suspension heated to boiling. The yellow nitrate passed into

solution with evolution of nitrous fumes and after 15 minutes the clear solution was poured into water (200 c.c.) and basified with sodium hydroxide. The *ethyl* 4-2′-*quinolyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* separated from aqueous ethanol in small white needles, m. p. 91°, readily soluble in ethanol or benzene (Found : C, 69·4; H, 5·5. $C_{22}H_{22}O_4N_2$ requires C, 69·8; H, 5·8%). This quinolyl-lutidinedicarboxylic ester (1·5 g.) was refluxed for 4 hrs. with potassium hydroxide (3·5 g.) in ethanol (10 c.c.). The solution was cooled, and the crystalline potassium salt collected and redissolved in the minimum quantity of water. The solution was precipitated with aqueous silver nitrate. The precipitated silver salt (0·85 g.) was gradually heated to 300—400°/15 mm. The liquid distillate was extracted with benzene (10 c.c.), and the solvent then removed from the extract to leave a crystalline mass of 2-*lutidylquinoline* (0·2 g.). The base, recrystallised from light petroleum, gave white needles, m. p. 135° (Found : N, 12·1. $C_{16}H_{14}N_2$ requires N, 12·0%). The *picrate*, prepared from alcoholic solutions of the components and crystallised from acetone–alcohol, had m. p. 230° (decomp.) (Found : N, 15·3. $C_{16}H_{14}N_2,C_6H_3O_7N_3$ requires N, 15·1%).

3-γ-2′ : 6′-*Dimethylpyridylquinoline*.—Quinoline-3-carboxylic ester (Gilman and Spatz, *J. Amer. Chem. Soc.*, 1941, **63**, 1556) (17 g.) was refluxed at 110° for 4 hrs. with 50% hydrazine hydrate (12 g.). After cooling, the pale yellow solid was collected and washed with water; *quinoline*-3-*carboxyhydrazide* formed colourless needles, m. p. 190°, from ethanol (Found : N, 22·5. $C_{10}H_9ON_3$ requires N, 22·5%). The hydrazide (12·5 g.) was dissolved in pyridine (70 c.c.), and *p*-toluenesulphonyl chloride (14 g.) added slowly. Excess of pyridine was removed in a vacuum, water added to the residue, and the p-*toluenesulphonyl* derivative (21 g.) crystallised from *cyclo*hexanone–ethanol; it had m. p. 232° (decomp.) (Found : N, 12·5. $C_{17}H_{15}O_3N_3S$ requires N, 12·3%). The toluenesulphonyl derivative (20 g.) was dissolved in glycol (100 c.c.) at 100°, and anhydrous sodium carbonate (20 g.) added, the temperature being maintained at 160° for 3 mins. The product was cooled, diluted with water, and extracted with ether. *Quinoline*-3-*aldehyde* (3 g.) was extracted; it was sublimed in a vacuum and then crystallised from water, forming colourless needles, m. p. 70° (Found : N, 8·8. $C_{10}H_7ON$ requires N, 9·0%). The aldehyde (1·8 g.), ethyl acetoacetate (3·24 g.), and 3% alcoholic ammonia (7 c.c.) were heated in a sealed tube for 7 hrs. at 100°. After removal of solvent and crystallisation of the residue from benzene, *ethyl* 4-3′-*quinolyl*-2 : 6-*dimethyldihydropyridine*-3 : 5-*dicarboxylate* was obtained in long colourless needles, m. p. 193° (yield, 79%) (Found : N, 7·2. $C_{22}H_{24}O_4N_2$ requires N, 7·4%). The preceding dihydro-ester (2·7 g.) was boiled for 10 mins. with 2N-nitric acid (11 c.c.), and the liquid then made alkaline. When the brown solid was crystallised from light petroleum, *ethyl* 4-3′-*quinolyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* was obtained in colourless rhombs (2·3 g.), m. p. 77° (Found : C, 70·1; H, 5·8; N, 7·4. $C_{22}H_{22}O_4N_2$ requires C, 69·8; H, 5·8; N, 7·4%). This ester (1·5 g.) was added to potassium hydroxide (2·3 g.) in ethanol (8 c.c.), and the solution refluxed for 12 hrs.; a little acetic acid was then added to neutralise free alkali, and the silver salt of the corresponding dicarboxylic acid (2·3 g.) precipitated with silver nitrate. On heating in a vacuum, the slightly moist silver salt gave a distillate of crude 4-*lutidylquinoline* (0·5 g.; 50%). After subliming in a vacuum and crystallising from light petroleum, it formed colourless needles, m. p. 100° (Found : N, 11·8. $C_{16}H_{14}N_2$ requires N, 12·0%).

