598. *Dialkylaminoalkylquinolines.*

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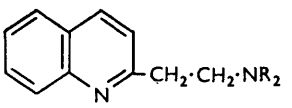
A number of 2-, 4-, 6-, and 8-dialkylaminoalkylquinolines and simple derivatives thereof have been prepared for pharmacological evaluation.

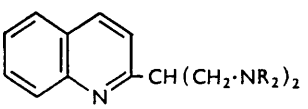
In view of the pharmacological significance of dialkylaminoalkyl compounds on the one hand and quinoline derivatives on the other, and the spasmolytic activity of certain pyridylquinolines [1] and 3-dialkylaminomethyl-4-hydroxyquinolines,[2] the scant attention paid to simple dialkylaminoalkylquinolines is somewhat surprising.

Apart from processes involving closure of the pyridine ring as the final stage,[3] syntheses of 2- and 4-2′-dialkylaminoethylquinolines have always utilised the reactivity of methyl groups in the 2- and the 4-position of the quinoline nucleus, the simplest procedure being the Mannich reaction with formaldehyde and a secondary amine. We confirmed the observation of Tseou Héou-Féo [4] that reaction of equimolecular amounts of quinaldine, formaldehyde, and diethylamine hydrochloride provides a satisfactory route to 2-2′-diethylaminoethylquinoline (I; R = Et), but in our hands the procedure was less satisfactory for certain other 2-2′-dialkylaminoethylquinolines.

Although Bartholomaus [5] reported the preparation of 2-2′-dimethylaminoethylquinoline (I; R = Me) by the Mannich reaction, Boekelheide and Marinetti [6] found that when only the calculated amount of quinaldine was used the main product was the bis-compound (II; R = Me), b. p. 139—145°/2 mm. Using twice the theoretical amount of



(I)



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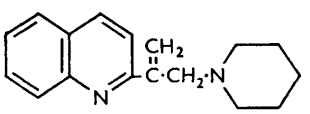

(III)

quinaldine the latter workers obtained the simple Mannich base (I; R = Me), b. p. 120—129°/0·7 mm., which they converted by methyl sulphate and ethyl sodiomalonate or the sodio-derivatives of β-keto-esters into α-substituted γ-2-quinolylbutyric esters. However, in view of the nearness of the reported boiling point to that of the bis-compound (II; R = Me) and the absence of analytical data, the purity of Boekelheide and Marinetti's sample is uncertain. Under various conditions we have invariably obtained good yields of the bis-product (II; R = Me), b. p. 102—106°/0·1 mm., from this reaction but no pure mono-derivative (I; R = Me).

The preparation of 2-2′-piperidinoethylquinoline (I; $R_2 = <[CH_2]_5$) from quinaldine, formaldehyde, and piperidine hydrochloride has been reported, the product being isolated by distillation under reduced pressure [4] or as the picrate,[3a] m. p. 155°. By the former

[1] Coates, Cook, Heilbron, Hey, Lambert, and Lewis, *J.*, 1943, 401, and later Parts of the Series.
[2] Ghosh, Kundu, and Chaudhuri, *J. Indian Chem. Soc.*, 1952, **29**, 368.
[3] (*a*) Kermack and Muir, *J.*, 1931, 3089; (*b*) Mannich and Schilling, *Arch. Pharm.*, 1938, **276**, 582.
[4] Tseou Héou-Féo, *Compt. rend.*, 1931, **192**, 1242; *Bull. Soc. chim. France*, 1935, **2**, 96.
[5] Bartholomaus, G.P. 497,907.
[6] Boekelheide and Marinetti, *J. Amer. Chem. Soc.*, 1951, **73**, 4015.

procedure our main fraction proved to be 2-(1-methylene-2-piperidinoethyl)quinoline (III), whilst a higher-boiling residue (possibly II; $R_2 = <[CH_2]_5$) appeared to decompose on strong heating, giving more (III). In our hands, attempted isolation of the picrate gave a mixture from which only the picrate of (III), m. p. 203—204°, was isolated in a pure state.

