72. *Antiplasmodial Action and Chemical Constitution. Part V. Carbinolamines derived from 6-Methoxyquinoline.*

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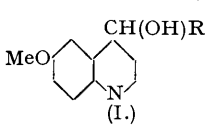
The aim of this investigation was the search for antiplasmodial substances based on the formula of quinine but of simpler structure. The preparation of a number of unsymmetrical dialkylamines is described and, from these, 1 : 2-carbinolamines have been synthesised containing the 6-methoxyquinoline nucleus. Although the structure of these carbinolamines was very close to that of active antiplasmodials described in Part III, these bases proved to be inactive when tested on bird-malaria in canaries.

In Part III (King and Work, J., 1940, 1307), it was shown that there was antiplasmodial activity, as tested on bird-malaria in canaries, in the *N*-dibutyl-, -diamyl- and -dihexyl-aminomethyl-6-methoxy-4-quinolylcarbinols (I, R = $CH_2 \cdot NR_1R_2$). The lower and the higher dialkyl homologues were, however, inactive. There was thus a zone of activity where the sum of the carbon atoms of the *N*-alkyl groups lay between eight and twelve. The present communication describes the synthesis of seven members of a series of secondary amines, in which the groups R_1 and R_2 are different from each other, and their combined carbon atom content is not greater than 12 and not less than 8. It has only been found possible to prepare bases of the structure (I, R = $CH_2 \cdot NR_1R_2$) from four of these unsymmetrical secondary bases. In the other cases catalytic reduction of the intermediate quinolylketo-bases was followed by fission of the basic group with formation of methyl-6-methoxy-4-quinolylcarbinol (I, R = CH_3).



(I.)

Ethyl-, *propyl-*, *butyl-* and *amyl-hexylamines* were prepared by the action of the appropriate alkyl iodides

or bromides on benzylhexylamine. The benzyl group was then removed by catalytic reduction in acetic acid at 70° in the presence of platinum oxide :

$$C_6H_{13}\cdot NH\cdot CH_2Ph + R\cdot Hal \longrightarrow C_6H_{13}\cdot NR\cdot CH_2Ph \longrightarrow C_6H_{13}\cdot NHR + Ph\cdot CH_3$$

In a similar manner *ethyl-* and *propyl-nonylamines* were obtained. Difficulties were, however, encountered in the preparation of *methylnonylamine*. When methyl iodide and *benzylnonylamine* were allowed to react, the products were mainly unchanged base and *benzyldimethylnonylammonium iodide*. This quaternary salt was, however, converted into the hydroxide and then into the hydrosulphide, following Clarke's method (J., 1913, **103**, 1689). On evaporation of the solution of this hydrosulphide under reduced pressure the products were *dimethylnonylamine*, benzylmercaptan and dibenzyl sulphide, the benzyl group showing a preference to be eliminated over the methyl group. This might have been anticipated from the known tendency for benzyl

$$\left[\begin{matrix}Me\\Me\end{matrix}\!\!>\!N\!<\!\begin{matrix}C_9H_{19}\\CH_2Ph\end{matrix}\right]SH \longrightarrow Me_2N\cdot C_9H_{19} + Ph\cdot CH_2\cdot SH + Ph\cdot CH_2\cdot S\cdot S\cdot CH_2Ph$$

groups to be eliminated over other groups in many reactions (compare Snyder and Speck, *J. Amer. Chem. Soc.*, 1939, **61**, 669, 2895, where several references are given). This easy elimination of benzyl groups limits the applicability of Clarke's useful method for the demethylation of quaternary ammonium salts to cases where the benzyl group is absent.

When nonyl iodide and methylamine were allowed to interact in methyl-alcoholic solution at 100°, methylnonylamine was formed, but the main product was *methyldinonylamine*. Methylnonylamine was eventually obtained in good yield by an application of Decker's method. Benzaldehyde and nonylamine were condensed to give *benzylidenenonylamine*, which on methylation gave an oily methiodide. On digestion of the latter with 90% alcohol and treatment with mineral acid benzaldehyde was liberated to ether, and the methylnonylamine recovered from the acid liquor.

The results of the tests on bird malaria due to *Plasmodium relictum* in canaries, of the carbinolamines described in this communication are shown below.