4-γ-2′ : 6′-*Dimethylpyridylquinoline*.—Quinoline-4-aldehyde (0·2 g.) was heated for 2 hrs. at 100° with ethyl β-aminocrotonate (0·4 g.). The brown liquid, on cooling and scratching with ether, gave *ethyl* 4-4′-*quinolyl*-2 : 6-*dimethyldihydropyridine*-3 : 5-*dicarboxylate* (0·2 g.). This separated in white crystals, m. p. 200°, from benzene (Found : C, 69·3; H, 6·1; N, 7·4. $C_{22}H_{24}O_4N_2$ requires C, 69·5; H, 6·3; N, 7·4%). This ester (5 g.) was boiled with 2N-nitric acid (20 c.c.) for 15 mins., the liquid made alkaline, and the *ethyl* 4-4′-*quinolyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* (4·5 g.) collected; it had m. p. 122° (Found : C, 69·8; H, 5·6. $C_{22}H_{22}O_4N_2$ requires C, 69·8; H, 5·8%). The above dicarbethoxypyridylquinoline (4 g.) was added to a solution of potassium hydroxide (6 g.) in ethanol (20 c.c.) and refluxed for 4 hrs. The liquid was cooled, and the crystalline potassium salt collected (yield, theoretical). The silver salt was prepared and decarboxylated as in the case of the 2-isomeride, 4 g. yielding 1·0 g. of 4-*lutidylquinoline* (58%), which separated from light petroleum in colourless crystals, m. p. 122° (Found : N, 11·9. $C_{16}H_{14}N_2$ requires N, 12·0%).

5-γ-2′ : 6′-*Dimethylpyridylquinoline*.—*m*-Aminobenzoic acid (100 g.), nitrobenzene (60 g.), glycerol (220 g.), boric acid (25 g.), and concentrated sulphuric acid (140 c.c.) were heated under reflux until reaction commenced; when the reaction had subsided, the whole was boiled for 14 hrs., diluted with 1 vol. of water, and strongly basified with sodium hydroxide. The black tar was decanted, and the clear solution acidified with acetic acid. Quinoline-5-carboxylic acid (yield, 95%; m. p. 350° with decomp.) was collected and dried at 120°. The finely powdered acid (10 g.) was refluxed with thionyl chloride (30 c.c.) for 3 hrs. After removal of the excess of thionyl chloride in a vacuum ethanol (20 c.c.) was added to the residue, and the whole refluxed for 30 mins. The clear liquid was poured on ice and made alkaline with ammonia, and the ester extracted with ether. On removal of solvent and distillation of the residue *ethyl quinoline*-5-*carboxylate* (9 g.) was collected as an oil, b. p. 190—192°/15 mm., m. p. 10° (Found : N, 6·5. $C_{12}H_{11}O_2N$ requires N, 7·0%). The ester (9 g.) was refluxed with 50% hydrazine hydrate (6·75 g.) for 2 hrs., the clear liquid allowed to cool, and the solid collected and washed with water. Quinoline-5-carboxyhydrazide, crystallised from ethanol, had m. p. 169°. The *toluenesulphonyl* derivative, prepared by the same method as was used for the 3-isomeride, separated from ethanol apparently as an alcoholate which lost solvent of crystallisation at 180°, thus affording the pure compound, m. p. 200° (Found : N, 12·4. $C_{17}H_{15}O_3N_3S$ requires N, 12·3%).

The crude *p*-toluenesulphonylhydrazide (25 g.), dissolved in glycol (125 c.c.), was heated to 100°, and anhydrous sodium carbonate (25 g.) added as rapidly as possible. The temperature was maintained at 160° for 3 mins., water then added, and the filtrate extracted three times with ether. After removal of solvent and sublimation of the residue in a vacuum, *quinoline*-5-*aldehyde* (1·5 g.) was obtained; it separated from water in colourless needles, m. p. 96° (Found : N, 8·8. $C_{10}H_7ON$ requires N, 8·9%).