The marked influence of the nature of the secondary amine on the course of Mannich reactions involving quinaldine finds a parallel in similar reactions with γ-picoline,[7] which gives pyridine analogues of (II) and (III) with dimethylamine or piperidine, but simple Mannich bases analogous to (I) with the less reactive diethylamine, di*iso*propylamine, di-*n*-butylamine, pyrrolidine, and morpholine. We therefore examined the reaction of quinaldine and formaldehyde with pyrrolidine hydrochloride and obtained two main fractions from which 2-2′-pyrrolidinoethylquinoline (I; $R_2 = <[CH_2]_4$) and the bis-compound (II; $R_2 = <[CH_2]_4$) were isolated as dipicrates.

In contrast to the complexities encountered in the reaction of quinaldine with formaldehyde and secondary amines, lepidine and substituted lepidines gave 4-2′-dialkylaminoethylquinolines as the only isolable products. Indeed the interaction of lepidine, formaldehyde, and diethylamine hydrochloride was so free from side-reactions that 4-2′-diethylaminoethylquinoline monohydrochloride could be isolated merely by evaporating the reaction mixture to dryness and recrystallising the residue. 4-2′-Dimethylaminoethyl-, 4-2′-pyrrolidinoethyl-, and 4-2′-piperidinoethyl-quinoline were similarly prepared, but were isolated by distilling the bases. 6-Chlorolepidine reacted similarly with formaldehyde and dimethylamine, diethylamine, or piperidine, as did 6-methoxylepidine with formaldehyde and diethylamine. Only impure Mannich bases were isolated from 6-methoxylepidine, formaldehyde, and dimethylamine or piperidine since distillation failed to effect separation from some accompanying 4-2′-hydroxyethyl-6-methoxyquinoline, but derivatives could be prepared satisfactorily from the crude bases. The yields of 4-2′-dialkylaminoethylquinolines were not high, but a fair proportion of the lepidine or substituted lepidine could usually be recovered.

Preparation of 8-2′-dimethylaminoethyl- and 8-2′-diethylaminoethyl-quinoline was conveniently effected from 8-quinolylacetic acid by reducing the dialkylamides with lithium aluminium hydride. Although certain quinoline derivatives are reduced to unstable 1 : 2-dihydroquinolines by this reagent the ease of reduction depends markedly on the nature and position of substituents.[8] In the present examples no reduction of the nucleus was observed, possibly because of the rapid separation of the ether-insoluble lithium aluminium hydride complexes of the dialkylaminoalkylquinolines. The diethylamide of quinoline-6-carboxylic acid was similarly reduced to 6-diethylaminomethylquinoline, whilst the isomeric 8-diethylaminomethylquinoline and its dimethylamino- and piperidino-analogues were prepared from 8-bromomethylquinoline by Kermack, Muir, and Wight's method.[9] The latter workers isolated their products only in the form of salts, but the pure bases have now been prepared as well.

Several 2- and 4-2′-dialkylaminoethylquinolines have been reported [4] to resinify in air but, except for the base (III) which has an unsaturated side-chain, all our dialkylaminoalkylquinolines were stable.

Most of the dialkylaminoalkylquinolines prepared in this work were characterised as monopicrates, which were often easier to purify than the dipicrates. Dihydrochlorides and monomethiodides were prepared for pharmacological examination: many of these salts were deliquescent and a number formed definite hydrates. Mr. D. M. Brown of these laboratories has shown that this group of compounds possesses no outstanding pharmacological properties.

[7] Matuszko and Taurins, *Canad. J. Chem.*, 1954, **32**, 538.
[8] Rosenmund and Zymalkowski, *Chem. Ber.*, 1953, **86**, 37; Rosenmund, Zymalkowski, and Schwarte, *ibid.*, 1954, **87**, 1229.
[9] Kermack, Muir, and Wight, *J.*, 1935, 1143.

Experimental

Derivatives of Dialkylaminoalkylquinolines.—The following general preparative methods were employed : Monopicrates were obtained by mixing warm alcoholic solutions of the bases and picric acid in equimolecular proportions, cooling, and collecting the products. Dihydrochlorides were produced by dissolving the bases in about twice the calculated quantity of 10% ethanolic hydrogen chloride at ordinary temperature and, if the salt did not separate within a few minutes, cautiously adding dry ether. Monomethiodides were prepared by adding methyl iodide in 10% excess to solutions of the bases in a little ethyl acetate and storage at room temperature until precipitation of product appeared to be complete (15 min. to 3 hr.).

