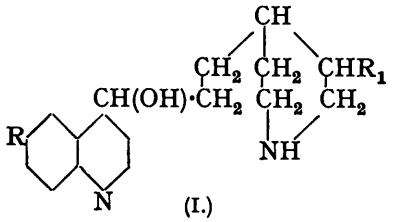
248. *Antiplasmodial Action and Chemical Constitution. Part III. Carbinolamines derived from Naphthalene and Quinoline.*

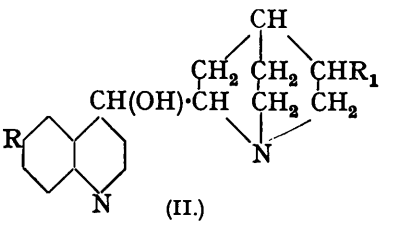
By HAROLD KING and THOMAS S. WORK.

The aim of this investigation was the preparation of antiplasmodial substances based on the formula of quinine but of simpler structure. A series of 1 : 2-carbinolamines has been prepared from naphthalene and quinoline and from their methoxy-derivatives. Antiplasmodial activity has been found in the dibutyl-, diamyl-, and dihexyl-aminomethyl-6-methoxy-4-quinolylcarbinols. These are among the simplest substances to show antiplasmodial activity.

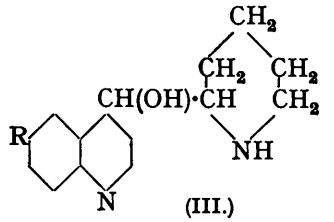
IN Part II (Ainley and King, *Proc. Roy. Soc.*, 1938, *B*, **125**, 60) it was shown that, although *d*- and *l*-dihydroquinicinols, which are γ-piperidine derivatives (I; R = OMe, R_1 = Et) bore so close a resemblance to dihydroquinine (II; R = OMe, R_1 = Et), they were devoid of any significant antiplasmodial action as tested on bird malaria. When, how-

ever, the piperidine ring was attached at its α-position through the carbinol group to the methoxyquinoline nucleus as in (III; R = OMe), two diastereoisomerides were obtained, both of which showed antiplasmodial activity.


(I.)


(II.)

Since the latter bases were difficult of access and modification by conversion into the tertiary bases led to loss of activity, it seemed desirable to prepare a more accessible series of simple carbinolamines (IV) in which the strongly basic nitrogen centre was still separated from the quinoline nucleus by two carbon atoms as in quinine or hydroquinine.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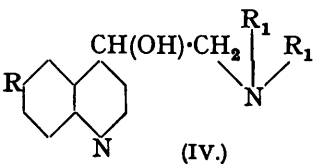
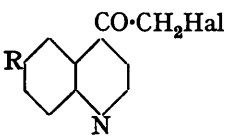

(IV.)

A few such bases, five in all, have already been prepared by Kaufmann (*Ber.*, 1913, **46**, 1823) and by Rabe, Pasternack, and Kindler (*Ber.*, 1917, **50**, 144), but beyond the statement by Kaufmann that they are of low toxicity to humans but strongly toxic to infusoria and paramecia there is no published record of their antiplasmodial activity. Schönhöfer, however, states (*Medicine in its Chemical Aspects*, 1938, **3**, 62) that compounds prepared by Kaufmann's method were examined in the laboratories of the I.G.Farbenindustrie and found inactive on avian malaria.

For the preparation of the required carbinolamines essential intermediates were 4-quinolyl and 6-methoxy-4-quinolyl halogenomethyl ketones (V), of which the bromo-representatives were available by the method of Rabe, Pasternack, and Kindler (*loc. cit.*).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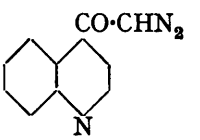
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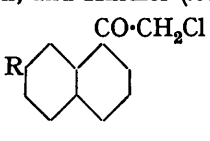
(VII.)

It seemed, possible, however, that the useful diazomethane reaction with acid chlorides could be applied to heterocyclic acid chlorides. In fact, the reaction between cinchoninic acid chloride and diazomethane was found to proceed normally with formation of *4-quinolyl diazomethyl ketone* (VI) and the latter readily gave *4-quinolyl chloromethyl ketone* in the usual way. The yields, however, precluded the use of this method for the preparation of large quantities of the chloromethyl ketone. Recently Baumgarten and Dornow (*Ber.*, 1940, **73**, 44; Dornow, *ibid.*, p. 185) have also applied the diazomethane reaction to other heterocyclic compounds such as the pyridinecarboxylic acid chlorides. Although the diazomethane reaction was not convenient for the reaction with cinchoninic acid, it proved quite suitable for the preparation of 1-naphthacyl chloride (VII, R = H) and 7-methoxy-1-naphthacyl chloride (VII, R = OMe) in excellent yield.

Naphthacyl chloride, 7-methoxynaphthacyl chloride, 4-quinolyl bromomethyl ketone, and 6-methoxy-4-quinolyl bromomethyl ketone were allowed to react with two molecular proportions of a series of secondary bases, usually in ethereal solution. When the separation of the secondary base hydrochloride or hydrobromide was complete, the keto-bases were straightway reduced catalytically, with palladised charcoal as catalyst, in methyl-

alcoholic solution containing aqueous mineral acid. The carbinolamines were then isolated as salts, usually with picric acid.