Quinoline-5-aldehyde (1 g.), ethyl acetoacetate (1·65 g.), and a solution of ammonia (0·12 g.) in ethanol (5 c.c.) were heated for 7 hrs. at 100° (sealed tube). The solvent was removed by evaporation, and the yellow crystalline residue recrystallised from benzene, yielding *ethyl* 4-5′-*quinolyl*-2 : 6-*dimethyldihydropyridine*-3 : 5-*dicarboxylate* in colourless rhombs, m. p. 201° (yield, 1·2 g.; 52%) (Found : N, 7·2. $C_{22}H_{24}O_4N_2$ requires N, 7·4%). When the dihydro-ester (1 g.) was added to boiling 2N-nitric acid (4 c.c.) and heating continued, a clear orange liquid was obtained. When this was made alkaline, *ethyl* 4-5′-*quinolyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* was precipitated; it separated in colourless rhombs, m. p. 79°, from light petroleum (Found : C, 70·1; H, 5·8; N, 7·4. $C_{22}H_{22}O_4N_2$ requires C, 69·8; H, 5·9; N, 7·4%). The ester (0·4 g.) was added to potassium hydroxide (0·6 g.) in ethanol (2 c.c.), and the solution refluxed for 10 hrs., then cooled and the yellowish salt collected and washed with ethanol. The silver salt was prepared, and heated in a vacuum. The yellow sublimate was extracted with hot benzene, the extract filtered, benzene removed from the filtrate, and the residue sublimed in a vacuum. 5-2′ : 6′-*Lutidylquinoline* separated from light petroleum in colourless rhombs, m. p. 151° (yield, 54%) (Found : N, 12·3. $C_{16}H_{14}N_2$ requires N, 12·0%). The picrate separated from ethanol in yellow needles, m. p. 231—234° (Found : N, 15·2. $C_{16}H_{14}N_2,C_6H_3O_7N_3$ requires N, 15·1%). It was identical with the product obtained from *m*-nitrobenzaldehyde as described below.

6-γ-2′ : 6′-*Dimethylpyridylquinoline*.—(*a*) Ethyl 4-*p*-nitrophenyl-2 : 6-dimethyldihydropyridine-3 : 5-dicarboxylate was best prepared by heating *p*-nitrobenzaldehyde (38 g.) on the steam-bath for 5 hrs. with ethyl β-aminocrotonate (64 g.). The viscous product crystallised on rubbing and was recrystallised from ethanol; m. p. 136° (yield, 52 g.; 56%) (cf. Hinkel, Ayling, and Morgan, J., 1931, 1835). The dihydropyridine ester (22 g.) was heated with 2N-nitric acid

(88 c.c.) until nitrous fumes were no longer evolved; the solution was then diluted with an equal volume of water and made alkaline with caustic alkali, and the *ethyl* 4-p-*nitrophenyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* collected; it separated from ethanol in pale yellow needles (20 g.), m. p. 115° (Found: C, 61·9; H, 5·3; N, 7·7. $C_{19}H_{20}O_6N_2$ requires C, 61·8; H, 5·4; N, 7·5%). This nitrophenylpyridine ester (15 g.) was heated for 2 hrs. at 100° with granulated tin (7 g.), concentrated hydrochloric acid (40 c.c.), and water (20 c.c.); the clear red solution was poured into an excess of sodium hydroxide solution, *ethyl* 4-p-*aminophenyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* extracted with ether, and the extract evaporated (yield, 13 g.; 95%). The amino-compound separated from ethanol in yellow plates, m. p. 145° (Found: N, 8·4. $C_{19}H_{22}O_4N_2$ requires N, 8·2%). The amino-ester (8 g.) was added to potassium hydroxide (11 g.) in ethanol (40 c.c.), and the solution heated under reflux for 4 hrs., then cooled, and the potassium salt collected, washed with ethanol, and dried (yield, 9 g.; 100%). The silver salt was precipitated by adding a slight excess of silver nitrate to an aqueous solution of the potassium salt. 4-*p*-Aminophenyl-2 : 6-dimethylpyridine-3 : 5-dicarboxylic acid was obtained by suspending the silver salt (5 g.) in water (60 c.c.) and decomposing it with hydrogen sulphide. After removal of silver sulphide the filtrate was evaporated until crystallisation set in, cooled, and the free acid collected. It formed yellow plates, m. p. above 360°, almost insoluble in all the usual solvents except water. The free acid (0·5 g.) was heated with copper powder (2 g.) in a high vacuum over a naked flame, the red oily distillate diluted with chloroform and filtered, and solvent removed. The yellow residue was extracted with boiling light petroleum; when the solution was cooled, 4-p-*aminophenyl*-2 : 6-*dimethylpyridine* was deposited in white needles (0·15 g.), m. p. 131° (Found: N, 14·4; *M*, cryoscopic in camphor, 191. $C_{13}H_{14}N_2$ requires N, 14·1%; *M*, 198). In a larger run, 16 g. of the dicarboxylic acid and 30 g. of copper powder gave 7 g. of aminophenyl-lutidine, m. p. 131° (yield, 63%). *p*-Aminophenyl-lutidine (4·8 g.) was boiled for 4 hrs. with glycerol (10 g.), 66% sulphuric acid (45 g.), and sodium *m*-nitrobenzenesulphonate (10 g.). The solution was diluted, filtered, made alkaline, and extracted twice with benzene (70 c.c. portions); the extract was evaporated, and the residue distilled in a vacuum. 6-*Lutidylquinoline* distilled at 220—230°/15 mm. (yield, 4·0 g.; 71%) and solidified to a mass of pale yellow crystals; recrystallised from light petroleum, it formed white needles, m. p. 84° (Found: N, 12·0. $C_{16}H_{14}N_2$ requires N, 12·0%). The *picrate* separated from *cyclo*hexanone–ethanol in needles, m. p. 224—225° (Found: N, 15·3. $C_{16}H_{14}N_2,C_6H_3O_7N_3$ requires N, 15·1%).

