344. *Attempts to find New Antimalarials. Part XIV. Derivatives of 8-Methylquinoline.*

By William O. Kermack and Thomas W. Wight.

When a chloroform solution of 8-methylquinoline is saturated with hydrogen bromide and treated with one mol. of bromine, a reddish-orange crystalline addition compound (Müller, Lang, Disserts., Freiburg, 1897, 1898, quoted by Howitz and Nöther, *Ber.*, 1906, **39**, 2709) is obtained. This melts at 160° and finally solidifies, with the evolution of hydrogen bromide, yielding a yellow product which is mainly 8-bromomethylquinoline.

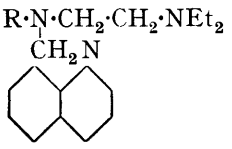
When the same method was applied to 6-methoxy-8-methylquinoline, a product was obtained which became grey on heating and yielded a base, m. p. 116—117°; this contained an inert bromine atom and was proved to be *5-bromo-6-methoxy-8-methylquinoline* by the synthesis described below.

When 6-nitro-*m*-cresol was treated with one mol. of bromine in chloroform solution, a mixture of monobromo-derivatives was obtained, from which a homogeneous product, m. p. 145—146°, was isolated. This was *4-bromo-6-nitro*-m-*cresol*, since successive methylation, reduction, and application of the Sandmeyer reaction produced 4 : 6-dibromo-*m*-tolyl methyl ether, m. p. 73—74°, identical with the compound obtained from 4-nitro-*m*-cresol by the same series of reactions (Lapworth and Haworth, J., 1923, **123**, 2995, give m. p. 75—76°). The *4-bromo-5-methoxy*-o-*toluidine* thus oriented, when subjected to the Skraup reaction, gave 5-bromo-6-methoxy-8-methylquinoline, m. p. 116—117°, identical with that mentioned above.

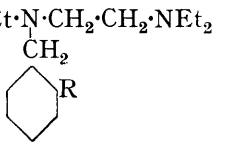
From the residual fraction of the product of bromination of 6-nitro-*m*-cresol, a substance, m. p. 95—97°, was isolated. This was a mixture of 4- and 2-bromo-6-nitro-*m*-cresol, since the methyl ether prepared from it gave, after reduction and treatment by the Skraup reaction, a product of indefinite melting point, separable into 5-bromo-6-methoxy-8-methylquinoline and an isomeride, which must be *7-bromo-6-methoxy-8-methylquinoline*.

In view of the failure to obtain 6-methoxy-8-bromomethylquinoline from 6-methoxy-8-methylquinoline, the bromination of 6-nitro-8-methylquinoline was examined. The method of Müller and Lang was unsuccessful, but treatment with bromine in boiling monochloroacetic acid solution yielded a monobromo-derivative. This compound did not react with piperidine and similar reagents. The bromine atom is therefore probably not in the ω-position or position 2 or 4. Positions 5 and 7 are unlikely, not only on account of the inhibitory influences of the nitro-group on the entrance of the bromine into these positions, but also because a bromine atom ortho to the nitro-group would probably react with piperidine and similar reagents. The compound is therefore probably *3-bromo-6-nitro-8-methylquinoline*.

After boiling with dilute sulphuric acid, 8-bromomethylquinoline yielded *8-quinolylmethyl alcohol* (cf. Howitz and Philipp, *Annalen*, 1912, **396**, 39), from which a satisfactory nitration product could not be obtained. However, on nitration, 8-bromomethylquinoline yielded a mononitro-derivative, presumably 5-nitro-8-bromomethylquinoline (cf. Howitz and Nöther, *loc. cit.*), which when boiled with dilute sulphuric acid yielded *5-nitro-8-quinolylmethyl alcohol*. With piperidine in ethereal solution, 5-nitro-8-piperidinomethylquinoline was formed.



(I.)



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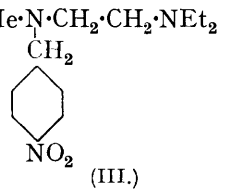


(III.)