2-(1-*Methylene-2-piperidinoethyl)quinoline.*—(*a*) A mixture of quinaldine (14 ml.), 38% aqueous formaldehyde (8·5 ml.), piperidine (10 ml.), alcohol (10 ml.), and 5N-hydrochloric acid (18 ml.) was heated at 50—55° for 90 min., then concentrated under reduced pressure. Sodium carbonate (15 g.) in water was added and the mixture was extracted with ether. Distillation of the dried extracts gave a yellow oil (9·25 g.), b. p. 140—157°/0·2 mm., which on refractionation afforded pure 2-(1-*methylene-2-piperidinoethyl)quinoline* (3·1 g.), b. p. 127—132°/0·15 mm. (Found : C, 80·7; H, 8·4; N, 10·9. $C_{17}H_{20}N_2$ requires C, 80·9; H, 8·0; N, 11·1%). On stronger heating (bath at 240—260°) a further quantity (3·4 g.) of yellow liquid distilled slowly at a fluctuating temperature; it was mainly more 2-(1-methylene-2-piperidinoethyl)-quinoline since both fractions afforded the same *monopicrate*, yellow needles (from ethyl methyl ketone), m. p. 203—204° (Found : C, 57·3; H, 4·8; N, 14·4. $C_{23}H_{27}O_7N_5$ requires C, 57·4; H, 4·8; N, 14·5%).

(*b*) The directions of Kermack and Muir [3a] for the preparation of 2-2′-piperidinoethylquinoline monopicrate were followed and a crude product, m. p. 137—139°, was obtained in good yield. Repeated recrystallisation from alcohol failed to raise the m. p. above 153—156° (Kermack and Muir report m. p. 155° for their supposedly pure derivative obtained in this way), but crystallisation from ethyl methyl ketone gave a rather small recovery of 2-(1-methylne-2-piperidinoethyl)quinoline monopicrate, m. p. and mixed m. p. 203—204°.

Reaction of Quinaldine with Formaldehyde and Pyrrolidine Hydrochloride.—Quinaldine (28 ml.), 38% aqueous formaldehyde (17 ml.), pyrrolidine (16·5 ml.), alcohol (40 ml.), and 5N-hydrochloric acid (36 ml.) were heated at 60° for 5 hr., then concentrated under reduced pressure. After addition of water unchanged quinaldine was removed by ether-extraction, the aqueous phase was basified with sodium carbonate (50 g.), and the oily products were extracted with ether. Distillation of the dried extracts gave two main fractions, b. p. 107—120°/0·05 mm. (6·1 g.), and 140—156°/0·07 mm. (6·9 g.), each of which was treated with alcoholic picric acid. The derivative from the first fraction crystallised from acetone in yellow prisms of 2-2′-*pyrrolidinoethylquinoline dipicrate*, m. p. 164—165° (decomp.) (Found : C, 47·6; H, 3·8; N, 16·4. $C_{27}H_{24}O_{14}N_8$ requires C, 47·4; H, 3·5; N, 16·4%). 1 : 3-*Dipyrrolidino*-2-2′-*quinolylpropane dipicrate*, prepared from the second fraction, had m. p. 178—179° (decomp.) after crystallisation from acetonitrile (Found : C, 50·1; H, 4·6; N, 17·0. $C_{32}H_{33}O_{14}N_9$ requires C, 50·1; H, 4·3; N, 16·4%).

6 : 7-Dimethoxy-2-2′-dimethylaminoethylquinoline was prepared by the reductive cyclisation of 5-(3 : 4-dimethoxy-6-nitrophenyl)-1-dimethylaminopent-4-en-2-one hydrochloride but whereas Mannich and Schilling [3b] isolated the quinoline monohydrochloride, m. p. 176°, our product was the *dihydrochloride*, which separated from methanol–ether as a white powder, m. p. 208° (decomp.) (Found : N, 8·0; Cl, 21·6. $C_{15}H_{22}O_2N_2Cl_2$ requires N, 8·4; Cl, 21·3%).