Representative carbinolamines have been made from a series of homologous secondary bases from dimethylamine to diheptylamine, from piperidine and from $\gamma\gamma'$-dipiperidyl. In the last-named case monosubstitution was ensured by use of the *monobenzoyl* derivative, the preparation of which was made possible by the application of the method used by Moore, Boyle, and Thorn (J., 1929, 39) for the monoacylation of piperazine.

The preparation of dihexylamine and diheptylamine presented difficulties, since they could not be made by a method analogous to the preparation of diethylamine from nitrosodiethylaniline, nor could they be obtained except in small yield by Vliet's method using sodium cyanamide (*Org. Synth., Coll. Vol.* **1**, 196). Eventually they were synthesised from *dihexyl-* and *diheptyl-benzylamine*, the benzyl group being removed by catalytic reduction with platinum oxide in glacial acetic acid at 70°.

$$CH_2Ph\cdot NH_2 + 2C_6H_{13}Br \longrightarrow CH_2Ph\cdot N(C_6H_{13})_2 \longrightarrow NH(C_6H_{13})_2$$

The removal of the *N*-benzyl group by catalytic reduction seems to have been used only (*a*) by the I.G.Farbenind. (compare B.P. 318,488, 1929, and others), where no details of the conditions or catalyst are recorded, and (*b*) by Baltzly and Buck (*J. Amer. Chem. Soc.*, 1940, **62**, 164) (compare, however, Bergmann and Zervas, *Ber.*, 1932, **65**, 1192, footnote).

The results of the tests on bird malaria due to *Plasmodium relictum* (= *Pl. præcox*) in canaries, of the carbinolamines described in this communication are shown in the following table.

Substance.	Dose in mg. per 20 g. of body weight.	Day of appearance of parasites in blood.	Remarks.
Dimethylaminomethyl-1-naphthylcarbinol	6 × 2·5 *	5	
	6 × 2·5	5	
Piperidinomethyl-1-naphthylcarbinol	6 × 1·25	5	
	6 × 1·25	5	
Piperidinomethyl-7-methoxy-1-naphthylcarbinol	6 × 0·625	5	M.T.D.†
	6 × 0·625	5	
Diethylaminomethyl-4-quinolylcarbinol	6 × 1·25	5	
	6 × 1·25	5	
Piperidinomethyl-4-quinolylcarbinol	6 × 5	5	
	6 × 5	5	
4′ : 4″-Piperidylpiperidinomethyl-4-quinolylcarbinol	6 × 5	5	M.T.D.
	6 × 5	5	
Diethylaminomethyl-6-methoxy-4-quinolylcarbinol	1 × 2·5 + 5 × 1·25	5	
	6 × 2·5	5	
Dibutylaminomethyl-6-methoxy-4-quinolylcarbinol	1 × 5 + 1 × 2·5 + 4 × 1·25	10	
	6 × 2·5	9	
	6 × 1·25	8	
Diamylaminomethyl-6-methoxy-4-quinolylcarbinol	6 × 10	10	
	6 × 10	11	
	6 × 5	5	M.T.D.
	6 × 5	9	
Di*iso*amylaminomethyl-6-methoxy-4-quinolylcarbinol	2 × 2·5 + 4 × 1·25	5	M.T.D.
	6 × 2·5	5	
Dihexylaminomethyl-6-methoxy-4-quinolylcarbinol	6 × 10	13	
	1 × 10 + 5 × 5	12	
	6 × 5	10	M.T.D.
	6 × 5	7	
Diheptylaminomethyl-6-methoxy-4-quinolylcarbinol	6 × 5	5	M.T.D.
	6 × 5	5	
Piperidinomethyl-6-methoxy-4-quinolylcarbinol	6 × 5	6	
	6 × 5	5	
4′ : 4″-Piperidylpiperidinomethyl-6-methoxy-4-quinolylcarbinol	6 × 5	6	M.T.D.
	6 × 5	5	
	6 × 2·5	5	
	6 × 2·5	6	
Quinine	6 × 2·5	12—14	
Control birds	—	5	

* This means a dose of 2·5 mg. was given daily for 6 days, the first dose being administered 4 hours after inoculation with malaria.

† M.T.D. = maximum tolerated dose.

A perusal of this table shows that no naphthyl, methoxynaphthyl, or quinolyl derivative had any noticeable activity. However, in the methoxyquinolyl series there was a zone of activity, the three bases dibutyl-, diamyl-, and dihexyl-aminomethyl-6-methoxy-4-quinolylcarbinols (IV) all being active, whereas the lower and the higher homologues were inactive. It is of interest that the dibutyl compound, for instance, differs in its molecular formula from dihydroquinine by having four extra hydrogen atoms.

Experimental.

α-Naphthoic Acid Derivatives.