It was desired to prepare basic quinoline derivatives (I) somewhat analogous to plasmoquin but having a side chain attached to the 8-position of the quinoline nucleus through a methylene group. The method of Skraup, although successful in some simple cases

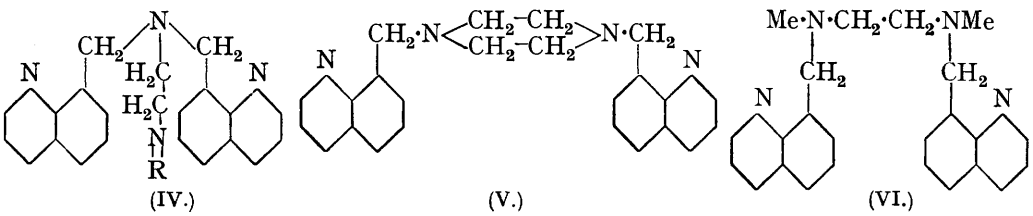
(cf. Kermack, Muir, and Wight, this vol., p. 1143), was in general unsatisfactory. β-(*o*-Nitrobenzylethylamino)triethylamine (II, R = NO_2), prepared from *o*-nitrobenzylethylamine and β-diethylaminoethyl chloride, was reduced to β-(*o*-aminobenzylethylamino)-triethylamine (II, R = NH_2), from which a crystalline product could not be obtained by the Skraup reaction. β-(Benzylethylamino)triethylamine (II, R = H) and β-(*p*-nitrobenzylmethylamino)triethylamine (III) were prepared from β-diethylaminoethyl chloride and the corresponding secondary base. However, as the desired compounds were obtained conveniently from 8-bromomethylquinoline, the Skraup process was abandoned.

β-Diethylaminoethylamine, β-diethylaminoethylmethylamine, β-diethylaminodiethylamine, β-diethylaminoethylpropylamine, β-diethylaminoethyl-*n*-butylamine, and β-diethylaminoethyl*iso*butylamine were prepared by treating β-diethylaminoethyl chloride with an excess of the corresponding primary amine in alcoholic solution. The yield of the secondary base increases with increase in the molecular weight of the amine, the low yield of β-diethylaminoethylmethylamine (and of β-diethylaminoethylamine) being no doubt due to a tendency to form the tertiary (or secondary) base. This tendency appears to decrease as the alkyl group becomes larger.

The secondary bases mentioned above condense smoothly with 8-bromomethylquinoline to yield compounds (I), conveniently isolated as their hydrobromides or picrates. In the case of the primary base β-diethylaminoethylamine two compounds were isolated, namely, 8-(β-diethylaminoethylaminomethyl)quinoline (I, R = H) and *bis*-(8-*quinolylmethyl*)-β-*diethylaminoethylamine* (IV, R = Et_2).

An analogous series of aliphatic bases was prepared from β-piperidinoethylmethylamine, β-piperidinodiethylamine, β-piperidinoethylpropylamine, β-piperidinoethyl-*n*-butylamine, and β-piperidinoethyl*iso*butylamine. The secondary bases condensed with 8-bromomethylquinoline to yield compounds of type (I), but the only product which could be isolated in the case of β-piperidinoethylamine was 1-β-*bis*-(8′-*quinolylmethyl*)*aminoethylpiperidine* (IV, R = C_5H_{10}).

Although inactive in bird malaria, these compounds have been found by Professor A. J. Clark and Dr. Sinha to possess marked local anæsthetic activity, a property also possessed by 1 : 4-*bis*-(8′-*quinolylmethyl*)*piperazine* (V) and *s*.-bis-(8-quinolylmethyl)dimethylethylenediamine (VI), formed by condensing 8-bromomethylquinoline with piperazine and *s*.-dimethylethylenediamine respectively.



(IV.) (V.) (VI.)

Experimental.

6-*Methoxy*-8-*methylquinoline*.—A mixture of ferrous sulphate (2 g.), glycerol (38 g.), 5-methoxy-*o*-toluidine (16·5 g.), arsenic acid (17 g.), and 96% sulphuric acid (36 g.) was boiled under reflux for 4 hours and the cooled product was diluted with water, made strongly alkaline, and steam-distilled. 6-Methoxy-8-methylquinoline, a light brown oil (9 g.) isolated by means of ether, formed a *hydrobromide*, light yellow plates, m. p. 268° (Found: Br, 31·5. $C_{11}H_{11}ON,HBr$ requires Br, 31·5%), and a picrate, yellow plates, m. p. 232—233°, both crystallised from alcohol.