4-2′-*Diethylaminoethylquinoline Monohydrochloride.*—Lepidine (6 ml.), 38% aqueous formaldehyde (4 ml.), diethylamine (4·5 ml.), alcohol (8 ml.), and 5N-hydrochloric acid (8 ml.) were heated at 60—65° for 5 hr., then evaporated *in vacuo*. After being washed with a little acetone, the residual solid crystallised from *iso*propanol as needles of the *monohydrochloride* (1·95 g.), m. p. 153—155° raised to 155—156° by recrystallisation from the same solvent (Found : C, 68·0; H, 8·2. $C_{15}H_{21}N_2Cl$ requires C, 68·0; H, 8·0%).

4-2′-*Dimethylaminoethylquinoline.*—Lepidine (14 ml.), 38% aqueous formaldehyde (8·5 ml.), dimethylamine hydrochloride (8·2 g.), and 50% aqueous alcohol (30 ml.) were stirred at 55—60° for 3 hr., concentrated under reduced pressure to remove alcohol, and then diluted with water. Unchanged lepidine (3·2 g.) was removed by ether-extraction, the aqueous phase was treated with sodium carbonate (30 g.), and the liberated 4-2′-dimethylaminoethylquinoline was

extracted with ether and distilled (7·6 g.; b. p. 103—108°/0·1 mm.) (Found : C, 77·8; H, 8·4; N, 14·4. Calc. for $C_{13}H_{16}N_2$: C, 78·0; H, 8·1; N, 14·0%). The *monopicrate* crystallised from ethyl methyl ketone in needles, m. p. 149—150° (Found : C, 52·7; H, 4·9; N, 16·4. $C_{19}H_{19}O_7N_5$ requires C, 53·1; H, 4·5; N, 16·3%). The *dihydrochloride* (from ethanol–ether) had m. p. 168—171° (Found : C, 54·1; H, 6·8; N, 9·0; Cl, 24·3. $C_{13}H_{18}N_2Cl_2,H_2O$ requires C, 53·6; H, 6·9; N, 9·6; Cl, 24·4%). The *monomethiodide* formed straw-coloured prisms (from methanol), decomp. above 220° (Found : C, 49·0; H, 5·6; N, 7·9. $C_{14}H_{19}N_2I$ requires C, 49·1; H, 5·6; N, 8·2%).

4-2′-*Pyrrolidinoethylquinoline*.—This was prepared from pyrrolidine by the method used for the dimethylamino-analogue except that the mixture was heated at 60° for 5 hr. The recovery of unchanged lepidine was 30% and the yield of 4-2′-*pyrrolidinoethylquinoline*, b. p. 122—130°/0·07 mm., was 44% (Found : C, 79·2; H, 7·6; N, 12·8. $C_{15}H_{18}N_2$ requires C, 79·6; H, 8·0; N, 12·4%). The *monopicrate* had m. p. 138—139° (from ethyl methyl ketone) (Found : C, 55·1; H, 4·6; N, 15·5. $C_{21}H_{21}O_7N_5$ requires C, 55·4; H, 4·6; N, 15·4%). The *dihydrochloride* (from dry ethanol) had m. p. 174—175° (Found : Cl, 23·3. $C_{15}H_{20}N_2Cl_2$ requires Cl, 23·7%).

4-2′-*Piperidinoethylquinoline Dihydrochloride*.—4-2′-Piperidinoethylquinoline,[4] m. p. 80—81°, gave a *dihydrochloride* which separated from *iso*propanol in prisms, m. p. 152—154° (Found : C, 57·6; H, 7·7; N, 8·8. $C_{16}H_{22}N_2Cl_2,H_2O$ requires C, 58·0; H, 7·3; N, 8·5%).