Ethyl 4-phenyl-2 : 6-dimethyldihydropyridine-3 : 5-dicarboxylate (Knoevenagel, *Ber.*, 1898, **31**, 738) was oxidised with boiling 2N-nitric acid as above. The resulting lutidine ester (85 g.) was finely powdered and added slowly to concentrated sulphuric acid (150 c.c.) below −20°. The solution was treated dropwise with nitric acid (*d* 1·4, 40 c.c.) with cooling, the mixture kept for 2 hrs. longer, poured on ice (1000 g.), and made alkaline, and the semi-solid mass of nitrolutidine ester separated, washed by decantation, and dissolved in the minimum quantity of boiling ethanol. On cooling, ethyl 4-*p*-nitrophenyl-2 : 6-dimethylpyridine-3 : 5-dicarboxylate, m. p. 115° (62 g.; 60%), separated. It was identical with the product prepared from *p*-nitrobenzaldehyde.

(*b*) Ethyl quinoline-6-carboxylate (Einhorn, *Ber.*, 1909, **42**, 4854) (40 g.) was heated with 50% hydrazine hydrate (30 g.) for 2 hours at 110°. On cooling, quinoline-6-carboxyhydrazide solidified; after being washed with water, it had m. p. 188° (yield, 35 g.). The p-*toluenesulphonyl* derivative, prepared from the hydrazide (6·2 g.) and *p*-toluenesulphonyl chloride (7 g.), formed white crystals, m. p. 218° (decomp.), from *cyclo*hexanone (Found: N, 12·2. $C_{17}H_{15}O_3N_3S$ requires N, 12·3%). The toluenesulphonyl compound (30 g.) in glycol (130 c.c.) was heated to 150°, and anhydrous sodium carbonate (30 g.) rapidly added. Much frothing took place and after 3 minutes the liquid was poured into hot water, cooled, filtered, and extracted with ether. On removal of the extractant quinoline-6-aldehyde (6·1 g.; 45%) remained; it had m. p. 72° and was identical with that prepared previously (cf. Howitz and Philipp, *Annalen*, 1913, **396**, 281).

Quinoline-6-aldehyde (0·2 g.) was heated for 2 hrs. at 100° with ethyl β-aminocrotonate (0·4 g.). On cooling, washing with ether, and crystallisation from benzene, *ethyl* 4-6′-*quinolyl*-2 : 6-*dimethyldihydropyridine*-3 : 5-*dicarboxylate* (0·33 g.), m. p. 209°, was obtained (Found: N, 7·3. $C_{22}H_{24}O_4N_2$ requires N, 7·4%). This dihydropyridine compound (1 part) was boiled with 3N-nitric acid (4 parts) until no more nitrous fumes were evolved, and the solution was diluted with an equal volume of water and made alkaline. The *ethyl* 4-6′-*quinolyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate*, recrystallised from light petroleum (charcoal), formed white needles, m. p. 97° (Found: C, 69·6; H, 5·7. $C_{22}H_{22}O_4N_2$ requires C, 69·8; H, 5·8%). This ester (2 g.) was boiled with potassium hydroxide (3 g.) in ethanol (20 c.c.) for 10 hrs. and the potassium salt (2 g.), which separated on cooling, was collected. The silver salt was heated in a vacuum as in earlier examples for 1 hr. From the distillate was obtained 6-lutidylquinoline, m. p. 84°, identical with the earlier preparation.