5-*Bromo*-6-*methoxy*-8-*methylquinoline*.—A solution of 6-methoxy-8-methylquinoline (9 g.) in chloroform (30 c.c.) was saturated with dry hydrogen bromide (hydrobromide may separate), cooled, and slowly treated with bromine (3 c.c.). After 12 hours the reddish-brown crystalline deposit was washed with dry chloroform and heated at 160—170° (oil-bath) for 3 hours, hydrogen bromide being evolved. An extract of the light grey product in hot sulphuric acid (20 c.c. each of concentrated acid and water) was diluted with water (40 c.c.) and made alkaline. The greyish-white 5-*bromo*-6-*methoxy*-8-*methylquinoline* obtained crystallised from light petroleum (b. p. 60—80°) in long white rectangular plates (6·2 g.), m. p. 116—117° (Found: Br, 31·9.

$C_{11}H_{10}ONBr$ requires Br, 31·8%), very readily soluble in ether, benzene, alcohol, and mineral acid (yielding a solution with a faint blue fluorescence) but only moderately soluble in hot ligroin and light petroleum. The hydrobromide crystallised from alcohol in light yellow plates, m. p. 230°.

4-*Bromo*-6-*nitro*-m-*cresol*.—To 6-nitro-*m*-cresol (40 g.), dissolved in chloroform (140 c.c.) at 35°, was added bromine (13·6 c.c.) in chloroform (14 c.c.). The mixture was heated at 40—50° for 3 hours, the solvent evaporated, and the residue dissolved in hot 2·5*N*-sodium hydroxide (160—180 c.c.). The yellow crystalline sodium salt (A) that separated on cooling was removed, the filtrate was acidified, and the cresol obtained was dissolved in hot 3*N*-sodium hydroxide (100 c.c.), yielding a second yellow crystalline salt. The cresol obtained from this on acidification was crystallised from much benzene; the first crop of crystals, m. p. 138—140°, gave after two or three recrystallisations faintly yellow needles of 4-*bromo*-6-*nitro*-m-*cresol*, m. p. 146° (Found: C, 36·3; H, 2·6. $C_7H_6O_3NBr$ requires C, 36·2; H, 2·6%), sparingly soluble in hot ligroin, soluble in hot benzene and in dilute potassium hydroxide solution, and very readily soluble in cold acetone, ether, alcohol, and dilute sodium hydroxide solution.

4-*Bromo*-6-*nitro*-m-*tolyl Methyl Ether*.—A mixture of 4-bromo-6-nitro-*m*-cresol (6 g., m. p. 140°), benzene (40 c.c.), methyl sulphate (4 c.c.), and anhydrous potassium carbonate (4 g.) was refluxed for 18 hours, the filtered solution evaporated, and the residue treated with dilute sodium hydroxide solution. The product was washed with water, dried in a vacuum, and recrystallised from light petroleum, forming white needles (3·4 g.), m. p. 110—111° (Found: Br, 32·6. $C_8H_8O_3NBr$ requires Br, 32·6%).

4-*Bromo*-5-*methoxy*-o-*toluidine*.—The preceding ether (4·4 g.) was reduced in methylated spirit (40 c.c.) and concentrated hydrochloric acid (2 c.c.) with iron filings (3 g.) (West, J., 1925, **127**, 494). The neutralised filtered solution was evaporated to dryness, and a solution of the residue in dilute acid was shaken with ether to remove unchanged nitro-compound, basified, and extracted with ether. This removed 4-*bromo*-5-*methoxy*-o-*toluidine*, which crystallised from light petroleum (b. p. 60—80°) in light pink needles (3 g.), m. p. 79—80° (Found: Br, 36·9. $C_8H_{10}ONBr$ requires Br, 37·0%).