α-Naphthoyldiazomethane.—Naphthoyl chloride (4·4 g.) in ether (25 c.c.) was run slowly into a cold solution of diazomethane in ether (from 10 g. of nitrosomethylurea). After being kept for 12 hours at room temperature, the ether was removed in a vacuum without heating, and the residue triturated with light petroleum. The pale yellow, crystalline product (3·5 g.), m. p. 56°, was sparingly soluble in petrol and readily soluble in benzene. A second crop of less pure material (0·9 g.) was obtained on concentrating the petroleum mother-liquor (Found: C, 73·6; H, 4·3; N, 14·3. $C_{12}H_8ON_2$ requires C, 73·5; H, 4·6; N, 14·3%).*

α-Naphthacyl Chloride.—Naphthoyldiazomethane (3·5 g.) was dissolved in ether, and dry hydrogen chloride passed into the solution until no more nitrogen was evolved; the ether was evaporated, and the oily product purified by distillation; yield, 94%.

Piperidinomethyl-1-naphthylcarbinol.—Naphthacyl chloride (5·15 g.), dissolved in ether (10 c.c.), was run slowly at room temperature into a solution of piperidine (4·6 g.) in ether (10 c.c.). Addition took about 10 minutes and the temperature rose to about 35°. After being kept for 1 hour, the precipitated piperidine hydrochloride (2·8 g.) was collected, and the filtrate evaporated in a vacuum at room temperature. No attempt was made to isolate the keto-amine, which was immediately dissolved in methyl alcohol, made acid to Congo by 3N-hydrochloric acid, and reduced catalytically with palladised charcoal as catalyst. Absorption ceased when 380 c.c. of hydrogen had been absorbed. The catalyst was removed, and the filtrate concentrated to a small volume; the desired hydroxy-amine *hydrochloride* (3·05 g.), sparingly soluble in water, then crystallised. A further crop (0·65 g.) was obtained from the mother-liquor. Crystallised from methyl alcohol, the pure product melted at 270° (Found: C, 70·4; H, 6·8; N, 4·8. $C_{17}H_{21}ON,HCl$ requires C, 70·0; H, 7·0; N, 4·8%).

Dimethylaminomethyl-1-naphthylcarbinol.—The method was the same as in the preceding experiment. Naphthacyl chloride (2·3 g.) condensed with dimethylamine (8 c.c. 33% solution) gave 2·1 g. of oily hydroxy-amine after reduction. The base gave a crystalline *picrate* sparingly soluble in methyl alcohol, m. p. 178—180° (Found: C, 54·0; H, 4·7; N, 13·1. $C_{14}H_{17}ON,C_6H_3O_7N_3$ requires C, 54·1; H, 4·5; N, 12·6%).

Diethylaminomethyl-1-naphthylcarbinol.—Naphthacyl chloride was condensed with diethylamine in ether. After reduction the hydroxy-amine was crystallised from alcohol as the *picrate*, m. p. 136°; yield, 60% (Found: C, 56·4; H, 4·9; N, 12·0. $C_{16}H_{21}ON,C_6H_3O_7N_3$ requires C, 55·9; H, 5·1; N, 11·9%).

Diethanolaminomethyl-1-naphthylcarbinol.—Naphthacyl chloride and diethanolamine were condensed in methyl alcohol and after catalytic reduction the desired product was isolated by prolonged fractional crystallisation of the *picrate*, m. p. 127—128°, from benzene and from methyl alcohol; yield, 20% (Found: C, 52·3; H, 4·7; N, 10·7. $C_{16}H_{21}O_3N,C_6H_3O_7N_3$ requires C, 52·3; H, 4·8; N, 11·1%).

Dipropylaminomethyl-1-naphthylcarbinol.—This was isolated with difficulty as the *picrate* in 25% yield, m. p. 149—150°, from methyl alcohol (Found: C, 57·8; H, 5·7; N, 11·2. $C_{18}H_{25}ON,C_6H_3O_7N_3$ requires C, 57·6; H, 5·6; N, 11·2%).

1-Cyanonaphthalene-7-sulphonic Acid.—1-Aminonaphthalene-7-sulphonic acid (23 g.) was diazotised as described by Royle and Schedler (*J.*, 1923, **123**, 1643). The diazonium chloride so obtained was made into a thick paste with water and added slowly to a solution of cuprous cyanide, prepared by adding potassium cyanide (29 g. in 80 c.c. of water) to copper sulphate (27 g. in 100 c.c. of water), the temperature being maintained at 60—70° throughout. Addition took ½ hour. The temperature was kept at 60° for a further ½ hour, sodium chloride (60 g.) then added, and the mixture kept in the ice-chest overnight. The cyanonaphthalenesulphonic acid was collected and purified by solution in hydrochloric acid, filtration, and reprecipitation by addition of potassium chloride (90 g.); yield, 78%.

* All analyses are micro.

7-Sulpho-1-naphthoic Acid.—The cyano-sulphonic acid was hydrolysed as described by Royle and Schedler (*loc. cit.*). The yield was almost quantitative. The product melted at 335°.

7-Hydroxy-1-naphthoic Acid.—The sulphonic acid was fused with potassium hydroxide as described by Royle and Schedler (*loc. cit.*); yield, 80%.