6-β-2′ : 6′-*Dimethylpyridylquinoline*.—64% Sulphuric acid (750 g.), *p*-nitroaniline (70 g.), sodium *m*-nitrobenzenesulphonate (200 g.), glycerol (175 g.), and vanadium pentoxide (2 g.) were refluxed at 145° for 1 hour. Working-up in the usual manner, followed by crystallisation, gave 6-nitroquinoline (62 g.), m. p. 149—150°. 5-Acetamidoquinoline (22 g.) was dissolved in glacial acetic acid (160 c.c.) containing acetic anhydride (68 c.c.) and phosphoric oxide (*ca.* 0·3 g.), and the solution stirred at 5—10° while nitrosyl chloride (14 g.) in acetic anhydride (14 g.) was added (½ hr.). The yellow solution was stirred for a further ¼ hr., poured on ice, and the product salted out with potassium acetate (250 g.). The solid nitrosoacylamine was collected, dried, and used directly. Half the product of the last reaction was added gradually with stirring to 2 : 6-lutidine (60 g.) at 70°, nitrogen being evolved. The dark-coloured solution was made alkaline, the lutidine distilled in steam, and the residue thoroughly extracted with warm benzene. Washing, drying and removal of solvent gave a black viscous oil, which was distilled at low pressure. Mixed 6-2′ : 6′-lutidylquinolines were obtained as a dark-coloured glass (3 g.), b. p. 190—205°/0·002 mm. They were converted into the picrates, and the product crystallised six times from glacial acetic acid, yielding a *picrate* in yellow needles, m. p. *ca.* 243° (much decomp. beginning at 230°) (Found: N, 15·3. $C_{16}H_{14}N_2,C_6H_3O_7N_3$ requires N, 15·1%). Regeneration of the base gave 6-β-2′ : 6′-*dimethylpyridylquinoline*, crystallising from petroleum (b. p. 40—60°) or ether in needles, m. p. 68° (Found: C, 81·9; H, 5·9. $C_{16}H_{14}N_2$ requires C, 82·0; H, 6·0%).

7 (and 5)-γ-2′ : 6′-*Dimethylpyridylquinoline*.—*m*-Nitrobenzaldehyde (6 g.) and ethyl β-aminocrotonate (10 g.) were heated at 100° for 5 hrs. The product was cooled, and the hard yellow mass crystallised from ethanol. The dihydropyridine (yield, 14 g.; 80%) had m. p. 103°. The dihydro-ester (50 g.) was warmed with 2N-nitric acid (200 c.c.) until vigorous reaction set in, on completion of which the product was poured into cold water (300 c.c.), and the whole made alkaline. The product (yield, theoretical) crystallised from ethanol in white needles of ethyl 4-3′-nitrophenyl-2 : 6-dimethylpyridine-3 : 5-dicarboxylate, m. p. 63° (Lepetit, *Ber.*, 1887, **20**, 1340, gives m. p. 64°). The foregoing ester was reduced to the amino-compound with tin and hydrochloric acid (cf. Lepetit, *loc. cit.*) (yield, 80%). Ethyl 4-3′-aminophenyl-2 : 6-dimethylpyridine-3 : 5-dicarboxylate was hydrolysed in the same manner as the 4′-amino-isomeride above; the slightly moist acid (18 g.) was mixed with copper powder (30 g.) and heated in five portions in a vacuum in a hard glass tube over a free flame. The bulked yellow viscous distillate soon solidified and was crystallised from light petroleum (b. p. 100—120°). *m*-Aminophenyl-lutidine formed needles, m. p. 117° (lit., 110°) (yield, 9·0 g.; 73%) (Found: N, 14·0. Calc. for $C_{13}H_{12}N_2$: N, 14·1%). *m*-Aminophenyl-lutidine (3·1 g.), 66% sulphuric acid (30 g.), glycerol (7 g.), and sodium *m*-nitrobenzenesulphonate (6 g.) were refluxed for 4 hours, the product diluted and filtered, and the filtrate made alkaline. The hot liquid was extracted with benzene (2 × 70 c.c.), the extractant evaporated, and the residue distilled in a vacuum. The mixed lutidylquinolines were collected at 220—230°/15 mm., and soon solidified to a pale yellow mass, m. p. 98—110° (yield, 2·4 g.; 60%); the yield was poorer (*ca.* 33%) when arsenic acid was used. The mixture (2·6 g.) was treated

