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339. *New Therapeutic Agents of the Quinoline Series. Part VII. 2-, 3-, and 4-Pyridylquinolines, 4-Pyridylquinaldines, and 2-Pyridyllepidines.*

By D. H. Hey and J. M. Williams.

Eight of the nine isomeric pyridylquinolines in which the pyridyl group is attached to the heterocyclic ring of the quinoline molecule have been prepared by unambiguous synthetic methods. In addition, the three isomeric 4-pyridylquinaldines as well as the three 2-pyridyllepidines have been prepared.

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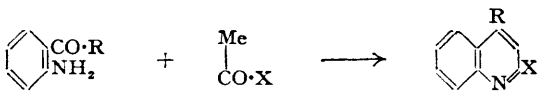
Previous communications in this series have described the preparation of a number of pyridylquinolines of many different types (Coates, Cook, Heilbron, Hey, Lambert, and Lewis, *J.*, 1943, 401 *et seq.*). With the exceptions of 2-2′-pyridylquinoline, first prepared by Smirnoff (*Helv. Chim. Acta*, 1921, **4**, 802), and two isomerides tentatively regarded as 3-2′- and 3-3′-pyridylquinoline (Coates *et al.*, *loc. cit.*), these communications were largely confined to the preparation of compounds in which the pyridyl group was attached to the carbocyclic ring of the quinoline molecule. Since many of the compounds thus described were found to possess spasmolytic properties in addition to a marked adrenaline action, attention has been redirected to this subject with the object of synthesising further members in which the pyridyl group is attached to the heterocyclic ring of the quinoline, quinaldine, or lepidine molecule. Such studies would also serve to establish the exact identity of the two 3-pyridylquinolines mentioned above. Further, Tscherne (*Monatsh.*, 1901, **22**, 615) has reported the formation of a pyridylmethylquinoline, regarded as 4-4′-pyridylquinaldine, from the cyclisation of the anil of 4-acetoacetylpyridine $PhN{:}CMe{\cdot}CH_2{\cdot}CO{\cdot}X$ (X = 4-pyridyl), but since the isomeric anil $PhN{:}CX{\cdot}CH_2{\cdot}CO{\cdot}Me$ (X = 4-pyridyl) may have been involved, the product may have been 2-4′-pyridyl-lepidine. This reaction has therefore been re-investigated.

The preparation of 2-2′-pyridylquinoline (I; R = H, X = 2-pyridyl) from 2-pyridyl methyl ketone and *o*-aminobenzaldehyde by the method of Smirnoff (*loc. cit.*) has been confirmed, and similar reactions have been carried out with 3-pyridyl and with 4-pyridyl methyl ketone to give the hitherto unknown 2-3′- and 2-4′-pyridylquinoline (I; R = H, X = 3-pyridyl) and (I; R = H, X = 4-pyridyl). All three 2-pyridylquinolines have been further characterised as the picrates.



(I.)

In order to establish the identity of the pyridylmethylquinoline prepared by Tscherne (*loc. cit.*) the three isomeric 2-pyridyl-lepidines (I; R = Me, X = 2, 3, and 4-pyridyl) were prepared by the condensation of the three pyridyl methyl ketones with *o*-aminoacetophenone, and the use of the anils of acetoacetylpyridines in the preparation of pyridylmethylquinolines has been further extended. Kuick and Adkins's procedure (*J. Amer. Chem. Soc.*, 1935, **57**, 143) for the preparation of 3-acetoacetylpyridine from ethyl nicotinate and acetone has been successfully applied to the preparation of the isomeric 2- and 4-acetoacetylpyridine from the ethyl esters of picolinic and *iso*nicotinic acid, respectively. The anils were prepared in acetic acid solution and cyclisation in concentrated sulphuric acid gave 4-2′-, 4-3′-, and 4-4′-pyridylquinaldine (II; X = 2-, 3-, and 4-pyridyl). The compound thus prepared from the anil of 4-acetoacetylpyridine had the same melting point as that reported by Tscherne (*loc. cit.*), and the melting point was depressed on admixture with an authentic specimen of 2-4′-pyridyl-lepidine, prepared as described above. This observation confirms the constitution of Tscherne's compound and shows that the intermediate anils must have the constitution $PhN{:}CMe{\cdot}CH_2{\cdot}CO{\cdot}X$ and not $PhN{:}CX{\cdot}CH_2{\cdot}CO{\cdot}Me$. Mixed melting point determinations with the picrates of the 3′- and 4′-isomerides in the two series could not be carried out, since the compounds in the quinaldine series yielded dipicrates, whereas those of the lepidine series gave monopicrates. The anil of 2-acetoacetylpyridine could not be obtained in crystalline form, unlike those of the 3- and 4-isomerides, and the yield of 4-2′-pyridylquinaldine obtained on cyclisation was low. Further, of the three isomeric 4-pyridylquinaldines, the 2′-isomeride alone gave a monopicrate.