Mannich Reactions with 6-*Chlorolepidine*.—In each experiment equimolecular quantities of 6-chlorolepidine [10] and the appropriate amine hydrochloride were heated with formaldehyde (10% excess) in 50% aqueous alcohol under the conditions stated. After removal of alcohol under reduced pressure the mixture was diluted with water, and unchanged 6-chlorolepidine was extracted with ether and recovered. The aqueous solution was then basified with sodium carbonate and the Mannich base was isolated by ether extraction and distillation. Details for individual compounds are as follows :

6-*Chloro*-4-2′-*dimethylaminoethylquinoline*. The mixture was heated for 4 hr. at 65—70°; 40% of the 6-chlorolepidine was recovered, and the yield of Mannich *base*, b. p. 111—112°/0·1 mm., was 40% (Found : C, 66·4; H, 6·8; N, 12·1; Cl, 15·4. $C_{13}H_{15}N_2Cl$ requires C, 66·5; H, 6·4; N, 11·9; Cl, 15·1%). The *monopicrate* formed plates (from ethyl methyl ketone), m. p. 172—173° (Found : C, 48·9; H, 4·1. $C_{19}H_{18}O_7N_5Cl$ requires C, 49·2; H, 3·9%). The *dihydrochloride* (from ethanol) had m. p. 172—173° (decomp.) (Found : C, 50·4; H, 5·5. $C_{13}H_{17}N_2Cl_3$ requires C, 50·7; H, 5·6%). The *monomethiodide* (from methanol), needles, decomposed above 200° (Found : C, 44·5; H, 5·2. $C_{14}H_{18}N_2ClI$ requires C, 44·6; H, 4·8%).

6-*Chloro*-4-2′-*diethylaminoethylquinoline*. Refluxing the mixture for 2 hr. on the steam-bath gave a 50% recovery of 6-chlorolepidine and a 23% yield of the Mannich *base*, b. p. 120°/0·1 mm. (Found : C, 67·6; H, 7·1. $C_{15}H_{19}N_2Cl$ requires C, 68·6; H, 7·3%). The *monopicrate* formed needles (from alcohol), m. p. 138—139° (Found : C, 51·5; H, 4·9; N, 13·8. $C_{21}H_{22}O_7N_5Cl$ requires C, 51·3; H, 4·5; N, 14·2%). The *dihydrochloride* crystallised from nitromethane in needles, m. p. 150—153° (Found : C, 52·6; H, 6·4; N, 7·5. $C_{15}H_{21}N_2Cl_3,0·5H_2O$ requires C, 52·3; H, 6·4; N, 8·1%). Straw-coloured prisms of the *monomethiodide*, m. p. 143—144°, separated from ethanol (Found : C, 47·2; H, 5·6; N, 6·4. $C_{16}H_{22}N_2ClI$ requires C, 47·5; H, 5·5; N, 6·9%).

6-*Chloro*-4-2′-*piperidinoethylquinoline*. The mixture was heated for 4½ hr. at 65—70°, 39% of the 6-chlorolepidine was recovered, and the yield of Mannich *base*, b. p. 146—147°/0·1 mm., was 25% (Found : Cl, 13·0. $C_{16}H_{19}N_2Cl$ requires Cl, 12·9%). Yellow needles of the *monopicrate* separated from alcohol, m. p. 135—137° (Found : Cl, 7·1. $C_{22}H_{22}O_7N_5Cl$ requires Cl, 7·0%). The *dihydrochloride*, crystallised from ethanol, had m. p. 167—169° (Found : N, 7·3; Cl, 29·6. $C_{16}H_{21}N_2Cl_3,H_2O$ requires N, 7·7; Cl, 29·6%). The *monomethiodide*, straw-coloured prisms from ethanol, had m. p. 123—124° (Found : C, 46·5; H, 5·3. $C_{17}H_{22}N_2ClI,H_2O$ requires C, 46·9; H, 5·6%).

