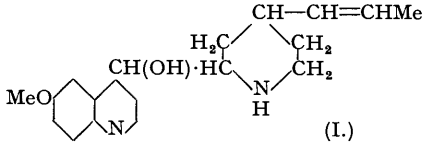
51. *The Synthesis of Antimalarial Compounds Related to Niquidine. Part I. Model Experiments on the Synthesis of Quinolyl Carbinols.*

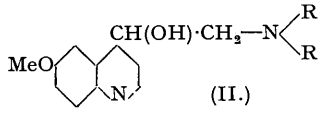
By T. S. Work.

Model experiments to examine the practicability of three alternative methods for the synthesis of compounds of niquidine type are described. Condensation of a quinoline-4-aldehyde with a 3-ketopiperidine without elimination of water was successfully achieved but the keto group could not be reduced. Condensation of an aliphatic aldehyde with a 4-acetylquinoline gave an unsaturated ketone which was reduced to a quinolylalkylcarbinol. Condensation of a quinoline-4-aldehyde with aliphatic nitro-compounds gave nitro-hydroxyderivatives of quinoline reducible to aminoquinolyl-carbinols. α-Piperidyl-6-methoxy-4-quinolylcarbinol was synthesised by this method.

Niquidine, a degradation product of quinidine, has been reported (Buttle, Henry, Solomon, Trevan and Gibbs, *Biochem. J.*, 1938, **32**, 47) to be more active than quinine in bird malaria. On the basis of degradative experiments, structure (I) was assigned by Gibbs and Henry (*J.*, 1939, 240) to niquidine.



(I.)



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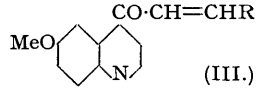
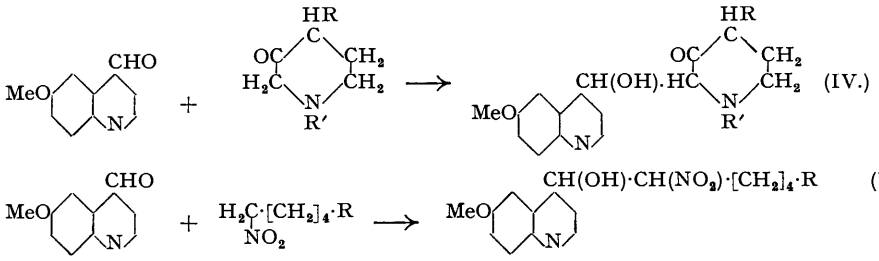


(III.)

Ainley and King (*Proc. Roy. Soc.*, 1938, **125**, B, 60) synthesised α-piperidyl-6-methoxy-4-quinolylcarbinol which may be regarded as niquidine with the unsaturated side-chain removed. This compound was rather less active than quinine in bird malaria. To study the effect of simplifying the " quinuclidine half " of the quinine molecule still further, King and Work (*J.*, 1940, 1307) synthesised a series of 6-methoxy-4-quinolyldialkylaminomethyl-carbinols (II). They found that, in a homologous series (R = methyl to R = heptyl), activity reached a peak at dibutylamino or diamylamino but that the most active member of the series was no more active than α-piperidyl-6-methoxy-4-quinolylcarbinol despite closer similarity to quinine in molecular weight. These results indicated that it might be more profitable to study the synthesis of α-piperidylquinolylcarbinols with suitable alkyl or alkenyl substituents in the piperidine ring.

Clearly such a synthesis might be possible starting from quininic ester and alkylpiperidines using the method of Ainley and King (*loc. cit.*), but as the higher alkylpiperidines are not readily obtainable and as the overall yield by this method was not high it was considered worth while to study alternative methods for linking the quinoline half of the molecule with suitable bases.

Three possible routes have been studied : (i) condensation of 6-methoxy-4-acetoquinoline with aldehydes to give unsaturated ketones; (ii) condensation of 6-methoxyquinoline-4-aldehyde with 3-ketopiperidines; and (iii) condensation of 6-methoxyquinoline-4-aldehyde with suitable nitro compounds.

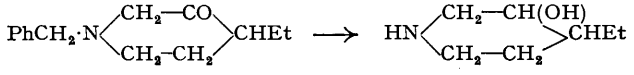


As a suitable model for (i), butyraldehyde was successfully condensed with 6-methoxy-4-acetoquinoline using alcoholic potassium hydroxide as a condensing agent to give 6-methoxy-4-quinolyl pentenyl ketone, (III; R = C_3H_7), isolated as the *picrate*.