Substance.	Dose in mg. per 20 g. of body weight.	Day of appearance of parasites in blood.	Remarks.
Ethylhexylaminomethyl-6-methoxy-4-quinolylcarbinol	6 × 5*	5	M.T.D.†
	1 × 5 + 5 × 2·5	6	
Propylhexylaminomethyl-6-methoxy-4-quinolylcarbinol	6 × 5	5	M.T.D.
	6 × 2·5	6	
Butylhexylaminomethyl-6-methoxy-4-quinolylcarbinol	6 × 5	5	M.T.D.
	6 × 5	5	
Methylnonylaminomethyl-6-methoxy-4-quinolylcarbinol	1 × 2·5 + 5 × 1·25	6	M.T.D.
	1 × 2·5 + 5 × 1·25	6	
2′ : 2′ : 6′-Trimethylpiperidinomethyl-6-methoxy-4-quinolylcarbinol	6 × 5	5	M.T.D.
	6 × 5	5	
Quinine dihydrochloride	6 × 2·5	10	
Control birds		5, 6, 5	

* This means a dose of 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.

In Part III (p. 139) it was found that piperidinomethyl-6-methoxy-4-quinolylcarbinol was inactive on bird malaria. It was thought possible that activity might be restored by bringing up the carbon content to the level shown necessary in the symmetrical secondary bases, that is, between eight and twelve carbon atoms. Accordingly 2′ : 2′ : 6′-trimethylpiperidinomethyl-6-methoxy-4-quinolylcarbinol (I, R = $\cdot N\!<\!\begin{matrix}CMe_2\!-\!CH_2\\CHMe\cdot CH_2\end{matrix}\!>\!CH_2$) was synthesised, but it proved to be without action in the dose shown in the table.

Experimental.

Benzyl-n-*hexylamine*.—This base is a by-product in the preparation of benzyldi-*n*-hexylamine (King and Work, J., 1940, 1313). It may be obtained as the main product by the following process: Hexyl bromide (66·0 g.; 1 mol.) and benzylamine (85·6 g.; 2 mols.) after about an hour deposited benzylamine hydrobromide. The mixture was heated on the boiling water-bath for an hour, cooled, and diluted with dry ether, and the benzylamine hydrobromide collected. The ethereal solution was shaken with aqueous sodium hydroxide, dried over potassium hydroxide, then fractionated, giving benzylamine (19·0 g.), b. p. 80—100°/18 mm., benzyl-*n*-hexylamine (51·6 g.), b. p. 142—160°/18 mm. (47 g. on redistillation, b. p. 149—150°/18 mm.; yield, 62% on the hexyl bromide used), and benzyldi-*n*-hexylamine 6·7 g.), b. p. 160—180°/18 mm.

Benzyl-n-*butylhexylamine*.—Benzylhexylamine (19·1 g.), *n*-butyl bromide (15·1 g.), and potassium hydroxide (7·7 g.) were heated at 140° for 5 hours. The product was cooled, diluted with aqueous alkali, and extracted with ether. The main non-ethereal fraction (22·75 g.), b. p. 165—171°/18 mm., on refractionation through a column gave *benzyl*-n-*butylhexylamine* (17·4 g.), b. p. 170°/18 mm. (Found: C, 82·7; H, 11·9; N, 5·7. $C_{17}H_{29}N$ requires C, 82·6; H, 11·7; N, 5·7%).

n-*Butylhexylamine*.—Benzylbutylhexylamine (24·7 g.), reduced at 70° (see amyl analogue, below), gave *butylhexylamine* (13·6 g.), b. p. 201°/738 mm. (Found: C, 76·1; H, 14·8; N, 9·0. $C_{10}H_{23}N$ requires C, 76·4; H, 14·6; N, 8·9%). The *hydrochloride* crystallised from acetone in filmy leaflets, m. p. 268° (Found: C, 62·0; H, 12·6. $C_{10}H_{23}N,HCl$ requires C, 62·0; H, 12·5%).