Both 4-3′- and 4-4′-pyridylquinaldine (II; X = 3- and 4-pyridyl) were converted by oxidation with chromic acid of the phthalone into the corresponding quinaldinic acid, isolated as the ethyl ester. The styryl derivatives proved to be less suitable for oxidation. The pure esters were hydrolysed to 4-3′- and 4-4′-pyridylquinaldinic acid (III; X = 3- and 4-pyridyl),

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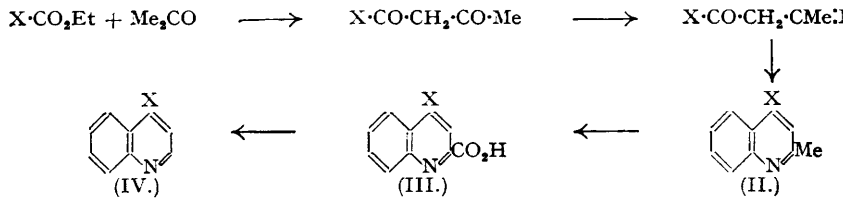
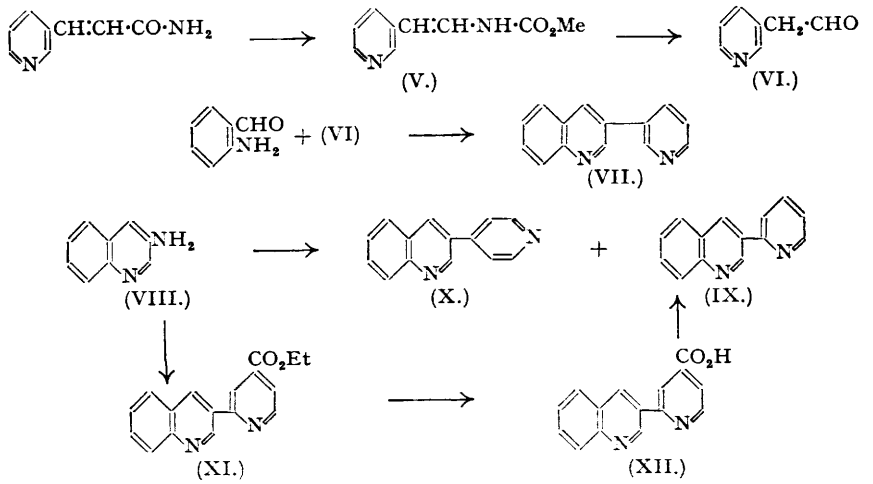
which in turn were subjected to decarboxylation by boiling in quinoline solution containing copper chromite. In this manner 4-3′- and 4-4′-pyridylquinoline (IV; X = 3- and 4-pyridyl) were obtained.



In order to obtain the 3-pyridylquinolines by methods which could leave no doubt concerning the identity of the products, attempts were first made to use an ester of 2-pyridylacetic acid for which convenient preparative methods were available (Clemo, Morgan, and Raper, *J.*, 1935, 1743; Bills and Noller, *J. Amer. Chem. Soc.*, 1948, **70**, 957). 3-2′-Pyridylcarbostyril was readily obtained from *o*-aminobenzaldehyde and ethyl 2-pyridylacetate in presence of piperidine, and 2 : 4-dihydroxy-3-2′-pyridylquinoline was obtained in good yield from methyl anthranilate and ethyl 2-pyridylacetate, but attempts to replace the hydroxyl groups in these compounds by chlorine (with phosphorus oxychloride and pentachloride) or by hydrogen (with phosphorus and iodine) were unsuccessful. By means of a Claisen condensation ethyl formyl-2-pyridylacetate was obtained in good yield from ethyl formate and ethyl 2-pyridylacetate, but attempts to cyclise the anil derived from this ester were abortive. Several unsuccessful attempts were also made to prepare 2-pyridylacetaldehyde, which should react with *o*-aminobenzaldehyde to give 3-2′-pyridylquinoline. Thus, the action of 2-picolyl-lithium on ethyl formate or on ethyl orthoformate led to products of doubtful aldehydic properties and the product obtained from the simultaneous hydrolysis and decarboxylation of ethyl formyl-2-pyridylacetate was of uncertain character. On the other hand, 3-pyridylacetaldehyde (VI) was prepared in solution by the hydrolysis of methyl 2-3′-pyridylvinylcarbamate (V), which in turn was obtained by the Hofmann rearrangement of β-3-pyridylacrylamide (cf. Panizzon, *Helv. Chim. Acta*, 1941, **24**,