4 : 6-*Dibromo*-m-*tolyl Methyl Ether*.—The preceding base (1·5 g.) in concentrated hydrochloric acid (1·5 c.c.) and water (0·9 c.c.) was diazotised (sodium nitrite, 0·6 g.), the solution added to a solution of cuprous bromide (copper sulphate, 1·8 g.; potassium bromide, 0·9 g.; sulphur dioxide in hydrobromic acid, 3 c.c., *d* 1·49), and the mixture poured into water. Steam-distillation removed 4 : 6-dibromo-*m*-tolyl methyl ether, which crystallised from light petroleum in colourless rectangular plates, m. p. 73—74° (Found: Br, 57·3. Calc. for $C_6H_8OBr_2$: Br, 57·5%).

6-*Bromo*-4-*nitro*-m-*tolyl Methyl Ether*.—6-Bromo-4-nitro-*m*-cresol was methylated by the modified method of Lapworth and Haworth described above. As, however, the sodium salt of the cresol was very sparingly soluble in water, it was necessary to extract the product with hot ligroin after the treatment with sodium hydroxide solution; yield, 90%. Recrystallised from ligroin, the *ether* formed white needles, m. p. 113—115° (Found: C, 38·8; H, 3·3. $C_8H_8O_3NBr$ requires C, 39·0; H, 3·4%). Its reduction gave a 90% yield of 2-*bromo*-5-*methoxy*-p-*toluidine*, which crystallised from light petroleum in fern-shaped masses of needle-like rods, m. p. 71—73° (Found: Br, 37·3. $C_8H_{10}ONBr$ requires Br, 37·0%). This base formed an *acetyl* derivative, white needles, m. p. 130—133°, from water (Found: C, 46·2; H, 4·7. $C_{10}H_{12}O_2NBr$ requires C, 46·5; H, 4·6%), and gave 4 : 6-dibromo-*m*-tolyl methyl ether when subjected to the Sandmeyer reaction.

Conversion of 4-*Bromo*-5-*methoxy*-o-*toluidine into* 5-*Bromo*-6-*methoxy*-8-*methylquinoline*.—A mixture of ferrous sulphate (0·4 g.), glycerol (8·4 g.), 4-bromo-5-methoxy-*o*-toluidine (6 g.), arsenic acid (4 g.), and 96% sulphuric acid (8 g.) was refluxed for 40 minutes and poured into water (500 c.c.). After 12 hours the liquid was filtered and made alkaline. The resulting precipitate was extracted with boiling alcohol, which removed 5-bromo-6-methoxy-8-methylquinoline, m. p. 116—117° after recrystallisation from light petroleum.

7-*Bromo*-6-*methoxy*-8-*methylquinoline*.—The mixture of bromo-6-nitro-*m*-cresols, m. p. 95—97°, obtained from the sodium salt A (above) gave on methylation a mixture of ethers (colourless rectangular plates, m. p. 63—65°, from light petroleum. Found: Br, 32·6%), and this furnished on reduction a mixture of bases (purplish needles, m. p. 52—54°, from light petroleum. Found: Br, 37·3%), a portion of which was converted by the Sandmeyer reaction into a small quantity of 4 : 6-dibromo-*m*-tolyl methyl ether, m. p. 73—74°, and an oil, presumably containing 2 : 6-dibromo-*m*-tolyl methyl ether. The mixed bases (6 g.) were submitted to the Skraup reaction under conditions similar to those employed for 4-bromo-5-methoxy-*o*-toluidine, boiling being

continued for 4 hours. The residue remaining after evaporation of the alcoholic extract was recrystallised from light petroleum, yielding a product, m. p. 100—110°. Solution of this in acetone and addition of an equal volume of alcohol saturated with hydrogen bromide precipitated a white hydrobromide. The base obtained from this salt by treatment with hot dilute sodium hydroxide solution was crystallised several times from light petroleum (b. p. 60—80°), giving white rectangular prisms, m. p. 134—135°, of 7-*bromo*-6-*methoxy*-8-*methylquinoline* (Found: C, 52·6; H, 4·2; N, 5·4; Br, 31·6. $C_{11}H_{10}ONBr$ requires C, 52·4; H, 4·0; N, 5·6; Br, 31·7%).