Benzyl-n-amylhexylamine.—Benzylhexylamine (19·1 g.), *n*-amyl bromide (16·6 g.), and potassium hydroxide (17·7 g.) were refluxed at 140° for 3 hours. The mixture obtained in ethereal solution after addition of aqueous caustic alkali gave (1) b. p. up to 100°/15 mm. (hexyl bromide), (2) 5·3 g., b. p. 150—170°/15 mm., (3) 18·0 g., b. p. 170—180°/15 mm. On refractionation (2) and (3) gave *benzyl-n-amylhexylamine* (16·8 g.), b. p. 175—177°/15 mm. (79% yield) (Found: C, 82·3; H, 11·9; N, 5·5. $C_{18}H_{31}N$ requires C, 82·7; H, 12·0; N, 5·4%).

n-*Amylhexylamine.*—Benzylamylhexylamine (26·1 g.) in glacial acetic acid (30 c.c.) and platinum oxide (0·4 g.) was hydrogenated at 70° for 12 hours, and the filtered solution diluted with water and made strongly alkaline. The dried ethereal extract gave n-*amylhexylamine* (14·4 g.), b. p. 108°/15 mm., 216—218°/763 mm. (Found: N, 7·9. $C_{11}H_{25}N$ requires N, 8·2%). The *hydrochloride* separated from acetone in pearly leaflets, m. p. 275—276° (Found: C, 63·8; H 12·4. $C_{11}H_{25}N$,HCl requires C, 63·6; H, 12·6%).

Benzyl-n-propylhexylamine, prepared from benzylhexylamine (19·1 g.), *n*-propyl iodide (17·0 g.), and potassium hydroxide (7·7 g.) at 140° (external bath), had b. p. 149—155°/15 mm. (yield, 20·5 g.) and on refractionation 155°/15 mm. (Found: C, 82·3; H, 11·3; N, 6·2. $C_{16}H_{27}N$ requires C, 82·3; H, 11·7; N, 6·0%).

n-*Propylhexylamine* obtained from benzylpropylhexylamine (34·9 g.) by reduction at 70°, had b. p. 171—181°/753 mm.; yield, 15·4 g. (Found: C, 75·2; H, 15·0; N, 9·5. $C_9H_{21}N$ requires C, 75·5; H, 14·7; N, 9·8%). The very soluble *hydrochloride*, obtained from hydrogen chloride and a low-boiling petroleum solution of the base, crystallised from acetone in pearly leaflets, m. p. 243° (Found: C, 60·2; H, 12·1. $C_9H_{21}N$,HCl requires C, 60·1; H, 12·3%).

Benzylethylhexylamine.—Benzylhexylamine (9·55 g.), ethyl iodide (8·6 g.), and potassium hydroxide (3·85 g.) were heated in sealed tubes at 140—150° for 4 hours. An ethereal extract of the basified product gave *benzylethylhexylamine* (15·6 g.), b. p. 145°/13 mm. (Found: C, 81·9; H, 11·6; N, 6·6. $C_{15}H_{25}N$ requires C, 82·3; H, 11·4; N, 6·4%).

Ethylhexylamine (10·9 g.), obtained from the above base (29 g.) by reduction at 70° and isolated by repeated extraction with ether of the strongly basified mixture, had b. p. 158°/743 mm. (Found: C, 74·2; H, 14·8; N, 10·6. $C_8H_{19}N$ requires C, 74·2; H, 14·8; N, 10·6%). The *hydrochloride* (see propyl analogue) crystallised in pearly leaflets, m. p. 191° (Found: C, 58·2; H, 11·9. $C_8H_{19}N$,HCl requires C, 58·0; H, 12·2%).

Benzyl-n-nonylamine (30·1 g.), obtained from benzylamine (42·8 g.) and nonyl bromide (41·4 g.) (see hexyl analogue), had b. p. 179°/12 mm. (Found: C, 82·0; H, 11·6; N, 6·2. $C_{16}H_{27}N$ requires C, 82·3; H, 11·7; N, 6·0%). *Benzyldinonylamine* (7·0 g.), b. p. 240°/12 mm., was also obtained (Found: C, 83·4; H, 12·3; N, 4·2. $C_{25}H_{45}N$ requires C, 83·5; H, 12·6; N, 3·9%). *Benzylnonylamine hydrochloride* separated from water in needles, m. p. 199—200° (Found: C, 70·9; H, 10·3. $C_{16}H_{27}N$,HCl requires C, 71·2; H, 10·5%).