24E) in methyl alcohol using a concentrated alkaline solution of sodium hypochlorite. Condensation of this aldehyde with *o*-aminobenzaldehyde gave 3-3′-pyridylquinoline (VII), which was characterised as the dipicrate. For purposes of comparison the 3-pyridylquinolines previously described by Coates *et al.* (*loc. cit.*) were prepared from diazotised 3-aminoquinoline (VIII) and pyridine, but neither of these proved to be identical with the authentic specimen of 3-3′-pyridylquinoline from evidence obtained from mixed melting point determinations on the picrates. In order to establish the identity of the isomerides obtained in the reaction between diazotised 3-aminoquinoline and pyridine a reaction was conducted between diazotised 3-aminoquinoline (VIII) and ethyl *iso*nicotinate which, it was expected, would yield mainly ethyl 2-3′-quinolyl*iso*nicotinate (XI) but which, in any case, could not give rise to substitution at the

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4-position. Hydrolysis of the product gave an acid (XII), which on decarboxylation gave a 3-pyridylquinoline (IX) identical with one of the products obtained as described above from the reaction between diazotised 3-aminoquinoline and pyridine. This compound must therefore be 3-2′-pyridylquinoline, in agreement with the original suggestion by Coates *et al.* (*loc. cit.*), but their second isomeride would now appear to be 3-4′-pyridylquinoline (X), although this conclusion requires confirmation by an independent synthesis.

Experimental.

2-2′-Pyridylquinoline (4·1 g.) was prepared by Smirnoff's method (*loc. cit.*) by the condensation of 2-pyridyl methyl ketone (5 g.) (Kolloff and Hunter, *J. Amer. Chem. Soc.*, 1941, **63**, 490) with *o*-aminobenzaldehyde (5 g.) in dilute potassium hydroxide solution (20 c.c.; 0·01%). After repeated crystallisation from light petroleum the base melted at 98° and the picrate at 182—183°. Smirnoff quotes m. p. 99° and 182—183° for the free base and picrate, respectively.

2-3′-*Pyridylquinoline*.—A solution of 3-pyridyl methyl ketone (5 g.) (Kolloff and Hunter, *loc. cit.*) and *o*-aminobenzaldehyde (5 g.) in dilute alcoholic potassium hydroxide (20 c.c.; 0·01%) was heated on a water-bath for one hour. The oil which separated on addition of water was extracted with ether. The viscous liquid, after removal of the ether, partially crystallised on being kept. The solid was separated from oily residues by spreading on a porous plate; repeated crystallisation from light petroleum (b. p. 60—80°) gave 2-3′-*pyridylquinoline* (3 g.) in robust rhombic crystals, m. p. 66·5° (Found: C, 81·2; H, 4·9. $C_{14}H_{10}N_2$ requires C, 81·5; H, 4·9%). The *picrate* crystallised from acetone–alcohol in fine yellow needles which sintered at 185° and melted at 199° (Found: C, 55·3; H, 3·3. $C_{14}H_{10}N_2,C_6H_3O_7N_3$ requires C, 55·2; H, 3·0%).

2-4′-*Pyridylquinoline*.—4-Pyridyl methyl ketone (4·2 g.) (Kolloff and Hunter, *loc. cit.*) and *o*-aminobenzaldehyde (4·2 g.) were condensed under identical conditions to those described above to give 2-4′-*pyridylquinoline* (5·3 g.), which crystallised from light petroleum (b. p. 80—100°) in leaflets, m. p. 96° (Found: C, 81·6; H, 4·8%). The *picrate* separated from acetone in fine yellow needles which sintered at 180° and melted at 207° (Found: C, 55·5; H, 3·2%).