with picric acid (2·6 g.), each being dissolved in hot ethanol (25 c.c.); the mixed picrates which separated on cooling (5·1 g., m. p. 188—209°) were fractionally crystallised from glacial acetic acid to give two pure *isomerides*: (*a*) Less soluble (3·3 g.), m. p. 223° (Found: N, 15·0. $C_{16}H_{14}N_2,C_6H_3O_7N_3$ requires N, 15·1%). This picrate (2·2 g.) was warmed with 10% sodium hydroxide solution (25 c.c.), and the liberated base extracted with benzene; 0·9 g. of slightly discoloured crystals, m. p. 120—122°, were obtained which on recrystallising from light petroleum gave 7-*lutidylquinoline* in rhombs, m. p. 125° (Found: N, 11·9. $C_{16}H_{14}N_2$ requires N, 12·0%). (*b*) More soluble (0·1 g.), m. p. 231—234° (Found: N, 15·55%); on regeneration as in the previous preparation 5-*lutidylquinoline* was obtained; it separated in hard white crystals, m. p. 151°, from light petroleum (Found: N, 12·3%). It was identified with the product prepared from quinoline-5-carboxylic acid above.

8-*γ*-2′ : 6′-*Dimethylpyridylquinoline*.—Quinoline-8-carboxylic acid (22 g.) was added slowly to thionyl chloride (40 c.c.), and the mixture refluxed for 4 hrs. The excess of chloride was removed in a vacuum, ethanol (60 c.c.) added to the residue, and the product again refluxed for 2 hrs., then poured on ice and made alkaline; *ethyl quinoline-8-carboxylate* was liberated as an oil. It was extracted with ether and eventually distilled in a vacuum; it had b. p. 194—197°/13 mm., solidifying to form white needles, m. p. 45° (Found: N, 7·2. $C_{12}H_{11}O_2N$ requires N, 7·0%). *Quinoline-8-carboxyhydrazide* was prepared as above; it formed a pale yellow mass, which was extracted from the aqueous medium by hot benzene; addition of light petroleum gave needles, m. p. 99° (Found: N, 21·9. $C_{10}H_9ON_3$ requires N, 22·5%). The *toluenesulphonyl* derivative of the hydrazide separated in pale yellow rhombs, m. p. 187°, from ethanol (yield, 80%) (Found: N, 12·3. $C_{17}H_{15}O_3N_3S$ requires N, 12·3%). When this was submitted to the usual reaction with sodium carbonate in glycol, quinoline-8-aldehyde was obtained in 25% yield. Quinoline-8-aldehyde (1·03 g.), ethyl acetoacetate (1·8 g.), and ammonia (0·15 g.) in ethanol (4 c.c.) were heated for 7 hours at 100° (sealed tube), ethanol removed, the brown residue dissolved in benzene (50 c.c.), and the solution filtered through a column of activated alumina (15 cm. × 1·5 cm. diameter). *Ethyl* 4-8′-*quinolyl*-2 : 6-*dimethyldihydropyridine*-3 : 5-*dicarboxylate* was adsorbed as a yellow band, eluted with a mixture of benzene (90 c.c.) and ethanol (10 c.c.). It crystallised from the same solvent in orange plates, m. p. 161° (Found: N, 7·1. $C_{22}H_{24}O_4N_2$ requires N, 7·4%). The dihydro-ester (0·6 g.) was boiled for 5 mins. with 2N-nitric acid (2·4 c.c.) and the clear yellow solution cooled and made alkaline. The oily deposit soon solidified and was recrystallised from aqueous ethanol; *ethyl* 4-8′-*quinolyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* (0·5 g.) separated in plates, m. p. 80° (Found: C, 70·3; H, 6·1. $C_{22}H_{22}O_4N_2$ requires C, 69·8; H, 5·8%). The last ester (0·5 g.) was added to a solution of potassium hydroxide (0·65 g.) in ethanol, (2 c.c.), and the whole refluxed for 8 hrs. The silver salt was precipitated from the resulting solution with silver nitrate and a little acetic acid. When it was heated in a vacuum, a pale yellow sublimate of 8-*lutidylquinoline* was obtained; recrystallised from light petroleum, it formed needles (100 mg.), m. p. 132° (Found: N, 12·0. $C_{16}H_{14}N_2$ requires N, 12·0%).

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