Benzyl-n-propylnonylamine (32·5 g.), obtained from benzylnonylamine (34·9 g.), *n*-propyl iodide (25·5 g.), and potassium hydroxide (11·5 g.) at 130°, had b. p. 185°/13 mm. (Found: C, 83·4; H, 12·0; N, 5·4. $C_{13}H_{33}N$ requires C, 82·8; H, 12·1; N, 5·1%).

Propylnonylamine (12·3 g.), obtained by reduction of benzylpropylnonylamine (32·5 g.), had b. p. 119°/14 mm. (Found: C, 77·7; H, 14·5. $C_{12}H_{27}N$ requires C, 77·8; H, 14·7%). The *hydrochloride* crystallised from dilute hydrochloric acid in pearly scales, m. p. 237° (Found: C, 64·3; H, 13·0. $C_{12}H_{27}N$,HCl requires C, 64·9; H, 12·7%).

Benzylethylnonylamine.—A mixture of benzylnonylamine (23·3 g.; 1 mol.) and ethyl iodide (17·16 g.; 1 mol.) became warm after 30 minutes and crystals separated. Potassium hydroxide (7·7 g.) was added, the mixture heated on the water-bath for 4 hours, and the product treated with water and ether. The solid (2·2 g.) that separated crystallised from ethyl acetate in white plates, m. p. 64—65°, of *benzyldiethylnonylammonium iodide* (Found: C, 57·2; H, 8·9; N, 3·4. $C_{20}H_{36}NI$ requires C, 57·5; H, 8·7%). The ethereal extract on fractional distillation gave *benzylethylnonylamine* (22·1 g.), b. p. 178°/11 mm. (Found: C, 82·7; H, 11·8. $C_{18}H_{31}N$ requires C, 82·7; H, 12·0%).

Ethylnonylamine (yield, 84·3%), obtained by catalytic reduction of benzylethylnonylamine (22·1 g.) at 70°, had b. p. 103°/14 mm. (Found: C, 77·1; H, 14·5. $C_{11}H_{25}N$ requires C, 77·1; H, 14·7%). The *hydrochloride* crystallised from acetone in pearly leaflets, m. p. 200—201° (Found: C, 63·8; H, 12·6. $C_{11}H_{25}N$,HCl requires C, 63·6; H, 12·6%).

Reaction between Benzylnonylamine and Methyl Iodide.—Benzylnonylamine (16 g.) and methyl iodide (10·7 g.; 1·1 mols.), gradually mixed, reacted vigorously, giving mainly unchanged benzylnonylamine (9·25 g.) and *benzyldimethylnonylammonium iodide*. The latter crystallised from ethyl acetate in plates (4·9 g.), m. p. 89° (Found: C, 54·9; H, 8·3; N, 3·6. $C_{18}H_{32}NI$ requires C, 55·5; H, 8·3; N, 3·6%).

A solution of the methochloride [obtained from the quaternary iodide (14·1 g.)] in water (100 c.c.) was treated with silver oxide, filtered, saturated with hydrogen sulphide, and evaporated to a syrup under reduced pressure at 50°; the residue was re-evaporated three times with a little absolute ethyl alcohol and then heated in a boiling water-bath for 4 hours. The product was now ether-soluble and on fractional distillation gave (*a*) 5·2 g., b. p. 97—99°/14 mm., and (*b*) 1·7 g., b. p. 170—180°/14 mm. As fraction (*a*) gave a nitroprusside reaction for thiol groups, it was dissolved in ether and extracted with aqueous sodium hydroxide. The ethereal solution now gave a sulphur-free product, b. p. 209°/741 mm., which proved to be *dimethylnonylamine* (Found: C, 77·1; H, 14·7. $C_{11}H_{25}N$ requires C, 77·7; H, 14·1%). The *methiodide* separated from water in filmy leaflets, m. p. 170° (Found: C, 45·9; H, 9·1. $C_{12}H_{28}NI$ requires C, 46·0; H, 9·0%). The thiol isolated from the sodium hydroxide extract by acidification in the presence of ether was benzylthiol (0·4 g.), b. p. 195—197°; the 2 : 4-dinitrophenyl thioether prepared from it had m. p. 128°; Bost, Turner, and Norton (*J. Amer. Chem. Soc.*, 1932, **54**, 1985) give m. p. 130° (Found: C, 54·2; H, 3·9. Calc.: C, 53·8; H, 3·7%).