2-2′-*Pyridyl-lepidine*.—To a solution of *o*-aminoacetophenone (3 g.) and 2-pyridyl methyl ketone (3 g.) in alcohol (15 c.c.) was added aqueous sodium hydroxide (0·05 c.c.; 20%), and the mixture was boiled for eighteen hours under reflux on a water-bath. Most of the alcohol was then distilled from the mixture, and the oil which separated on addition of water was extracted with ether. The ethereal extract was dried (K_2CO_3) and, after removal of the ether, the residue was distilled under reduced pressure to give 2-2′-*pyridyl-lepidine* (3·1 g.; b. p. 156°/0·5 mm.), which separated from light petroleum (b. p. 60—80°) in needles, m. p. 67° (Found: C, 81·3; H, 5·2. $C_{15}H_{12}N_2$ requires C, 81·8; H, 5·5%). The *picrate* separated from alcohol in fine needles, m. p. 160° (Found: C, 55·8; H, 3·0. $C_{15}H_{12}N_2,C_6H_3O_7N_3$ requires C, 56·1; H, 3·4%).

2-3′-*Pyridyl-lepidine*.—*o*-Aminoacetophenone (3 g.) and 3-pyridyl methyl ketone (3 g.) were condensed under identical conditions to those described above for 2-2′-pyridyl-lepidine; 2-3′-*pyridyl-lepidine* (3·3 g.; b. p. 176—180°/0·7 mm.) separated from light petroleum (b. p. 60—80°) in needles, m. p. 66·5° (Found: C, 81·7; H, 5·5%). The *picrate* separated from dioxan in needles, m. p. 219—220° (Found: C, 56·2; H, 3·4%).

2-4′-*Pyridyl-lepidine*.—*o*-Aminoacetophenone (3 g.) and 4-pyridyl methyl ketone (3 g.) were condensed under identical conditions to those given above. 2-4′-*Pyridyl-lepidine* (3·0 g.; b. p. 178°/0·7 mm.) separated from benzene–light petroleum (b. p. 60—80°) in hard needles, m. p. 101—102° (Found: C, 81·7; H, 5·5%). The *picrate* separated from dioxan–*cyclo*hexanone in fine needles, which melted with decomposition at 250—252° (Found: C, 55·8; H, 3·5%).

The three acetoacetylpyridines were prepared from the appropriate pyridinecarboxylic ester and acetone by the modified conditions described by Kuick and Adkins (*loc. cit.*) for the preparation of 3-acetoacetylpyridine. 2-Acetoacetylpyridine (b. p. 97—98°/0·4 mm.), prepared in 55% yield, separated from light petroleum (b. p. 40—60°) in hard needles, m. p. 51°. Micko (*Monatsh.*, 1896, **17**, 442) gives m. p. 49—50° for this ketone. 4-Acetoacetylpyridine (b. p. 143—145°/0·4 mm.), prepared in 52% yield, separated from light petroleum (b. p. 60—80°) in fine needles, m. p. 63°. Tscherne (*loc. cit.*) give m. p. 62° for this ketone.

4-2′-*Pyridylquinaldine*.—2-Acetoacetylpyridine (5 g.), aniline (2·8 g.), and acetic acid (2·5 g.) were heated at 80° for four hours. The oil which was liberated on pouring the mixture on crushed ice failed to crystallise on being kept. The oil was therefore extracted with ether, the ether extract dried (K_2CO_3), and, after concentration of the extract to 30 c.c., light petroleum (b. p. 40—60°) was added until a turbidity appeared in the solution. The mixture was then boiled with animal charcoal and filtered. The pale yellow oil resulting after evaporation of the filtrate was dissolved in concentrated sulphuric acid (25 c.c.; *d* 1·84) and heated in an oil-bath at 110° for two hours. When the cold dark-coloured mixture was poured on crushed ice and the acid neutralised with aqueous ammonia an oil separated which was extracted with ether. After removal of the ether there remained a viscous oil, which partly solidified on cooling. The solid, separated from oily residues by spreading on a porous plate, was repeatedly crystallised from light petroleum (b. p. 60—80°) and gave 4-2′-*pyridylquinaldine* (0·5 g.) in needles, m. p. 84° (Found: C, 82·0; H, 5·6. $C_{15}H_{12}N_2$ requires C, 81·8; H, 5·5%). The *picrate* separated from dioxan in fine orange needles, m. p. 186—187° (Found: C, 56·4; H, 3·9. $C_{15}H_{12}N_2,C_6H_3O_7N_3$ requires C, 56·1; H, 3·4%).