Evaporation of the acetone-alcoholic filtrate and re-treatment of the recovered bases in the same way furnished a further small quantity of the insoluble hydrobromide. The final acetone-alcoholic filtrate, evaporated to dryness, yielded a yellow crystalline salt, from which 5-bromo-6-methoxy-8-methylquinoline, m. p. 116—117° after several recrystallisations from light petroleum, was obtained.

3-*Bromo*-6-*nitro*-8-*methylquinoline*.—6-Nitro-8-methylquinoline (5 g.) was dissolved in hot monochloroacetic acid (40 g.), bromine (2·5 c.c.) added slowly, and the whole refluxed for 15 minutes. 2*N*-Hydrochloric acid (200 c.c.) was added, the whole boiled for a few minutes, and the residue again extracted with 2*N*-hydrochloric acid. The crystalline deposit which separated from the cooled filtrates was recrystallised from benzene, forming light yellow needles (4 g.), m. p. 188—189° (Found: Br, 30·2. $C_{10}H_7O_2N_2Br$ requires Br, 30·0%), slightly soluble in light petroleum, alcohol, ether, and ligroin, soluble in acetone and benzene, but insoluble in water and cold dilute mineral acids.

8-*Quinolylmethyl Alcohol*.—*N*-Sulphuric acid (20 c.c.) was refluxed over-night with 8-bromomethylquinoline (2 g.), cooled, and neutralised with sodium carbonate solution. The solid obtained was washed with water and dried; it crystallised from light petroleum in white needles, m. p. 75—76° (Found: C, 75·7; H, 5·8. $C_{10}H_9ON$ requires C, 75·5; H, 5·6%).

5-*Nitro*-8-*quinolylmethyl alcohol*, similarly obtained from 5-nitro-8-bromomethylquinoline, crystallised from alcohol in light brown, minute needles, m. p. 148—149° (Found: C, 59·0; H, 4·1. $C_{10}H_8O_3N_2$ requires C, 58·8; H, 3·9%).

5-*Nitro*-8-*piperidinomethylquinoline*.—5-Nitro-8-bromomethylquinoline (2 g.) was added slowly to piperidine (1·6 g.) in ether (50 c.c.). The yellow solution was refluxed for 3 hours, cooled, washed with dilute sodium carbonate solution and with water, dried (potassium carbonate), and evaporated. The residual oil was converted into the *hydrobromide*, which formed light brown, rectangular plates, m. p. 248—249°, from alcohol (Found: Br, 22·8. $C_{15}H_{17}O_2N_3$,HBr requires Br, 22·7%).

β-(o-*Nitrobenzylethylamino*)*triethylamine* (II; R = NO_2).—A mixture of *o*-nitrobenzylethylamine (15 g.), benzene (50 c.c.), β-diethylaminoethyl chloride hydrochloride (15 g.), anhydrous potassium carbonate (15 g.), and a trace of copper-bronze was refluxed for 4 hours, the liquid filtered, the residue washed with hot dry benzene, and the filtrate and washings saturated with dry hydrogen chloride. The sticky mass obtained was boiled with acetone (200 c.c.), the insoluble *o*-nitrobenzylethylamine hydrochloride washed with a small quantity of hot acetone, and the filtrate and washings evaporated to dryness. The crude oily β-(*o*-nitrobenzylethylamino)triethylamine was extracted with ether and converted into its *picrate*, which was twice boiled with alcohol and crystallised from much hot water, forming light yellow needles (15 g.), m. p. 167—168° (Found: N, 17·2. $C_{27}H_{31}O_{16}N_9$ requires N, 17·1%). The yield of the base recovered from the picrate was 6·5 g.

β-(o-*Aminobenzylethylamino*)*triethylamine*.—The preceding nitro-compound (6 g.) in boiling methylated spirit (20 c.c.) and concentrated hydrochloric acid (6 c.c.) was reduced with iron filings (4 g.), added in 1 g.-portions during 15 minutes. After refluxing for 2 hours, the solution was neutralised with alcoholic caustic soda, filtered, and evaporated; the residue was treated with dilute alkali solution and extracted with ether. The base recovered from the ether formed a *picrate* which, recrystallised several times from alcohol, yielded light yellow plates, m. p. 134° (Found: C, 52·2; H, 7·5. $C_{27}H_{33}O_{14}N_9$ requires C, 52·7; H, 7·3%).