7-Methoxy-1-naphthoic Acid.—7-Hydroxy-1-naphthoic acid (36 g.) was dissolved in aqueous sodium hydroxide (7·6 g. in 80 c.c. of water) and heated to 90° in a flask fitted with a stirrer and two dropping-funnels, one containing methyl sulphate (48 g.) and the other sodium hydroxide (22·7 g. in 120 c.c. of water). About 20 c.c. of sodium hydroxide were run in first and then sodium hydroxide and methyl sulphate simultaneously so that both were added in about 45 minutes. The solution was maintained at 90° for a further 15 minutes, cooled, washed with ether, and made acid by addition of concentrated hydrochloric acid. The white precipitate was collected and recrystallised from alcohol. The first crop melted at 165—167° (26·5 g.) and the second at 180—220°. The second crop was partially methylated and was used again in subsequent preparations. Dziewonski, Galitzerowna, and Kocwa (*Bull. Acad. Polonaise*, 1926, *A*, 209) give m. p. 167·5°.

Ethyl 7-Methoxy-1-naphthoate.—Methoxynaphthoic acid was esterified by refluxing with alcohol and concentrated sulphuric acid for 5 hours; b. p. 157—160°/0·9 mm.

7-Methoxy-1-naphthoyl Chloride.—Methoxynaphthoic acid (62·0 g.) was treated with phosphorus pentachloride (64·0 g.) in benzene, the phosphorus oxychloride and the benzene distilled off, and the white solid residue distilled at 150°/0·9 mm.; m. p. 74—76°, yield 95%.

7-Methoxy-1-naphthacyl Bromide.—The method of preparation was the same as that used for naphthacyl chloride. The acid chloride (18·0 g.) was treated with excess of diazomethane, and dry hydrogen bromide passed into the solution. The *product* was purified with difficulty by distillation, as at the pressure used there was appreciable decomposition; b. p. 165—170°/1 mm., yield 20·4 g. (Found: C, 55·7; H, 4·0. $C_{13}H_{11}O_2Br$ requires C, 55·9; H, 3·9%).

7-Methoxy-1-naphthacyl chloride was prepared similarly and had b. p. 155—160°/1 mm.

Piperidinomethyl-7-methoxy-1-naphthylcarbinol.—Methoxynaphthacyl bromide (3·0 g.) in ether was added to piperidine (1·93 g.) in ether (15 c.c.). After 1 hour the solution was warmed at 35° for 10 minutes, and the piperidine hydrobromide (1·6 g.) collected. The oil left on removing the ether was reduced at once in methyl alcohol–hydrochloric acid solution with a palladised charcoal catalyst, the consumption of hydrogen being 250 c.c. The basic fraction of the condensation (2·7 g.) was crystallised from methyl alcohol–acetone as the *hydrochloride*, m. p. 225—227° (Found: C, 67·4; H, 7·0. $C_{18}H_{23}O_2N$,HCl requires C, 67·2; H, 7·4%).

Cinchoninic Acid Derivatives.

4-Quinolyl Diazomethyl Ketone.—Cinchoninic acid chloride (4 g.), prepared by Späth's method (*Ber.*, 1926, **59**, 1484), in dry ether (30 c.c.) was added slowly to a solution of diazomethane (from 10 g. of nitrosomethylurea) in ether (50 c.c.). After 24 hours, the ether was removed by a current of dry air, and the residue triturated with dry ether containing 10% of its volume of benzene. The solid was crystallised from ether; yield 2·5 g., m. p. 80—81°. One more crystallisation gave the pure *4-quinolyl diazomethyl ketone*, m. p. 83—84° (Found: C, 67·3; H, 3·9; N, 21·3. $C_{11}H_7ON_3$ requires C, 67·0; H, 3·6; N, 21·3%).

4-Quinolyl Chloromethyl Ketone.—The foregoing diazomethyl ketone (2·5 g.) was dissolved in ether (50 c.c.), and dry hydrogen chloride passed into the vigorously stirred solution. When nitrogen ceased to be evolved, the ethereal solution was washed with aqueous sodium carbonate, dried, and evaporated. The yellow solid was crystallised from benzene; yield 1·25 g., m. p. 101° (Found: C, 64·4; H, 4·0; Cl, 17·5. $C_{11}H_8ONCl$ requires C, 64·2; H, 3·9; Cl, 17·2%).

Ethyl 4-Quinoloylacetate.—The following method was found superior to that given by Rabe and Pasternack (*Ber.*, 1913, **46**, 1033). To a mixture of ethyl cinchoninate (40·2 g.) and ethyl acetate (20·0 g.), both dried over phosphoric oxide, sodamide (10 g.), powdered under benzene (60 c.c.), was added, and the mixture heated on the water-bath under reflux for 13 hours. The product was poured into water, and a solid (2·0 g.), which proved to be cinchoninic acid amide, removed. The filtrate was diluted with ether, and unchanged ethyl cinchoninate (5·5 g.) recovered from the ether–benzene solution. The alkaline aqueous solution was cooled in ice, made acid to Congo-paper and then treated with sodium bicarbonate until no more oil separated. The oil was collected and purified by precipitation of the acid sulphate from 25% sulphuric acid solution; yield 29—32 g. of base.