Fraction (*b*) solidified and crystallised from methyl alcohol in bold plates, m. p. and mixed m. p. with dibenzyl sulphide 47°. The dibenzylsulphine-*p*-toluenesulphonylimine prepared from it had m. p. 191° (Mann and Pope, J., 1922, **121**, 1053, give m. p. 193°).

Methylnonylamine.—(*a*) Nonyl bromide (20·7 g.) was converted into nonyl iodide (24·0 g.), b. p. 116°/15 mm. by Finkelstein's method. The iodide was mixed with methylamine (20 c.c.; 33% solution) in methyl alcohol and heated at 100° for 6 hours. The product was treated with aqueous sodium hydroxide, and the excess of methylamine and alcohol distilled off on the water-bath. The product extracted from the alkaline solution by ether was fractionally distilled, giving methylnonylamine (2·6 g.), b. p. 92—94°/15 mm., identified as its hydrochloride, m. p. 179—180° (see below), and *methyldinonylamine* (10·0 g.), b. p. 190—192°/15 mm. (Found: C, 80·5; H, 14·4. $C_{19}H_{41}N$ requires C, 80·6; H, 14·5%).

(*b*) *By Decker's method.* Nonylamine (9·0 g.), b. p. 85°/13 mm., was condensed with benzaldehyde (7 g.; 1·1 mols.) by heating on the water-bath for 1 hour. The *benzylidenenonylamine* was distilled under reduced pressure (yield, 13·6 g.), b. p. 179°/14 mm. (Found: C, 82·5; H, 11·2; N, 6·6. $C_{16}H_{25}N$ requires C, 83·1; H, 10·8; N, 6·3%). This was mixed with methyl iodide (8·4 g.; 1·1 mols.) and after 1 hour heated on the water-bath for 3 hours. The dark red, viscous oil was diluted with 90% ethyl alcohol (40 c.c.) and digested on the water-bath for 1 hour; the alcohol was then removed by distillation, the residue acidified, and the benzaldehyde removed by ether extraction. *Methylnonylamine* (6·6 g.), recovered from the acid solution, had b. p. 95°/14 mm. (Found: N, 9·1. $C_{10}H_{23}N$ requires N, 9·1%). The *hydrochloride* separated from acetone in needles or plates, m. p. 180—181° (Found: C, 61·6; H, 12·6. $C_{10}H_{23}N$,HCl requires C, 62·0; H, 12·5%).

Quininic Acid.—Thielepape's procedure (*Ber.*, 1939, **72**, 1432) was in the main followed, but it was found advan-

tageous when preparing α-ethoxalyl-*N*-methyl-*p*-methoxyacetanilide to dissolve the *N*-methyl-*p*-methoxyacetanilide (17·9 g.) in the ethyl oxalate (13·4 c.c.) and to add this slowly to a hot solution of sodium ethoxide (2·3 g. of sodium in 11·6 c.c. of absolute ethyl alcohol). Heating was continued for 2 hours, and the product (16·5 g.) isolated and purified as described by Thielepape.

Conversion of ethyl 2-chloroquininate into quininic acid as described by Thielepape was laborious and the yields were not satisfactory. The following process gave better results: Ethyl 2-chloroquininate (53 g.) was boiled vigorously with sodium hydroxide (9·0 g. in 1 l. of water) for 2 hours, the solution concentrated under reduced pressure to 350 c.c., sodium hydroxide (9·0 g.) and a palladium–strontium carbonate catalyst (2·0 g.) added, and the solution hydrogenated at 5 atms. for 45 minutes. The catalyst was collected and re-used for subsequent batches. Quininic acid was precipitated by addition of hydrochloric acid until the reaction of the solution was definitely acid to Congo-paper. The yield was almost quantitative.