β-(*Benzylethylamino*)*triethylamine* (II; R = H).—Benzylethylamine (15 g.) and β-diethylaminoethyl chloride hydrochloride (15 g.) were condensed in similar manner to the above, and the product converted into hydrochloride. This crystallised from acetone in colourless feathery plates, m. p. 180—185°, but as analysis indicated a percentage of chlorine intermediate between those required of the mono- and the di-hydrochloride, the substance was converted into a *picrate*, which crystallised from alcohol in small yellow plates, m. p. 150—152° (Found: N, 16·1. $C_{27}H_{32}O_{14}N_8$ requires N, 16·2%).

β-(*p*-Nitrobenzylmethylamino)triethylamine (III) was prepared from *p*-nitrobenzylmethyl-

amine (4 g.) and β-diethylaminoethyl chloride (3·4 g.) as in the case of the above *o*-nitro-compound and converted into the *picrate*, which crystallised from alcohol in small yellow plates, m. p. 195—197° (Found : N, 17·3. $C_{26}H_{29}O_{16}N_9$ requires N, 17·4%).

β-*Diethylaminoethylpropylamine*.—*n*-Propylamine (8 g.) was dissolved in alcohol (24 c.c.), and β-diethylaminoethyl chloride hydrochloride (8 g.) added slowly. After addition of anhydrous potassium carbonate (3—4 g.) the whole was refluxed for 2 hours, the solution diluted with water and made strongly alkaline, and the oil extracted in ether, dried (potassium carbonate), and distilled. The fraction, b. p. 184—200° (yield, 60%), gave a *monopicrate*, which crystallised from alcohol in yellow rectangular plates, m. p. 133—135° (Found : N, 18·2. $C_{15}H_{25}O_7N_5$ requires N, 18·1%).

β-Diethylaminoethyl-*n*-butylamine was similarly prepared from *n*-butylamine (8 g.) and β-diethylaminoethyl chloride hydrochloride (8 g.). The fraction, b. p. 207—212° (yield, 70%), gave a *dipicrate*, yellow plates, m. p. 234°, from alcohol and acetone (Found : C, 42·0; H, 4·8. $C_{22}H_{30}O_{14}N_8$ requires C, 41·9; H, 4·8%).

β-Diethylaminoethyl*iso*butylamine was prepared from *iso*butylamine (8 g.) and β-diethylaminoethyl chloride hydrochloride (8 g.). The fraction, b. p. 194—200° (yield, 70%), gave a *dipicrate*, yellow rods, m. p. 141°, from alcohol and acetone (Found : C, 42·2; H, 4·8%).

β-Diethylaminodiethylamine (cf. B.P. 310,074), prepared from β-diethylaminoethyl chloride hydrochloride (6 g.) and 33% ethylamine (14 c.c.) in 50% yield, formed a mono- and a di-picrate, crystallising from alcohol in light yellow needles, m. p. 139—140°, and yellow plates, m. p. 150—151°, respectively.

β-Diethylaminoethylmethylamine (cf. B.P. 269,615) was prepared from β-diethylaminoethyl chloride hydrochloride (6 g.) and alcoholic methylamine (15 g. of 33%). The fraction, b. p. 157—160° (yield, 40%), was collected.

β-Diethylaminoethylamine (cf. Ristenpart, *Ber.*, 1896, **29**, 2526) was prepared from β-diethylaminoethyl chloride hydrochloride (8 g.), aqueous ammonia (25 c.c., *d* 0·880) and alcohol (25 c.c.) by refluxing for 2 hours; the fraction, b. p. 145—155°, was retained.

β-Piperidinoethyl chloride hydrochloride, white needles from alcohol, m. p. 228—230°, was prepared from β-piperidinoethyl alcohol by the method of Gough and King (J., 1928, 2436).