4-3′-*Pyridylquinaldine*.—3-Acetoacetylpyridine (5 g.), aniline (2·8 g.), and acetic acid (2·5 g.) were heated at 80° for four hours. The mixture was poured on crushed ice (50 g.) and after the acetic acid had been neutralised with sodium carbonate the solid which separated was filtered from the solution, washed with water, and dried in a vacuum desiccator ($CaCl_2$). Crystallisation from light petroleum (b. p. 60—80°) gave the *anil* (5·7 g.) in yellow platelets, m. p. 83° (Found: C, 75·5; H, 5·8. $C_{15}H_{14}ON_2$

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requires C, 75·65; H, 5·9%). The anil (5 g.) was dissolved in cold concentrated sulphuric acid (25 c.c.; *d* 1·84) and heated in an oil-bath at 105° for two hours. The solution now showed a green fluorescence. The mixture was poured on crushed ice, and made alkaline with ammonia solution, and the liberated oil extracted with ether. The extract was dried (K_2CO_3) and after removal of the solvent the residue was distilled under reduced pressure to give **4-3′-*pyridylquinaldine*** (3·5 g.; b. p. 150—152°/0·5 mm.), which separated from light petroleum in cubic crystals, m. p. 107° (Found: C, 82·1; H, 5·2%). The picrate, prepared in the normal manner, decomposed on crystallisation from dioxan–*cyclo*hexanone. It was therefore prepared by mixing hot acetone solutions of the base and picric acid. After cooling, the crystals were filtered off and washed with cold acetone. The *dipicrate* thus prepared sintered at 182° and melted with decomposition at 202—203° (Found: C, 47·5; H, 3·0. $C_{15}H_{12}N_2,2C_6H_3O_7N_3$ requires C, 47·8; H, 2·8%).

4-4′-*Pyridylquinaldine*.—4-Acetoacetylpyridine (5 g.), aniline (2·8 g.), and acetic acid (2·5 g.) were heated together at 80° for four hours. The *anil* (5·5 g.) obtained on treatment of the mixture with ice and water and neutralisation of the acid with sodium carbonate, separated from light petroleum (b. p. 60—80°) in flat needles, m. p. 101° (Found: C, 75·7; H, 5·6%). Tscherne (*loc. cit.*), who prepared the anil from aniline hydrochloride and the diketone, records m. p. 103°. The anil (5 g.) was condensed under identical conditions to those given above for 4-3′-pyridylquinaldine. 4-4′-Pyridylquinaldine (4·0 g.; b. p. 162—164°/0·5 mm.) separated from light petroleum (b. p. 60—80°) in hard needles, m. p. 103° (Found: C, 81·7; H, 5·6%). The melting point on admixture with 2-4′-pyridyl-lepidine was found to be *ca.* 80°. Tscherne (*loc. cit.*) records m. p. 101—102° for the cyclised product. The *dipicrate* separated from dioxan in orange needles, m. p. 186—187° (Found: C, 47·9; H, 2·9%).

4-3′-*Pyridyl-2-styrylquinoline*.—A mixture of 4-3′-pyridylquinaldine (7·2 g.), benzaldehyde (3·13 g.), and acetic anhydride (3·4 g.) was boiled under reflux for thirty hours. The mixture was then distilled with steam to remove excess of benzaldehyde. The viscous dark brown oil solidified on cooling and crystallisation from dioxan gave crude **4-3′-*pyridyl-2-styrylquinoline*** (7·8 g.). A sample, after repeated crystallisation from dioxan, melted at 164° (Found: C, 84·9; H, 5·1. $C_{22}H_{16}N_2$ requires C, 85·6; H, 5·2%).