4-Quinolyl Bromomethyl Ketone.—This ketone was prepared from the preceding ester as described by Rabe, Pasternack, and Kindler (*Ber.*, 1917, **50**, 152). The hydrobromide melted at 225—227° (decomp.), the base at 75·5°.

Piperidinomethyl-4-quinolylcarbinol.—The following general method for the preparation of these basic carbinols was found more convenient than that described by Rabe *et al.* (*loc. cit.*). Powdered quinolyl bromomethyl ketone hydrobromide (2·5 g.) was added in portions during 10 minutes to a solution of piperidine (2·0 g.) in dry ether (15 c.c.), the mixture being shaken after each addition. After keeping for 1 hour at room temperature, the piperidine hydrobromide was collected, and the ether quickly removed without heating in a vacuum. The residue was dissolved in methyl alcohol (50 c.c.) and 3N-hydrochloric acid (25 c.c.) and reduced catalytically with palladised charcoal (0·25 g.). When hydrogen absorption (210 c.c.) was complete, the catalyst was collected, the methyl alcohol removed, and the aqueous liquor made alkaline. The ether-soluble oil which separated was purified through the dipicrate, m. p. 168° (decomp.). Rabe *et al.* gave m. p. 172—174° (decomp.) (Found: C, 47·4; H, 4·1; N, 14·4. Calc.: C, 47·1; H, 3·7; N, 14·3%). The hydrochloride had m. p. 160°. The yield in this instance was almost quantitative.

Diethylaminomethyl-4-quinolylcarbinol.—Powdered quinolyl bromomethyl ketone hydrobromide (5·9 g.), condensed with diethylamine (4·2 g.) in ether in the same way as is described above, gave diethylamine hydrobromide (4·5 g.) and a crystalline base, which was reduced catalytically (500 c.c. of hydrogen). The required product was isolated as the *dipicrate* (4·7 g.), m. p. 168° (Found: C, 46·5; H, 3·7. $C_{15}H_{20}ON_2,2C_6H_3O_7N_3$ requires C, 46·1; H, 3·7%). The hydrochloride, crystallised from alcohol, had m. p. 182°.

Dipropylaminomethyl-4-quinolylcarbinol.—The powdered bromo-ketone hydrobromide (6·2 g.) was added slowly to dipropylamine (5·3 g.) in ether (10 c.c.) and shaken vigorously after each addition. The temperature was maintained at 40° for 90 minutes, and the dipropylamine hydrobromide (5·4 g.) collected. The oil left on removal of the ether was reduced catalytically (460 c.c. of hydrogen) in methyl alcohol–hydrochloric acid solution. The required carbinol was crystallised from ethyl alcohol–acetone as the *dipicrate*, m. p. 153° (Found: C, 47·7; H, 4·3; N, 14·8. $C_{17}H_{24}ON_2,2C_6H_3O_7N_3$ requires C, 47·7; H, 4·1; N, 15·3%).

Diamylaminomethyl-4-quinolylcarbinol.—In this case the powdered bromo-ketone hydrobromide (5·0 g.) was added to diamylamine (7·43 g.) in acetone (10 c.c.). After being shaken for 1 hour at room temperature, the mixture was warmed at 50° for another hour, then cooled and diluted with dry ether, and the diamylamine hydrobromide (6·0 g.) collected. The solvent was removed at the ordinary temperature, and the residual oil dissolved in methyl alcohol–hydrochloric acid and reduced catalytically (340 c.c. of hydrogen). The required base was isolated with difficulty as the *dipicrate*, m. p. 142°, after repeated crystallisation from methyl alcohol–acetone; yield, 1·1 g. (Found: C, 50·0; H, 5·0; N, 14·7. $C_{21}H_{32}ON_2,2C_6H_3O_7N_3$ requires C, 50·4; H, 4·9; N, 14·3%).

N-*Benzoyl-4 : 4'-dipiperidyl.*—The monobenzoylation of dipiperidyl is a difficult process, but it can be effected by applying the method of Moore, Boyle, and Thorn (J., 1929, 39). After numerous trials the following method gave the best results. 4 : 4'-Dipiperidyl (22 g.) was dissolved in water (140 c.c.) and neutralised to bromphenol-blue with 3N-hydrochloric acid, a volume of acetone equal to the total volume of water present being then added. The solution was kept mechanically stirred at 50°, and benzoyl chloride (25 g.) run in drop by drop. The p_H of the solution was simultaneously adjusted to 3·8, *i.e.*, reddish-purple, bromphenol-blue being used as internal indicator, by running in saturated aqueous sodium acetate solution. When the addition of benzoyl chloride was complete, the acetone was removed by distillation under reduced pressure, and concentrated hydrochloric acid added. The mixture of benzoic acid and *dibenzoyl-4 : 4'-dipiperidyl* was taken up in the chloroform which had been used to extract the acidic filtrate. The chloroform solution was extracted with aqueous alkali to remove benzoic acid and then concentrated to 30 c.c. and mixed with an equal volume of ether; dibenzoyl-4 : 4'-dipiperidyl (16·5 g.) crystallised, m. p. 167° (Found: C, 76·4; H, 7·4. $C_{24}H_{28}O_2N_2$ requires C, 76·6; H, 7·5%).