The following piperidino-compounds were prepared similarly to the analogous diethylamino-compounds. The dipicrates all crystallised in yellow plates from alcohol and acetone. β-Piperidinoethylpropylamine, b. p. 220—230°; yield, 60% (*dipicrate*, m. p. 169°. Found : C, 42·3; H, 4·5. $C_{22}H_{28}O_{14}N_8$ requires C, 42·0; H, 4·5%). β-Piperidino-*n*-butylamine, b. p. 230—240°; yield, 70% (*dipicrate*, m. p. 191—192°. Found : C, 43·1; H, 4·8. $C_{23}H_{30}O_{14}N_8$ requires C, 43·0; H, 4·7%). β-Piperidino*iso*butylamine, b. p. 230—240°; yield, 70% (*dipicrate*, m. p. 167—168°. Found : C, 43·3; H, 4·8%). β-Piperidinoethylmethylamine, b. p. 190—200°; yield, 45% (*dipicrate*, m. p. 174°. Found : C, 40·2; H, 4·0. $C_{20}H_{24}O_{14}N_8$ requires C, 40·0; H, 4·0%). β-Piperidinodiethylamine, b. p. 200—210°; yield, 55% (*dipicrate*, m. p. 154°. Found : C, 41·2; H, 4·4. $C_{21}H_{26}O_{14}N_8$ requires C, 41·0; H, 4·2%).

s.-*Dimethylethylenediamine*.—Ethylene dibromide (9·0 g.) was added slowly to aqueous methylamine (40 c.c. of 21% soln.) in alcohol (40 c.c.) and refluxed for 2 hours. The base was extracted in the usual way and distilled; the fraction, b. p. 150—160° (yield, 50%), gave a *picrate*, which crystallised from alcohol and acetone in rectangular plates, m. p. 160° (Found : C, 38·1; H, 4·7. $C_{10}H_{15}O_7N_5$ requires C, 37·9; H, 4·7%).

8-(β-*Diethylaminoethylmethylaminomethyl*)*quinoline* (I; R = Me).—Diethylaminoethylmethylamine (1·3 g.) was dissolved in benzene (10 c.c.), and 8-bromomethylquinoline (2 g.) added slowly; after addition of anhydrous potassium carbonate (2 g.), the mixture was refluxed for 2 hours and extracted with dilute hydrochloric acid. The extract was basified and the oil that separated was extracted in ether, dried (potassium carbonate), recovered, and dissolved in alcohol; addition of alcoholic hydrogen bromide precipitated the *trihydrobromide*, which crystallised from alcohol in small white plates, m. p. 215—216° (Found : Br, 46·3. $C_{17}H_{25}N_3$,3HBr requires Br, 46·7%).

By condensation of 8-bromomethylquinoline with the corresponding secondary amines, bases were obtained (as the following salts). 8-(β-*Diethylaminodiethylaminomethyl*)*quinoline trihydrobromide*, white plates, m. p. 218—219°, from alcohol (Found : Br, 45·6. $C_{18}H_{27}N_3$,3HBr requires Br, 45·4%); *picrate*, yellow plates, m. p. 131—132°, from alcohol (Found : N, 15·9. $C_{24}H_{30}O_7N_6$ requires N, 16·3%). 8-(β-*Diethylaminoethylpropylaminomethyl*)*quinoline monopicrate*, light yellow plates, m. p. 113—115°, from alcohol (Found : C, 56·8; H, 6·1. $C_{25}H_{32}O_7N_6$ requires C, 56·8; H, 6·1%); *dipicrate*, deep yellow plates, m. p. 163—164°, from acetone and alcohol (Found : C, 49·0; H, 4·5. $C_{31}H_{35}O_{14}N_9$ requires C, 49·1; H, 4·6%). 8-(β-*Diethyl-*