Mannich Reactions with 6-*Methoxylepidine*.—4-2′-Dialkylaminoethyl-6-methoxyquinolines were prepared from 6-methoxylepidine hydrate [11] by similar procedures to those used for the 6-chloro-compounds. The only difference noted was that neither the dimethylamino- nor the piperidino-compound could be purified completely by distillation, although derivatives were prepared normally from the impure distillates. Cautious dilution of either distilled base with

[10] Campbell and Kerwin, *J. Amer. Chem. Soc.*, 1946, **68**, 1837.
[11] Campbell and Schaffner, *ibid.*, 1945, **67**, 86.

light petroleum caused the precipitation of a small amount of 4-2′-*hydroxyethyl*-6-*methoxyquinoline*, which crystallised from water in plates, m. p. 125—127° (Found : C, 65·5; H, 6·9; N, 6·8. $C_{12}H_{13}O_2N,H_2O$ requires C, 65·1; H, 6·8; N, 6·3%). Details for the individual Mannich bases are as follows :

4-2′-*Dimethylaminoethyl*-6-*methoxyquinoline*. The crude base, b. p. 115—127°/0·08 mm., was obtained in 32% yield and 37% of 6-methoxylepidine was recovered. The *dihydrochloride* (from methanol–ethyl acetate) had m. p. 172—175° (Found : C, 49·9; H, 7·4; N, 8·0. $C_{14}H_{20}ON_2Cl_2,2H_2O$ requires C, 49·6; H, 7·1; N, 8·3%). The *monomethiodide* separated from methanol in straw-coloured needles, decomp. *ca.* 140° (Found : C, 46·3; H, 6·1. $C_{15}H_{21}ON_2I,H_2O$ requires C, 46·2; H, 5·9%).

4-2′-*Diethylaminoethyl*-6-*methoxyquinoline*. The pure *base* (42% yield) distilled at 128°/0·08 mm. (Found : N, 10·9. $C_{16}H_{22}ON_2$ requires N, 10·9%). The yellow *monopicrate*, crystallised from alcohol, had m. p. 129—131° (Found : C, 53·7; H, 5·3; N, 14·1. $C_{22}H_{25}O_8N_5$ requires C, 54·2; H, 5·2; N, 14·4%). The *dihydrochloride*, platelets (from *iso*propanol), had m. p. 154—156° (Found : C, 56·8; H, 7·3; N, 8·0. $C_{16}H_{24}ON_2Cl_2,0·5H_2O$ requires C, 56·5; H, 7·4; N, 8·2%). The *monomethiodide* formed amber-coloured prisms (from ethanol), m. p. 121—123° (Found : C, 48·6; H, 6·8; N, 6·5. $C_{17}H_{25}ON_2I,H_2O$ requires C, 48·8; H, 6·5; N, 6·7%).

6-*Methoxy*-4-2′-*piperidinoethylquinoline*. The yield of impure base, b. p. 137—157°/0·1 mm., was 26% and the recovery of 6-methoxylepidine 51%. The cream-coloured *dihydrochloride* (from ethanol–ether), had m. p. 182—184° (Found : C, 56·1; H, 7·2; N, 7·8; Cl, 19·1. $C_{17}H_{24}ON_2Cl_2,H_2O$ requires C, 56·5; H, 7·3; N, 7·8; Cl, 19·6%).

Methyl 8-*Quinolylacetate*.—Treatment of 8-quinolylacetic acid [12] with diazomethane in ether gave the pale yellow ester, b. p. 107°/0·1 mm., almost quantitatively (Found : C, 71·3; H, 5·5; N, 7·2. Calc. for $C_{12}H_{11}O_2N$: C, 71·6; H, 5·5; N, 7·0%). Gall and Erlenmeyer,[13] who prepared the ester by the Fischer–Speier method, report b. p. 176—179°/13 mm. The *picrate* of the ester crystallised from ethyl methyl ketone in plates, m. p. 184—185° (Found : C, 50·0; H, 3·5. $C_{18}H_{14}O_9N_4$ requires C, 50·2; H, 3·3%).

NN-*Dimethyl*-8-*quinolylacetamide*.—Methyl 8-quinolylacetate (25·5 g.) and 33% methanolic dimethylamine (200 ml.) were heated in an autoclave at 115° for 16 hr. and then for 4 hr. at 150°. After concentration of the mixture under reduced pressure the residue was distilled, to give the *dimethylamide* (19·8 g.), b. p. 153—162°/0·5 mm., m. p. 54—57°. Further purification was best effected by redistillation (b. p. 143—144°/0·1 mm.) (Found : C, 72·5; H, 6·4; N, 12·7. $C_{13}H_{14}ON_2$ requires C, 72·9; H, 6·6; N, 13·1%). The *picrate* crystallised from acetone in needles, m. p. 141—142° (Found : C, 50·9; H, 4·0; N, 15·3. $C_{19}H_{17}O_8N_5$ requires C, 51·4; H, 3·9; N, 15·8%).