The acidic aqueous mother-liquor was treated with aqueous potassium hydroxide so long as any oil separated, rise of temperature being avoided. The oil was taken up in chloroform, the mother-liquor being thoroughly extracted with more chloroform. On removal of the chloroform the residual oil was triturated with ether; the monobenzoate then went into solution, leaving 4 : 4'-dipiperidyl undissolved (5·4 g.). The monobenzoate (15·5 g.) was purified by crystallisation from acetone–methyl alcohol as the hydrobromide, m. p. 233°, or from methyl alcohol as the *perchlorate*, m. p. 268° (Found: C, 55·0; H, 6·5; N, 7·9. $C_{17}H_{24}ON_2,HClO_4$ requires C, 54·7; H, 6·7; N, 7·5%).

4' : 4''-*Piperidylpiperidinomethyl-4-quinolylcarbinol.*—Powdered 4-quinolyl bromomethyl ketone (3·65 g.) was added slowly with shaking to monobenzoyl-4 : 4'-dipiperidyl (9·5 g.) in

acetone (20 c.c.), and the mixture kept for 2 hours. The monobenzoyldipiperidyl hydrobromide was collected, and the acetone removed. The residual oil was reduced in methyl alcohol–hydrochloric acid solution palladised charcoal being used as catalyst (240 c.c. of hydrogen). After removal of the catalyst and solvent, the free base (2·9 g.) was extracted from alkaline solution and hydrolysed by heating with constant-boiling hydrochloric acid for 48 hours on the boiling water-bath. The solution was made alkaline, and the base extracted with a large volume of ether, since it was sparingly soluble in this solvent. The yellow oil obtained on removal of the ether gave a crystalline trihydrochloride (2·1 g.), m. p. above 300° (decomp.), from alcoholic solution, and a crystalline *tripicrate*, m. p. 195° (Found: C, 45·9; H, 3·7; N, 15·5. $C_{21}H_{29}ON_3,3C_6H_3O_7N_3$ requires C, 45·6; H, 3·7; N, 16·3%).

Quininic Acid Derivatives.

6-*Methoxy*-4-*quinolyl Bromomethyl Ketone*.—Ethyl quininate (21·7 g.) and ethyl acetate (9·0 g.) were condensed in the presence of sodamide (5·0 g.) as described in the corresponding preparation from ethyl cinchoninate. The resulting β-keto-ester (14·7 g.) was converted into the bromo-ketone named above by the method of Rabe, Pasternack, and Kindler (*loc. cit.*).

Piperidinomethyl-6-*methoxy*-4-*quinolylcarbinol*.—The method of preparation was the same as is described above for the compound without the methoxy-group. The carbinol base was isolated in almost quantitative yield (Rabe *et al.* give a 75% yield). The *hydrochloride* was crystallised from alcohol–acetone; m. p. 164° (Found: C, 62·9; H, 7·4; N, 9·0. $C_{17}H_{22}O_2N_2,HCl$ requires C, 63·2; H, 7·2; N, 8·7%).

Diethylaminomethyl-6-*methoxy*-4-*quinolylcarbinol*.—Prepared in the same way as the compound without the methoxy-group, this carbinol was isolated as the *dihydrochloride*, m. p. 182—183°; yield, 48% (Found: C, 55·7; H, 7·4; N, 8·3. $C_{16}H_{22}O_2N_2,2HCl$ requires C, 55·3; H, 6·9; N, 8·1%).

Dibutylaminomethyl-6-*methoxy*-4-*quinolylcarbinol*.—The condensation of the bromo-ketone hydrobromide (5·5 g.) with dibutylamine (6·0 g.) was carried out in the same way as is described above for diamylaminomethyl-4-quinolylcarbinol. The resultant oily keto-base (3·64 g.) required 460 c.c. of hydrogen for reduction to the carbinol. The required product was isolated with difficulty as the crystalline dihydrochloride, m. p. 142°, from methyl alcohol–acetone and gave a *dipicrate*, m. p. 169°, from ethyl alcohol–acetone (Found: C, 49·2; H, 4·6. $C_{20}H_{30}O_2N_2,2C_6H_3O_7N_3$ requires C, 48·8; H, 4·6%).

When the reaction was carried out with di*iso*butylamine, di*iso*butylamine hydrobromide separated as usual. The residual base was catalytically reduced. All attempts to isolate the di*iso*butylaminomethoxyquinolylcarbinol were unsuccessful. The only product which could be isolated crystalline gave analytical figures agreeing with *methyl*-6-*methoxy*-4-*quinolylcarbinol hydrochloride*, m. p. 217° (from ethyl alcohol) (Found: C, 59·9; H, 5·9. $C_{12}H_{13}O_2N,HCl$ requires C, 60·1; H, 5·8%).