Ethyl **4-3′-*Pyridylquinaldinate*.**—4-3′-Pyridylquinaldine (9 g.) was heated in a sealed tube at 160—170° for eight hours with phthalic anhydride (9 g.) and fused zinc chloride (2 g.). After cooling, the phthalone was dissolved in sulphuric acid (200 c.c.; 66%) and a solution of chromium trioxide (4·8 g.) in the minimum quantity of water was added in one portion. The mixture was maintained at 90° for ½ hour and then the excess of chromic acid was destroyed by the addition of alcohol (5 c.c.). While the mixture was externally cooled by an ice–salt mixture, sodium hydroxide solution was slowly added until a pH of 3 was reached. The mixture was then filtered and the residue was extracted several times with aqueous sodium hydroxide (10%). The combined alkaline extracts and filtrate were evaporated to dryness on a water-bath. The residue, containing much sodium sulphate, was suspended in absolute alcohol (100 c.c.), concentrated sulphuric acid (25 c.c.) was added, and the mixture was heated on a steam-bath for eight hours. It was then poured on crushed ice, and after the acid had been neutralised with aqueous ammonia the ester was extracted with benzene. The benzene extracts were shaken with dilute hydrochloric acid (50 c.c.; 10%); neutralisation of the acid extract with aqueous ammonia caused the immediate precipitation of the ester which, on crystallisation from benzene, gave *ethyl* **4-3′-*pyridylquinaldinate*** (3 g.) in fine needles, m. p. 160—161° (Found: C, 73·35; H, 5·2. $C_{17}H_{14}O_2N_2$ requires C, 73·35; H, 5·1%).

In a second method the styryl derivative (7·8 g.) was oxidised with chromic anhydride as described above for the phthalone and gave ethyl 4-3′-pyridylquinaldinate (0·9 g.) in needles, m. p. 160—161°, from benzene.

Ethyl **4-4′-*Pyridylquinaldinate*.**—4-4′-Pyridylquinaldine (11 g.) was heated in a sealed tube at 160—170° for eight hours with phthalic anhydride (11 g.) and zinc chloride (2·5 g.). The resulting phthalone was oxidised as described above for the 3′-isomeride. The isolation and preparation of the ester were also effected as previously described. *Ethyl* **4-4′-*pyridylquinaldinate*** (1·5 g.) separated from alcohol in fine needles, m. p. 146° (Found: C, 73·3; H, 5·0%).

4-3′-*Pyridylquinaldinic Acid*.—Ethyl 4-3′-pyridylquinaldinate (3·6 g.) was hydrolysed with alcoholic potassium hydroxide. The potassium salt was filtered off and decomposed by dissolving it in the minimum quantity of water and adding acetic acid. The free *acid* (3·1 g.), purified by precipitation from potassium carbonate solution, separated in plates, m. p. 203° (Found: C, 72·0; H, 4·0. $C_{15}H_{10}O_2N_2$ requires C, 72·0; H, 4·0%).

4-4′-*Pyridylquinaldinic Acid*.—Ethyl 4-4′-pyridylquinaldinate (1·4 g.) was hydrolysed with alcoholic potassium hydroxide. The acid, isolated as described above, gave **4-4′-*pyridylquinaldinic acid*** (1·2 g.), which separated from water in fine needles, m. p. 225° (decomp.) (Found: C, 72·0; H, 4·1%).

4-3′-*Pyridylquinoline*.—4-3′-Pyridylquinaldinic acid (3·0 g.) was boiled under reflux for one hour with copper chromite (0·1 g.) in quinoline (20 c.c.). Most of the quinoline was distilled from the mixture, the last traces being removed by distillation with steam. The residual oil, which failed to crystallise, was dissolved in ether, the solution was filtered, and after removal of the ether the residue was distilled under reduced pressure to give **4-3′-*pyridylquinoline*** (2·2 g.; b. p. 156—157°/1 mm.), which separated from light petroleum (b. p. 60—80°) containing a trace of benzene in cubic crystals, m. p. 74° (Found: C, 81·7; H, 5·2%). The *dipicrate* separated from dioxan in fine needles, m. p. 210—212° having first sintered at 190° (Found: C, 46·5; H, 2·4. $C_{14}H_{10}N_2,2C_6H_3O_7N_3$ requires C, 47·0; H, 2·4%).

4-4′-*Pyridylquinoline*.—4-4′-Pyridylquinaldinic acid (1·2 g.) was decarboxylated under identical conditions to those described above. 4-4′-Pyridylquinoline (0·5 g.; b. p. 152°/0·1 mm.) separated from light petroleum (b. p. 40—60°) in needles, m. p. 83° (Found: C, 81·75; H, 4·8%). The picrate decomposed on crystallisation from dioxan. Hot acetone solutions of the base and picric acid were therefore mixed and the resulting *dipicrate* was found to sinter at 176° and to melt at 225° (Found: C, 47·0; H, 2·4%).