To extend this synthesis to compounds of the niquidine type phenoxyethylvaleraldehyde was condensed with 6-methoxy-4-acetoquinoline by this method (see following paper).

The practicability of (ii) was examined by synthesising 3-*keto*-N-*benzyl*-4-*ethylpiperidine* by the following series of reactions : *ethyl* α-(β′-*ethoxyethyl*)*acetoacetate* was alkylated with ethyl iodide to give *ethyl* α-*ethyl*-α-(β′-*ethoxyethyl*)*acetoacetate* which was brominated to give *ethyl* γ-*bromo*-α-*ethyl*-α-(β′-*ethoxyethyl*)*acetoacetate*; the latter was condensed with benzylamine and hydrolysed with hydrobromic acid to give *benzyl*-(ε-*bromo*-β-*keto*-γ-*ethylamyl*)*amine hydrobromide*; this on treatment with alkali gave the desired 3-*keto*-N-*benzyl*-4-*ethylpiperidine*. Catalytic reduction of this base gave 3-hydroxy-4-ethylpiperidine, thus :

$$Me\cdot CO\cdot CH(C_2H_4OEt)\cdot CO_2Et \longrightarrow Me\cdot CO\cdot CEt(C_2H_4OEt)\cdot CO_2Et \longrightarrow$$
$$CH_2Br\cdot CO\cdot CEt(C_2H_4OEt)\cdot CO_2Et \longrightarrow PhCH_2\cdot NH\cdot CH_2\cdot CO\cdot CHEt(C_2H_4Br)$$



Condensation of 6-methoxyquinoline-4-aldehyde and 3-keto-*N*-benzyl-4-ethylpiperidine in presence of sodium methoxide yielded α-(3-*keto*-N-*benzyl*-4-*ethyl*)*piperidyl*-6-*methoxy*-4-*quinolylcarbinol* (IV; R = Et, R′ = CH_2Ph), but it was not found possible to reduce the keto to a methylene group (cf. Clemo and Hoggarth, *J.*, 1939, 1241).

As a model for (iii) 6-methoxyquinoline-4-aldehyde was condensed with nitrobutane using sodium methoxide as a condensing agent : 6-*methoxy*-4-*quinolyl*-α-*nitrobutylcarbinol* was obtained in fairly good yield and it was reduced catalytically to 6-methoxy-4-quinolyl-α-aminobutylcarbinol isolated as the *dihydrobromide*. To extend this method to the synthesis of piperidylquinolyl-carbinols, ε-*nitroamyl benzoate*, synthesised from ε-bromoamyl benzoate, was condensed with 6-methoxyquinoline-4-aldehyde and the product catalytically reduced to give 6-*methoxy*-4-*quinolyl*-(α-*amino*-ε-*benzoxyamyl*)*carbinol* (as V; R = $PhCO_2$). This base could not be cyclised to the desired piperidine so the method was modified by using α-*bromo*-ε-*nitropentane* in place of ε-nitroamyl benzoate, bromonitropentane being obtained from αε-dibromopentane by controlled reaction with silver nitrite.

α-Bromo-ε-nitropentane with the bisulphite compound of 6-methoxyquinoline-4-aldehyde and sodium ethoxide (cf. U.S.P. 2,151,517) gave a good yield of 6-*methoxy*-4-*quinolyl*-(ε-*bromo*-α-*nitroamyl*)*carbinol* (V; R = Br). The two externally compensated forms of this compound were separated by fractional crystallisation and reduced catalytically. The yields of the desired α-piperidyl-6-methoxy-4-quinolyl-carbinols were not good owing, apparently, to partial reduction of the ε-bromo group before cyclisation, but both externally compensated forms of the piperidyl carbinol were obtained for comparison with specimens prepared by Ainley and King (*loc. cit.*). One isomeride melted at 166° and was probably identical with that prepared by Ainley and King. The second isomeride melted at 181° and appeared to differ from that reported by Ainley and King.

By the application of this method to a suitably substituted nitropentane, a compound having the structure assigned by Henry and Gibbs (*loc. cit.*) to dihydroniquidine has been synthesised. (See following paper.)