Diamylaminomethyl-6-*methoxy*-4-*quinolylcarbinol*.—The bromo-ketone hydrobromide (5·0 g.), condensed with diamylamine (6·7 g.), gave diamylamine hydrobromide (6·3 g.) and an oil requiring 300 c.c. of hydrogen for reduction. The required base was difficult to isolate, but was eventually obtained in the most strongly basic fraction when the bases were fractionated by the method of differing basicities (King, J., 1919, **117**, 991; 1935, 1381; 1936, 1276; 1939, 1157). It was crystallised as the *dipicrate* (0·9 g.), m. p. 155°, from methyl alcohol (Found: C, 49·9; H, 5·0; N, 13·8. $C_{22}H_{34}O_2N_2,2C_6H_3O_7N_3$ requires C, 50·0; H, 4·9; N, 13·7%).

*Di*iso*amylaminomethyl*-6-*methoxy*-4-*quinolylcarbinol*.—The bromo-ketone hydrobromide (5·5 g.), condensed with di*iso*amylamine (7·06 g.), gave di*iso*amylamine hydrobromide (6·8 g.) and an oil which required 380 c.c. of hydrogen on reduction. The required base was isolated as the *dipicrate*, m. p. 156°, from methyl alcohol, after separation into fractions of different basicities (Found: C, 49·7; H, 4·8; N, 13·7. $C_{22}H_{34}O_2N_2,2C_6H_3O_7N_3$ requires C, 50·0; H, 4·9; N, 13·7%).

Di-n-*hexylbenzylamine*.—Technical hexyl alcohol contains unsaturated substances. These were conveniently removed from the hexyl bromide prepared by the hydrobromic–sulphuric acid method (*Organic Syntheses*, Coll. Vol., I, 26) by shaking with small quantities of sulphuric acid until the extracts were practically colourless. Molecular quantities of benzylamine (21·4 g.), hexyl bromide (66 g.), and potassium hydroxide pellets (26·4 g.) were refluxed at 150° for 8 hours. The oil obtained on dilution with water was fractionally distilled at 14 mm. and gave (1) 9·3 g., b. p. to 100°, (2) 14·2 g., b. p. 140—170°, and (3) 33·0 g., b. p. 170—186°. On careful refractionation 7·4 g., b. p. 146—148°/14 mm., of n-*hexylbenzylamine* (Found: C, 81·3; H, 11·0; N, 7·5. $C_{13}H_{21}N$ requires C, 81·6; H, 11·1; N, 7·3%), and 29·7 g. of *di*-n-

hexylbenzylamine, b. p. 185°/14 mm. (Found: C, 83·1; H, 11·9; N, 5·2. $C_{19}H_{33}N$ requires C, 82·8; H, 12·1; N, 5·1%), were obtained. The latter does not form a hydrochloride, but n-*hexylbenzylamine hydrochloride* crystallises from acetone in woolly needles, m. p. 217—218° (Found: C, 68·4; H, 9·2; N, 6·0. $C_{13}H_{21}N,HCl$ requires C, 68·5; H, 9·7; N, 6·1%).

Di-n-*hexylamine*.—Di-*n*-hexylbenzylamine (27·0 g.) in glacial acetic acid (30 c.c.) was reduced at 70° in presence of 0·4 g. of freshly prepared platinum oxide for 6 hours. The filtered solution was made strongly alkaline and extracted with ether, and the ethereal solution dried over potassium hydroxide pellets. The residue left on removal of the ether was fractionated under reduced pressure, a first fraction containing toluene being removed up to a temperature of 110°/14 mm., followed by an almost quantitative yield of di-*n*-hexylamine, b. p. 122°/15 mm. (Found by Kjeldahl: N, 7·4. Calc.: N, 7·6%). If the drying with potash was omitted, a hydrated base was obtained, b. p. 114—116°/14 mm., which almost completely crystallised on keeping and corresponded to a *tetrahydrate* (Found by Kjeldahl: N, 5·5. $C_{12}H_{27}N,4H_2O$ requires N, 5·2%). The *hydrochloride*, prepared from either form of the base by solution in a little alcohol and addition of concentrated hydrochloric acid, crystallised from acetone in pearly scales, m. p. 270° (Found: C, 65·3; H, 12·4; N, 6·3. $C_{12}H_{27}N,HCl$ requires C, 65·0; H, 12·7; N, 6·3%).

Di-n-*hexylaminomethyl*-6-*methoxy*-4-*quinolylcarbinol*.—The reaction between dihexylamine (3·0 g.) and the bromo-ketone hydrobromide (1·8 g.) was carried out in the usual way, but it was necessary to heat to 60° to complete the reaction. Dihexylamine hydrobromide (2·2 g.) was recovered and the basic condensation product was reduced, with Adams's catalyst, in ethyl alcohol after neutralisation with hydrochloric acid, the hydrogen consumption being 160 c.c. The basic carbinol (1·2 g.) was purified by fractional crystallisation as the *dipicrate*, m. p. 173°, from ethyl alcohol (Found: C, 51·2; H, 5·2; N, 13·3. $C_{24}H_{38}O_2N_2,2C_6H_3O_7N_3$ requires C, 51·5; H, 5·5; N, 13·2%).