NN-*Diethyl*-8-*quinolylacetamide*.—A solution of methyl 8-quinolylacetate (19·5 g.) in diethylamine (200 ml.) was heated under pressure at 200° for 30 hr., then evaporated *in vacuo*. Distillation of the residue gave 2·7 g. of fore-run, b. p. 123°/13 mm., which was identified as 8-methylquinoline (picrate, m. p. and mixed m. p. 202—204°), followed by the *diethylamide* (14·5 g.), b. p. 141—142°/0·04 mm. The amide solidified on trituration with dry ether and crystallised therefrom in needles, m. p. 67—68° (Found : C, 73·7; H, 7·6; N, 11·3. $C_{15}H_{18}ON_2$ requires C, 74·4; H, 7·5; N, 11·6%). The *picrate*, crystallised from ethyl methyl ketone, had m. p. 146° (Found : C, 53·7; H, 4·7; N, 14·7. $C_{21}H_{21}O_8N_5$ requires C, 53·5; H, 4·5; N, 14·9%).

8-2′-*Dimethylaminoethylquinoline*.—A solution of *NN*-dimethyl-8-quinolylacetamide (12 g.) in dry ether (175 ml.) was added with stirring to lithium aluminium hydride (10 g.) in ether during 1 hr.; the mixture was refluxed for 3 hr., cooled, and treated with water (10 ml.) followed by 5% sodium hydroxide solution (30 ml.). The granular solid was removed and extracted with hot ether, and the combined ether solutions were dried and distilled, to give 8-2′-*dimethylaminoethylquinoline* (7·9 g.), b. p. 98—99°/0·05 mm. (Found : C, 77·9; H, 8·6; N, 14·0. $C_{13}H_{16}N_2$ requires C, 78·0; H, 8·1; N, 14·0%). The *monopicrate* crystallised from acetone in orange plates, m. p. 156—157° (Found : C, 52·9; H, 4·3; N, 16·6. $C_{19}H_{19}O_7N_5$ requires C, 53·1; H, 4·5; N, 16·3%). The *dihydrochloride*, colourless needles from ethanol, had m. p. 177—178° (Found : C, 50·7; H, 7·0; N, 8·5. $C_{13}H_{18}N_2Cl_2,2H_2O$ requires C, 50·5; H, 7·2; N, 9·1%). The straw-coloured *monomethiodide*, crystallised from methanol, had m. p. 197—198° (decomp.) (Found : C, 48·8; H, 5·2. $C_{14}H_{19}N_2I$ requires C, 49·1; H, 5·6%).

8-2′-*Diethylaminoethylquinoline*.—*NN*-Diethyl-8-quinolylacetamide (11·8 g.) was reduced

[12] Prijs, Gall, Hinderling, and Erlenmeyer, *Helv. Chim. Acta*, 1954, **37**, 90.
[13] Gall and Erlenmeyer, *ibid.*, 1955, **38**, 1421.

as described for the dimethylamide, to give 8-2′-*diethylaminoethylquinoline* (10·4 g.), b. p. 105—106°/0·01 mm. (Found : C, 78·8; H, 8·9; N, 12·0. $C_{15}H_{20}N_2$ requires C, 78·9; H, 8·8; N, 12·3%). The *monopicrate* separated from ethyl methyl ketone as orange plates, m. p. 125° (Found : C, 54·6; H, 5·4; N, 15·0. $C_{21}H_{23}O_7N_5$ requires C, 55·1; H, 5·1; N, 15·3%). The cream-coloured *monomethiodide* (from ethanol–ether) had m. p. 134° (Found : C, 52·0; H, 6·2; N, 7·9. $C_{16}H_{23}N_2I$ requires C, 51·9; H, 6·3; N, 7·6%).