αε-Dinitropentane, available as a by-product in the preparation of bromonitropentane, condensed in the same way with 6-methoxyquinoline-4-aldehyde to give 6-*methoxy*-4-*quinolyl*-αε-*dinitroamylcarbinol* (V; R = NO_2), which was reduced to the corresponding amine isolated as 6-*methoxy*-4-*quinolyl*-αε-*diaminoamylcarbinol trihydrochloride*. In contrast with the corresponding cyclised base, this compound had no antimalarial properties.

Experimental.

Ethyl α-(β′-Ethoxyethyl)acetoacetate.—To ethyl acetoacetate (150 g.) and sodium ethoxide (25 g. Na) in boiling alcohol bromomethyl ether (150 g.) was added slowly. After boiling for twenty-four hours, alcohol was removed and the cooled mixture acidified. The separated product was fractionally distilled under reduced pressure and the fraction (118 g.), b. p. 118—120°/11 mm., was collected (Found : C, 59·4; H, 8·9. $C_{10}H_{18}O_4$ requires C, 59·4; H, 8·9%).

Ethyl α-Ethyl-α-(β′-ethoxyethyl)acetoacetate.—Sodamide (22·6 g.) was added to a solution of the above ethyl ethoxyethylacetoacetate (117 g.) in benzene (300 c.c.) and, when the initial reaction was complete, ethyl iodide (90·6 g.) was added and the solution refluxed for eight hours. The product, isolated in the usual way, was fractionally distilled at reduced pressure and the fraction (91·5 g.), b. p. 132—134°/12 mm., was collected (Found : C, 62·9; H, 9·5. $C_{12}H_{22}O_4$ requires C, 62·6; H, 9·5%).

Ethyl γ-Bromo-α-ethyl-α-(β′-ethoxyethyl)acetoacetate.—To the product from the above preparation (60 g.) in dry chloroform (750 c.c.) was added slowly dry bromine (42 g.) in chloroform (300 c.c.) with stirring and in absence of moisture. The product in chloroform was washed with sodium bicarbonate solution and the solvent removed. The residual oil was distilled and the fraction (60·4 g.), b. p. 142—148°/3 mm., was collected (Found : C, 46·5; H, 7·0. $C_{12}H_{21}O_4Br$ requires C, 46·6; H, 6·8%).

Benzyl-(ε-bromo-β-keto-γ-ethylamyl)amine.—To a solution of ethyl γ-bromo-α-ethyl-α-ethoxyethylacetoacetate (38·4 g.) in dry ether (150 c.c.) a solution of benzylamine (38 g.) in ether (150 c.c.) was added and the mixture left in darkness for 70 hours. Benzylamine hydrobromide (21·1 g.) was collected and the ether solution washed with sodium carbonate. The product was extracted into dilute hydrochloric acid from the ether and liberated by addition of alkali. This oil (35·7 g.) was boiled for four hours with a mixture of hydrobromic acid (45 c.c., *d* 1·7) and glacial acetic acid (150 c.c.). Charcoal was then added to clear the solution, solvent removed under reduced pressure and the residual gum dissolved in 1% hydrobromic acid (800 c.c.), the small insoluble residue being discarded. The product, from the concentration of the solution, crystallised. After crystallisation from aqueous alcohol the *hydrobromide* (26·7 g.) had m. p. 127° (Found : C, 44·4; H, 5·5; Br, 41·6. $C_{14}H_{20}ONBr,HBr$ requires C, 44·3; H, 5·5; Br, 42·2%).

3-*Keto*-N-*benzyl*-4-*ethylpiperidine.*—The crystalline hydrobromide from the previous preparation (20 g.) was suspended in saturated sodium bicarbonate solution and shaken continuously for 24 hours. The *product* was taken up in ether and fractionally distilled under reduced pressure. The fraction (11 g.), b. p. 124°/7 mm., was collected (Found : C, 77·3; H, 8·7; N, 6·3. $C_{14}H_{19}ON$ requires C, 77·4; H, 8·7; N, 6·4%). The base gave a crystalline *picrate*, needles, m. p. 129° (Found : C, 54·1; H, 5·0. $C_{14}H_{19}ON,C_6H_3O_7N_3$ requires C, 53·9; H, 4·9%).

3-*Hydroxy*-4-*ethylpiperidine.*—3-Keto-*N*-benzyl-4-ethylpiperidine was reduced at normal pressure in aqueous alcohol with Adams' platinum oxide catalyst. The basic product was isolated as a *picrate*, m. p. 138°, which crystallised as needles from methanol (Found : C, 44·2; H, 5·3; N, 15·2. $C_7H_{15}ON,C_6H_3O_7N_3$ requires C, 43·6; H, 5·0; N, 15·6%).