Di-n-*heptylbenzylamine*.—*n*-Heptyl bromide (16·3 g.; 1 mol.), benzylamine (5·0 g.; 1 mol.), and potassium hydroxide pellets (6·15 g.; 1 mol.) were mixed and heated in an oil-bath. There was a vigorous reaction at 150°; this temperature was maintained for 8 hours. When cold, the product was diluted with water, and the oily layer separated and fractionated. The first fraction distilled between 160° and 180°/14 mm. but mainly at 167°; yield, 2·6 g. This proved to be heptylbenzylamine. It was converted in aqueous alcoholic solution into the *hydrochloride*, which crystallised in woolly needles, m. p. 196° (Found: C, 69·1; H, 9·5; N, 6·1. $C_{14}H_{23}N,HCl$ requires C, 69·5; H, 10·1; N, 5·8%). The second main fraction, *di*-n-*heptylbenzylamine* (9·35 g.), boiled at 205°/16 mm. and showed the same b. p. on redistillation before analysis (Found: C, 83·1; H, 12·3; N, 4·6. $C_{21}H_{37}N$ requires C, 83·2; H, 12·0; N, 4·7%).

Di-n-*heptylamine*.—Diheptylbenzylamine (6·0 g.) in glacial acetic acid (10 c.c.) was catalytically reduced in presence of platinum (Adams's catalyst) at 70° approx. Reduction was complete in 6 hours. The filtered solution was made alkaline and extracted with ether, and the ethereal layer dried over potassium hydroxide. The residue after removal of the ether was fractionally distilled, the first fraction up to 120°/15 mm. containing some toluene. The main fraction, di-*n*-heptylamine, boiled between 120° and 150°/15 mm. and on redistillation had b. p. 147—148°/15 mm. The presence of water lowers the b. p. (Found by Kjeldahl: N, 6·4. Calc.: N, 6·6%). This anhydrous form has m. p. 1°, but readily becomes hydrated and then has m. p. 32—33° (Found by Kjeldahl: N, 5·1. $C_{14}H_{31}N,3H_2O$ requires N, 5·2%). When the hydrated form is kept in a desiccator over calcium chloride, it liquefies, but the crystalline trihydrate is instantly formed on treatment with water. Sabatier and Mailhe (*Ann. Chim. Phys.*, 1909, **16**, 70) and Skita and Keil (*Ber.*, 1928, **61**, 1452), however, give m. p. 30° for the anhydrous base. Sabatier and Mailhe describe the hydrochloride as hygroscopic, but this is incorrect, as was also shown by Skita and Keil. The hydrochloride crystallises in woolly needles, m. p. 255°; Skita and Keil give 250° (Found: C, 67·1; H, 12·2; N, 5·8. Calc.: C, 67·3; H, 12·9; N, 5·6%).

Di-n-*heptylaminomethyl*-6-*methoxy*-4-*quinolylcarbinol*.—The condensation of diheptylamine (12·8 g.) and the bromo-ketone hydrobromide (7·0 g.) was carried out as in the preceding experiment. Diheptylamine hydrobromide (11·0 g.) was recovered and during catalytic hydrogenation 610 c.c. of hydrogen were consumed. The acid-soluble portion of the product was fractionated by the method of differing basicities. From the most basic fraction, methyl-6-methoxy-4-quinolylcarbinol, m. p. 118°, was isolated (Found: C, 70·8; H, 6·2; N, 6·6. Calc.: C, 70·9; H, 6·5; N, 6·9%). Kaufmann, Kunkler, and Peyer (*Ber.*, 1913, **46**, 57) give m. p. 120—121°. The picrate had m. p. 183° and the hydrochloride 217°. From a slightly less basic fraction, di-*n*-heptylaminomethyl-6-methoxy-4-quinolylcarbinol (0·75 g.) was isolated as the

dipicrate, m. p. 130°, from ethyl alcohol (Found : C, 52·1 ; H, 5·4 ; N, 13·1. $C_{26}H_{42}O_2N_2,2C_6H_3O_7N_3$ requires C, 52·3 ; H, 5·6 ; N, 12·8%).

4′ : 4″ - *Piperidylpiperidinomethyl* - 6 - *methoxy* - 4 - *quinolylcarbinol*.—Monobenzoyldipiperidyl (10·4 g.) and the appropriate bromo-ketone hydrobromide (4·4 g.) combined to give an oily base (6·0 g.) requiring 370 c.c. of hydrogen for reduction. After hydrolysis with concentrated hydrochloric acid, the benzoic acid was removed, the solution made alkaline, and the required base extracted with ether. The product crystallised from aqueous acetone as the hydrated *trihydrochloride*, which was difficult to purify and decomposed above 300° without melting (Found : C, 50·1 ; H, 7·5 ; N, 8·3. $C_{22}H_{31}O_2N_3,3HCl,2H_2O$ requires C, 51·3 ; H, 7·4 ; N, 8·1%. Found for salt dried at 100° : C, 54·3 ; H, 7·3. $C_{22}H_{31}O_2N_3,3HCl$ requires C, 55·1 ; H, 6·5%).

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