Ethyl 2-*Pyridylacetate*.—Copper 2-pyridylacetate (44 g.; Bills and Noller, *loc. cit.*) was converted into

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ethyl 2-pyridylacetate (20 g.; b. p. 120—121°/15 mm.) by the method described by these authors for the methyl ester. The same ester was also prepared as described by Clemo, Morgan, and Raper (*loc. cit.*).

3-2′-*Pyridylcarbostyril*.—Ethyl 2-pyridylacetate (5 g.) was heated at 120° in an oil-bath with *o*-aminobenzaldehyde (3·34 g.) in the presence of piperidine (0·5 c.c.). Crystallisation from dioxan of the resulting solid gave 3-2′-*pyridylcarbostyril* (5 g.) in fine needles, m. p. 233° (Found: C, 75·6; H, 4·5; N, 12·6. $C_{14}H_{10}ON_2$ requires C, 75·7; H, 4·5; N, 12·6%).

2 : 4-*Dihydroxy*-3-2′-*pyridylquinoline*.—Coarsely granulated sodium (0·6 g.) was added to a mixture of ethyl 2-pyridylacetate (3·5 g.) and methyl anthranilate (3·2 g.). When the initial reaction had subsided the mixture was heated on a steam-bath for two hours and finally in an oil-bath at 120°. The mixture was cooled and ethyl alcohol (10 c.c.) added. The mixture was then poured into water and neutralised with acetic acid. The white crystalline solid which separated was filtered off and crystallised from acetic acid. 2 : 4-*Dihydroxy*-3-2′-*pyridylquinoline* (3·75 g.) separated in colourless needles, m. p. 290° (Found: C, 70·3; H, 4·2. $C_{14}H_{10}O_2N_2$ requires C, 70·6; H, 4·2%).

Ethyl Formyl-2-*pyridylacetate*.—To granulated sodium (0·8 g.) in anhydrous ether (30 c.c.) was added a mixture of ethyl 2-pyridylacetate (5 g.) and ethyl formate (3 g.) in anhydrous ether (10 c.c.). The mixture was mechanically stirred and externally cooled by an ice–salt mixture. After three hours the sodium had all dissolved and the sodio-derivative of ethyl formyl-2-pyridylacetate began to separate. The mixture was shaken with water, and the aqueous solution extracted with ether to remove unchanged starting materials. The aqueous layer was made just acid by the addition of dilute sulphuric acid and the excess of acid was neutralised with sodium hydrogen carbonate. The resulting crystalline solid was filtered off and recrystallisation from light petroleum (b. p. 60—80°) containing a trace of benzene gave *ethyl formyl*-2-*pyridylacetate* (3·5 g.) in fine needles, m. p. 98° (Found: C, 61·9; H, 5·7. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7%). The ester was rapidly hydrolysed with simultaneous decarboxylation by dilute mineral acids. The resulting solutions showed aldehydic properties, but no aldehyde could be extracted from the solution.

Methyl 2-3′-*Pyridylvinylcarbamate*.—A concentrated alkaline solution of sodium hypochlorite was prepared by the passage of chlorine (3·5 g.) into a mixture of sodium hydroxide (10 g.), water (15 c.c.), and ice (20 g.) cooled by an ice–salt mixture. The volume was then adjusted to 50 c.c. with cold water. The freshly prepared sodium hypochlorite solution (6·8 c.c.) was added to a solution of β-3-pyridylacrylamide (1·7 g.; Panizzon, *loc. cit.*) in methyl alcohol (20 c.c.). The mixture was warmed on a water-bath for five minutes, and the methyl alcohol was then distilled off under reduced pressure, which caused the separation of a crystalline solid. After ½ hour at 0° the solid was filtered off; recrystallisation from carbon tetrachloride gave *methyl* 2-3′-*pyridylvinylcarbamate* (1·2 g.) in needles, m. p. 145° (Found: C, 60·3; H, 5·3; N, 16·1. $C_9H_{10}O_2N_2$ requires C, 60·7; H, 5·6; N, 15·7%).