Ethylhexylaminomethyl-6-methoxy-4-quinolylcarbinol.—Powdered 6-methoxy-4-quinolyl bromomethyl ketone hydrobromide (6·6 g.) (King and Work, *loc. cit.*) was added slowly to ethylhexylamine (7·1 g.) in acetone (10 c.c.). After 1 hour the mixture was warmed at 45° for 45 mins. and diluted with dry ether, and the ethylhexylamine hydrobromide collected (7·0 g.). The ethereal solution was washed with water, and the ether removed in a vacuum. A portion of the residual oil (2·5 g.) was dissolved in ethyl alcohol, concentrated hydrochloric acid added until the solution was acid to Congo-paper, and the product reduced, platinum oxide being used as catalyst (hydrogen consumed, 250 c.c.). *Ethylhexylaminomethyl-6-methoxy-4-quinolylcarbinol dipicrate*, isolated from the reduction mixture in 20% yield, had m. p. 170° and was soluble in hot ethyl alcohol (Found: C, 48·8; H, 4·5; N, 14·6. $C_{20}H_{30}O_2N_2,2C_6H_3O_7N_3$ requires C, 48·8; H, 4·6; N, 14·2%). Methyl-6-methoxy-4-quinolylcarbinol picrate was isolated as a by-product and its formation in quantity accounts for the low yield of the desired base.

Propylhexylaminomethyl-6-methoxy-4-quinolylcarbinol.—The product obtained from the appropriate bromomethyl ketone hydrobromide (7·1 g.) and propylhexylamine (8·5 g.) was reduced in the usual way. The resultant oil (5·8 g.) had to be fractionated by the method of differing basicities (cf. King and Ware, J., 1941, 331) before any crystalline derivatives could be obtained. The required *dipicrate*, m. p. 169°, was crystallised from acetone–ethyl alcohol; yield, 17% (Found: C, 49·8; H, 5·1. $C_{21}H_{32}O_2N_2,2C_6H_3O_7N_3$ requires C, 49·5; H, 4·8%).

Methylnonylaminomethyl-6-methoxy-4-quinolylcarbinol.—Condensation of methylnonylamine (4·0 g.) with 6-methoxy-4-quinolyl bromomethyl ketone hydrobromide (3·07 g.), reduction, and fractionation of the product gave an oil (1·06 g.), which was separated by fractional crystallisation into methylmethoxyquinolylcarbinol picrate and *methylnonylaminomethyl-6-methoxy-4-quinolylcarbinol dipicrate*, m. p. 151°, readily soluble in hot ethyl alcohol (Found: C, 50·9; H, 5·2; N, 13·4. $C_{22}H_{34}O_2N_2,2C_6H_3O_7N_3$ requires C, 50·0; H, 4·9; N, 13·7%).

Butylhexylaminomethyl-6-methoxy-4-quinolylcarbinol.—The condensation with butylhexylamine (9·4 g.) and subsequent reduction were carried out as described for the lower homologue. The *dipicrate* (0·7 g.), m. p. 158—159°, was sparingly soluble in ethyl alcohol (Found: C, 50·8; H, 5·2; N, 14·5. $C_{22}H_{34}O_2N_2,2C_6H_3O_7N_3$ requires C, 50·0; H, 4·9; N, 13·7%).

2′ : 2′ : 6′-Trimethylpiperidinomethyl-6-methoxy-4-quinolylcarbinol.—2 : 2 : 6-Trimethylpiperidine (6·0 g.) was condensed with the bromoketone hydrobromide (5·73 g.), and the product reduced (hydrogen consumed, 340 c.c.). From the ether-soluble fraction of the product a crystalline hydrochloride (0·7 g.), m. p. 214—218° (decomp.), was isolated by fractional crystallisation from ethyl alcohol. Although apparently homogeneous, this hydrochloride did not give satisfactory analytical figures. It was converted into the *dipicrate*, m.p. 214°, which was crystallised repeatedly from acetone containing 5% of free picric acid (Found: C, 49·4; H, 3·8. $C_{20}H_{28}O_2N_2,2C_6H_3O_7N_3$ requires C, 48·9; H, 4·3%).

Attempts to obtain morpholinomethyl-6-methoxy-4-quinolylcarbinol were unsuccessful, reduction always leading to formation of methyl-6-methoxy-4-quinolylcarbinol.

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