α-3-*Keto*-N-*benzyl*-4-*ethylpiperidyl*-6-*methoxy*-4-*quinolylcarbinol.*—To a solution of 6-methoxyquinoline-4-aldehyde (4·8 g.) and 3-keto-*N*-benzyl-4-ethylpiperidine (5·6 g.) in methanol (10 c.c.) a solution of sodium methoxide (11·3 c.c. containing 0·05 g. sodium per c.c.) was added during one hour. The mixture after 20 hours at 37° was poured into water and the water insoluble fraction taken up in ether. The *base* was taken into acid from ether, liberated by excess alkali and re-extracted with ether. The ether extract (3·5 g.) after removal of solvent crystallised slowly when triturated with benzene and, when pure, had m. p. 127° (Found : C, 74·4; H, 7·0. $C_{25}H_{28}O_3N_2$ requires C, 74·3; H, 6·9%). A crystalline *monopicrate* had m. p. 175° (Found : C, 58·7; H, 5·1; N, 10·9. $C_{25}H_{28}O_3N_2,C_6H_3O_7N_3$ requires C, 58·8; H, 4·9; N, 11·1%).

6-*Methoxy*-4-*quinolyl*-α-*nitrobutylcarbinol.*—α-Nitrobutane (1·03 g.) and 6-methoxyquinoline-4-aldehyde (1·87 g.) were dissolved in alcohol (5 c.c.) and sodium methoxide (4·4 c.c. containing 0·05 g. Na per c.c.) was added very slowly, the mixture warmed to 50° for 5 minutes and then poured into water. The aqueous solution was washed with ether and acidified with dilute acetic acid. The *product* (1·65 g.) after crystallisation from benzene melted at 148° (Found : C, 62·4; H, 6·1; N, 9·7. $C_{15}H_{18}O_4N_2$ requires C, 62·1; H, 6·2; N, 9·6%). An isomer was present in a subsequent experiment but was not obtained in a pure state.

6-*Methoxy*-4-*quinolyl*-α-*aminobutylcarbinol.*—The product from the above preparation was reduced catalytically in ethanol using Adams' platinum oxide. The product crystallised from alcohol in needles as the *dihydrobromide*, m. p. 230° (decomp.) (Found : C, 42·9; H, 5·3; Br, 38·4. $C_{15}H_{20}O_2N_2,2HBr$ requires C, 42·7; H, 5·2; Br, 37·9%).

ε-*Nitroamyl Benzoate.*—Powdered silver nitrite (14·0 g.) was added slowly with stirring during eight hours to ε-bromoamyl benzoate (20·8 g.) at room temperature; the temperature was then raised to 70—80° and stirring continued for four hours. The silver bromide was separated and the *product* fractionated twice under reduced pressure giving the fraction (10·4 g.) having b. p. 170°/1 mm. (Found : C, 60·5; H, 6·4; N, 6·0. $C_{12}H_{15}O_4N$ requires C, 60·7; H, 6·3; N, 5·9%).

6-*Methoxy*-4-*quinolyl*-(α-*amino*-ε-*benzoxyamyl*)*carbinol.*—ε-Nitroamyl benzoate (2·37 g.) was added to solution of sodium ethoxide (0·23 g. sodium) in ethyl alcohol at 0° and, after shaking for thirty seconds, was added rapidly to an aqueous solution of the bisulphite compound of 6-methoxyquinoline-4-aldehyde maintained at a temperature of 50°. The mixture was agitated vigorously for 20 minutes, the precipitated oil extracted with benzene, the benzene washed with dilute bisulphite and then with sodium bicarbonate and the solvent removed. The residual oil was dissolved in methanol and reduced in hydrogen at a pressure of 5 atmospheres in the presence of Raney nickel with carbon dioxide as a buffer (cf. U.S.P. 2,157,391). The product was isolated as a *hydrochloride* (0·9 g.) which on crystallisation from alcohol separated as needles melting with decomposition between 190° and 200° (Found : C, 59·7; H, 6·3; N, 6·2; Cl, 15·3. $C_{23}H_{26}O_4N_2,2HCl$ requires C, 59·1; H, 6·1; N, 6·0; Cl, 15·2%). The *base* crystallised with difficulty from ether and had m. p. 64—66° (Found : C, 70·3; H, 6·6. $C_{23}H_{26}O_4N_2$ requires C, 70·1; H, 6·6%).