NN-*Diethylquinoline*-6-*carboxyamide*.—A mixture of quinoline-6-carboxylic acid [14] (30 g.) and thionyl chloride (100 ml.) was refluxed for 1 hr., then evaporated *in vacuo*, and the residue dissolved in benzene (100 ml.). Diethylamine (70 ml.) was added gradually with cooling and the mixture was refluxed for 1 hr., allowed to cool overnight, and poured into water. The aqueous phase was thoroughly extracted with ether, and the combined organic solutions were dried. Distillation gave the *diethylamide* (18·4 g.), b. p. 138—146°/0·1 mm. (Found : N, 12·0. $C_{14}H_{16}ON_2$ requires N, 12·3%). The *picrate* crystallised from alcohol in needles, m. p. 207—208° (Found : N, 15·6. $C_{20}H_{19}O_8N_5$ requires N, 15·3%).

6-*Diethylaminomethylquinoline*.—Reduction of the diethylamide (11·8 g.) with lithium aluminium hydride (7 g.) in ether in the usual way gave 6-*diethylaminomethylquinoline* (4·7 g.), b. p. 92—110°/0·1 mm. Redistillation gave a purer specimen, b. p. 88°/0·07 mm. (Found : N, 13·3. $C_{14}H_{18}N_2$ requires N, 13·1%). The *dihydrochloride* (from ethanol) had m. p. 239—241° (decomp.) (Found : C, 58·0; H, 7·2; Cl, 25·0. $C_{14}H_{20}N_2Cl_2$ requires C, 58·5; H, 7·0; Cl, 24·7%).

8-*Dimethylaminomethylquinoline*.—A solution of 8-bromomethylquinoline [12] (15 g.) and dimethylamine (7 g.) in toluene (100 ml.) was allowed to stand over potassium carbonate (15 g.) for 41 hr., filtered, and distilled, to give 8-*dimethylaminomethylquinoline* (10·3 g.), b. p. 80°/0·1 mm. (Found : N, 15·5. $C_{12}H_{14}N_2$ requires N, 15·1%). The *dihydrochloride*, crystallised from ethanol, had m. p. 238—240° (decomp.) (Found : N, 10·5. $C_{12}H_{16}N_2Cl_2$ requires N, 10·8%). The *monomethiodide*, cream-coloured plates (from ethanol), had m. p. 108—110° (Found : C, 44·8; H, 5·2. $C_{13}H_{17}N_2I,H_2O$ requires C, 45·1; H, 5·5%).

8-*Diethylaminomethylquinoline*.—A solution of 8-bromomethylquinoline (12 g.) and diethylamine (6 g.) in benzene (80 ml.) was refluxed for 2 hr. in the presence of potassium carbonate (12 g.), filtered, and distilled, to give the pale yellow base (9·2 g.), b. p. 100°/0·1 mm. (Found : N, 13·2. Calc. for $C_{14}H_{18}N_2$: N, 13·1%). The *dihydrochloride* separated from ethanol in needles, m. p. 200—202° (Found : C, 58·3; H, 7·1; N, 10·1. $C_{14}H_{20}N_2Cl_2$ requires C, 58·5; H, 7·0; N, 9·8%). The colourless *monomethiodide*, crystallised from ethanol, had m. p. 166—168° (Found : C, 50·5; H, 5·9; N, 7·6. $C_{15}H_{21}N_2I$ requires C, 50·6; H, 5·9; N, 7·9%).

8-*Piperidinomethylquinoline*.—This base, b. p. 118—122°/0·04 mm., was prepared in similar fashion to the diethylamino-analogue (yield 69%) (Found : C, 79·3; H, 8·0; N, 12·6. Calc. for $C_{15}H_{18}N_2$: C, 79·6; H, 8·0; N, 12·4%). It gave a colourless *dihydrochloride* which, crystallised from ethanol, had m. p. 221—222° (decomp.) (Found : C, 57·0; H, 6·6; Cl, 22·1. $C_{15}H_{20}N_2Cl_2,H_2O$ requires C, 56·8; H, 7·0; Cl, 22·4%). The *monomethiodide* formed colourless needles (from ethanol), m. p. 169—170° (Found : N, 7·4. $C_{16}H_{21}N_2I$ requires N, 7·6%).

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