aminoethyl-n-*butylaminomethyl*)*quinoline dipicrate*, yellow rectangular prisms, m. p. 178—180°, from acetone and alcohol (Found : C, 50·1; H, 4·9. $C_{32}H_{37}O_{14}N_9$ requires C, 49·9; H, 4·8%). 8-(β-*Diethylaminoethyl*iso*butylaminomethyl*)*quinoline dipicrate*, deep yellow, rectangular prisms, m. p. 169—171°, from acetone and alcohol (Found : C, 50·0; H, 4·8%). 8-(β-*Piperidinoethyl-propylaminomethyl*)*quinoline trihydrobromide*, small white plates, m. p. 210°, from alcohol (Found : Br, 43·1. $C_{20}H_{29}N_3$,3HBr requires Br, 43·3%). 8-(β-*Piperidinoethyl*-n-*butylamino-methyl*)*quinoline trihydrobromide*, as small white plates, m. p. 211—212°, from alcohol (Found : Br, 42·2. $C_{21}H_{31}N_3$,3HBr requires Br, 42·3%). 8-(β-*Piperidinoethyl*iso*butylaminomethyl*)*quinoline dipicrate*, small yellow plates, m. p. 210—211°, from acetone and alcohol (Found : C, 50·8; H, 4·7. $C_{33}H_{37}O_{14}N_9$ requires C, 50·6; H, 4·7%). 8-(β-*Piperidinoethylmethylaminomethyl*)-*quinoline dipicrate*, yellow plates, m. p. 205—206°, from acetone and alcohol (Found : C, 48·8; H, 4·2. $C_{30}H_{31}O_{14}N_9$ requires C, 48·6; H, 4·2%). 8-(β-*Piperidinodiethylaminomethyl*)*quinoline trihydrobromide*, small white plates, m. p. 222°, from alcohol (Found : Br, 44·3. $C_{19}H_{27}N_3$,3HBr requires Br, 44·4%). s.-*Bis*-(8-*quinolylmethyl*)*dimethylethylenediamine dihydrobromide* (as VI), small white plates, m. p. 232°, from alcohol (Found : Br, 29·9. $C_{24}H_{26}N_4$,2HBr requires Br, 30·1%).

Bis-(8-*quinolylmethyl*)-β-*diethylaminoethylamine* (IV; R = Et_2) was similarly obtained from β-diethylaminoethylamine (3 g.), benzene (10 c.c.), 8-bromomethylquinoline (3 g.), and anhydrous potassium carbonate (3 g.); the oil obtained from the ethereal extract quickly solidified and then crystallised from light petroleum (b. p. 60—80°) in white needles, m. p. 97—98° (Found : C, 78·0; H, 7·5. $C_{26}H_{30}N_4$ requires C, 78·4; H, 7·5%). The picrate crystallised from alcohol in yellow plates, m. p. 191°.

8-(β-*Diethylaminoethylaminomethyl*)*quinoline* (I; R = H).—The mother-liquor from the first treatment with light petroleum in the above experiment was evaporated to dryness, the residual oil dissolved in alcohol, and alcoholic hydrogen bromide added. The *trihydrobromide* which separated crystallised from alcohol in long white prisms, m. p. 223—224° (Found : Br, 47·9. $C_{16}H_{23}N_3$,3HBr requires Br, 48·0%).

1-β-*Bis*-(8′-*quinolylmethyl*)*aminoethylpiperidine* (IV; R = C_5H_{10}).—β-Piperidinoethylamine (Kermack and Smith, J., 1931, 3098) (2 g.) was dissolved in alcohol (6 c.c.), 8-bromomethylquinoline (2 g.) added slowly, and the mixture refluxed for 2 hours, diluted with water, made alkaline with ammonia, and kept over-night. The sticky brown solid obtained crystallised from aqueous alcohol in white rhombic prisms, m. p. 97—98° (Found : C, 78·9; H, 7·3. $C_{27}H_{30}N_4$ requires C, 79·0; H, 7·3%). The picrate formed pale yellow needles, m. p. 228—229° from a large volume of alcohol.

1 : 4-*Bis*-(8′-*quinolylmethyl*)*piperazine* (V).—8-Bromomethylquinoline (2 g.) and piperazine hexahydrate (2 g.) were heated under reflux at 130—140° for 2 hours. The brown mass was extracted with hot dilute hydrochloric acid, and the extract made faintly alkaline with sodium carbonate solution. The oil formed gradually solidified and then crystallised from a little hot alcohol in light brown plates, m. p. 153—154° (Found : C, 76·6; H, 6·4; N, 14·6. $C_{24}H_{24}N_4$,$\frac{1}{2}H_2O$ requires C, 76·4; H, 6·6; N, 14·9%). The hydrobromide crystallised from alcohol in white plates, m. p. 265—267°.

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