α-*Bromo*-ε-*nitropentane.*—To αε-dibromopentane (57 g.) in a flask fitted with a high-speed stirrer was added, in small lots, powdered freshly prepared silver nitrite (18 g.) during 3 hours. The reaction was allowed to proceed for a further 48 hours at room temperature and the product fractionally distilled at 15 mm. The first fraction (110—118°) (29·33 g.) was dibromopentane. The intermediate fraction (118—128°) (3·7 g.) was discarded and the final fraction (128—148°) was refractionated and the *distillate* collected between 140—144° (10·0 g.) (Found : N, 7·2. $C_5H_{10}O_2NBr$ requires N, 7·2%).

6-*Methoxy*-4-*quinolyl*-(ε-*bromo*-α-*nitroamyl*)*carbinol.*—6-Methoxyquinoline-4-aldehyde (2·2 g.) dissolved in methanol was added to an excess of aqueous sodium bisulphite and the crystalline product collected. This was suspended in water at 40° and to the suspension was added a solution of bromonitropentane (2·4 g.) in alcoholic sodium oxide (2 mols. Na) at 0°. The mixture was shaken vigorously for 30 minutes and the solid collected. Crystallisation from chloroform gave a product, m. p. 130—140°, which was fractionally crystallised from chloroform–ether, two isomeric nitro compounds being isolated; one (1·3 g.) (m. p. 158°) was sparingly and the other (0·65 g.) (m. p. 136—137°) was readily soluble in cold chloroform (Found : C, 50·1; H, 5·0; N, 7·3; Br, 20·7. $C_{16}H_{19}O_4N_2Br$ requires C, 50·1; H, 5·0; N, 7·3; Br, 20·9%).

α-*Piperidyl*-6-*methoxy*-4-*quinolylcarbinol.*—Both isomers were reduced in the same way. The methoxyquinolyl-

bromonitroamylcarbinol was dissolved in methanol, solid CO_2 added, and reduction effected by hydrogen at 5 atms. with Raney nickel catalyst. After removal of the catalyst the product was isolated as a crystalline base. The isomer having m. p. 158° gave a base, m. p. 181°, and the isomer having m. p. 136° gave an isomeric base, m. p. 166°, which, mixed with a specimen of the same base (m. p. 164°) prepared by the method of Ainley and King, gave no depression of the m. p.

6-*Methoxy-4-quinolyl-αε-dinitroamylcarbinol.*—αε-Dinitropentane was condensed with the bisulphite compound of 6-methoxyquinoline-4-aldehyde by the method described above. The solid product crystallised from alcohol but, although two isomers were obviously present, only one of these, m. p. 163°, was obtained pure; after numerous fractional crystallisations the final *product* separated as sparingly soluble platelets from alcohol (1·1 g.) (Found: C, 55·3; H, 5·4; N, 11·7. $C_{16}H_{19}O_6N_3$ requires C, 55·0; H, 5·4; N, 12·0%).

6-*Methoxy-4-quinolyl-αε-diaminoamylcarbinol.*—The methoxyquinolyldinitroamylcarbinol was reduced by hydrogen at 5 atms. with Raney nickel as catalyst in the presence of carbon dioxide, an 80% yield being obtained. Methoxyquinolyldiaminoamylcarbinol was isolated as the *trihydrochloride*, m. p. 226° (decomp.), which crystallised as fine needles from methanol–acetone (Found: C, 47·9; H, 6·6; N, 9·6. $C_{16}H_{23}O_2N_3$,3HCl requires C, 48·2; H, 6·5; N, 10·5%).

6-*Methoxy-4-quinolyl Pentenyl Ketone.*—6-Methoxy-4-acetylquinoline (1 g.) in alcoholic potassium hydroxide (5 c.c., 5%) was heated to 70° in a flask fitted with reflux condenser, and butyraldehyde (0·36 g.) in alcohol (5 c.c.) was run into the solution. The mixture was boiled for ten minutes, cooled and poured into hydrochloric acid (100 c.c., 1%). The acid was washed with ether and the base liberated by excess alkali. The base (0·7 g.) could not be crystallised but gave a crystalline *picrate*, m. p. 218°, sparingly soluble in cold acetone (Found: C, 54·6; H, 4·3; N, 11·0. $C_{16}H_{17}O_2N$,$C_6H_3O_7N_3$ requires C, 54·5; H, 4·1; N, 11·6%).

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