3-3′-*Pyridylquinoline*.—Methyl 2-3′-pyridylvinylcarbamate (0·5 g.) was dissolved in absolute alcohol (5 c.c.) and sulphuric acid (1·8 c.c.; 6N.) was added to the hot solution. The mixture was gently boiled on a water-bath for five minutes. A test portion of the solution was added to 2 : 4-dinitrophenylhydrazine in sulphuric acid. The 2 : 4-*dinitrophenylhydrazone sulphate* separated from the solution almost immediately and after recrystallisation from dilute sulphuric acid melted at 211° with decomposition (Found: C, 39·6; H, 3·1. $C_{13}H_{11}O_4N_5,H_2SO_4$ requires C, 39·1; H, 3·3%). The remainder of the above mixture was neutralised with a solution of sodium ethoxide in alcohol and *o*-aminobenzaldehyde (0·3 g.) was added. The hydrogen-ion concentration was then adjusted to pH 11 with aqueous sodium hydroxide, and the mixture again heated on a water-bath for two hours. Most of the alcohol was then distilled from the solution and the oil liberated on addition of water was extracted with ether. After removal of the ether by distillation the residue solidified on cooling. 3-3′-*Pyridylquinoline* (0·1 g.) separated from benzene–light petroleum (b. p. 80—100°) in needles, m. p. 124° (Found: C, 81·7; H, 5·1%). The *dipicrate* separated from dioxan in small orange needles which sintered at 180° and melted at 222—223° (Found: C, 47·5; H, 2·5%).

2-3′-*Quinolyl*-*iso*-*nicotinic Acid*.—A solution of 3-aminoquinoline (7·7 g.) in concentrated hydrochloric acid (35 c.c.) and water (15 c.c.) was diazotised at 0—5° with a concentrated aqueous solution of sodium nitrite (4 g.). The suspension of the diazonium salt was added in small portions to well stirred ethyl *iso*nicotinate (75 g.) at 50°. After the addition the mixture was warmed to 90° for ten minutes to complete the reaction. The mixture was then cooled by the addition of crushed ice and made alkaline with aqueous ammonia. The mixture was extracted with ether, the ethereal extract dried (K_2CO_3), and the ether removed by distillation. The excess of ethyl *iso*nicotinate was distilled off under reduced pressure and the residue partly distilled and partly sublimed to give a mixture of bases (4·3 g.; b. p. 160—180°/7 × 10^{-3} mm.). On crystallisation from acetone 3-hydroxyquinoline (2·9 g.) separated in cubic crystals, m. p. 190°, and further crystallisation raised the melting point to 196°. Mills and Watson (*J.*, 1910, **97**, 741) record m. p. 198° for 3-hydroxyquinoline. Removal of the acetone from the original mother-liquors left an oil and a further quantity of 3-hydroxyquinoline. The oil was removed from the crystalline solid by trituration with alcohol. After the addition of potassium hydroxide (1 g.) to the alcoholic extracts the mixture was boiled under reflux for two hours. On cooling, the potassium salt of 2-3′-quinolyl*iso*nicotinic acid (0·5 g.) separated, and a further quantity was obtained from the mother-liquors. The potassium salt was dissolved in the minimum quantity of water and the free acid liberated by the addition of acetic acid. The acid was purified by dissolving it in aqueous sodium carbonate and stirring with animal charcoal. Acidification of the colourless filtrate with acetic acid gave 2-3′-*quinolyl*-*iso*-*nicotinic acid* as a white flocculent precipitate, which crystallised from dioxan in fine needles, m. p. 290° (Found: C, 72·0; H, 3·9. $C_{15}H_{10}O_2N_2$ requires C, 72·0; H, 4·0%). No trace of a second isomeride could be detected.

3-2′-*Pyridylquinoline*.—2-3′-Quinolyl*iso*nicotinic acid (0·4 g.) was ground with soda–lime (1 g.) and the mixture dried in an air-oven at 120° for two hours and then strongly heated in a Pyrex tube. 3-2′-Pyridylquinoline distilled from the mixture and, after recrystallisation from light petroleum (b. p. 60—80°) containing a trace of benzene, melted at 99° (Found: N, 13·1. Calc. for $C_{14}H_{10}N_2$: N, 13·6%). No depression in melting point was observed when this compound was mixed with a specimen of 3-2′-pyridylquinoline prepared by the method of Coates *et al.* (*loc. cit.*).

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Thanks are due to Professor G. R. Clemo, F.R.S., for providing experimental details for the preparation of ethyl 2-pyridylacetate from the oxime of 2-phenacylpyridine. One of us (J. M. W.) also thanks the South African Council for Industrial and Scientific Research for the award of a Post-M.Sc. Research Bursary held during the present investigation.

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[*Received, March 23rd*, 1950.]

Published on 01 January 1950. Downloaded by University of Birmingham on 19/07/2015 15:52:43.