

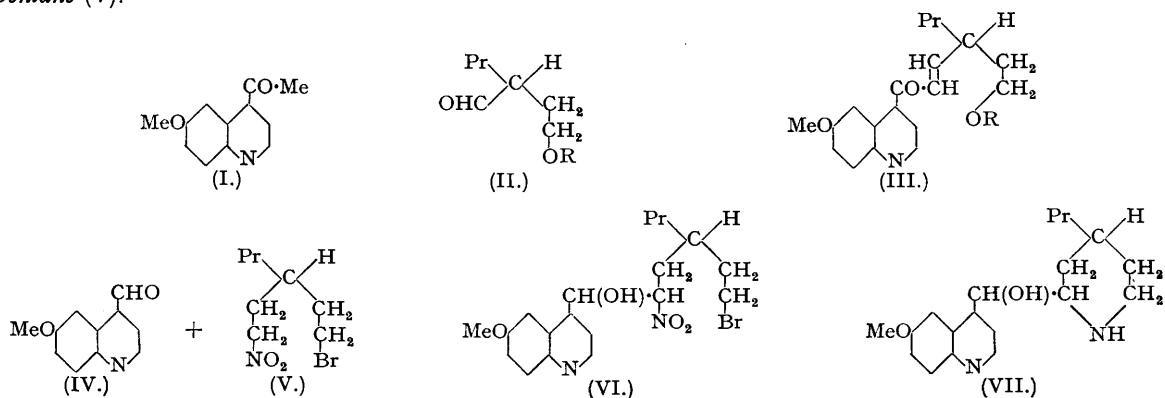
52. *The Synthesis of Antimalarial Compounds Related to Niquidine. Part II. Synthesis of a Dihydro-x-niquidine.*

By T. S. WORK.

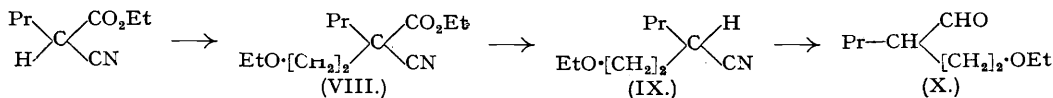
A synthesis of dihydro-*x*-niquidine has been developed. Condensation of 6-methoxyquinoline-4-aldehyde (IV) with 5-bromo-1-nitro-3-propylpentane (V) gave (VI) which on reduction cyclised spontaneously to give dihydroniquidine (VII). Only one of the four possible racemates was obtained pure. Synthetic dihydroniquidine was found to be a highly active antimalarial.

An alternative synthesis, suggested by preliminary experiments (Part I), the condensation of alkoxyethyl-valeraldehydes (II) with 6-methoxy-4-quinolyl methyl ketone (I) was abandoned owing to the impossibility of purifying the product (III).

In Part I (previous paper) general methods for linking the quinoline and piperidine "halves" of the niquidine structure were studied. In order to extend these methods to the synthesis of dihydroniquidine it was necessary to devise methods for the preparation of $\alpha(\beta'$ -alkoxyethyl)valeraldehyde (II) and 5-bromo-1-nitro-3-propylpentane (V).



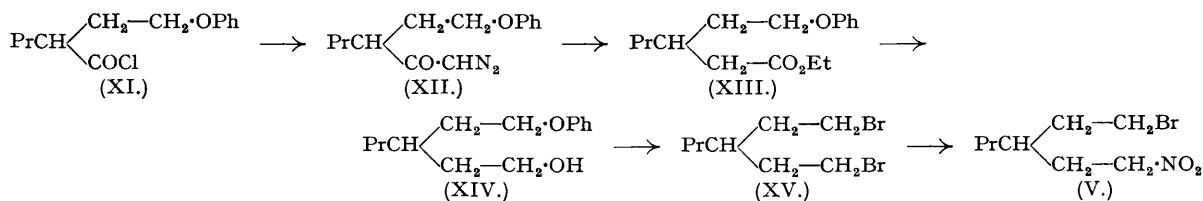
Ethyl propylcyanoacetate condensed with β -ethoxyethyl bromide to give *ethyl $\alpha(\beta'$ -ethoxyethyl)propylcyanoacetate* (VIII). Hydrolysis of the ester gave *$\alpha(\beta'$ -ethoxyethyl)propylcyanoacetic acid* which distilled at low pressure without decarboxylation. Decarboxylation was achieved by distilling slowly at normal pressure to give *$\alpha(\beta'$ -ethoxyethyl)valeronitrile* (IX). Application of the stannous chloride method of Stephen (*J.*, 1925, 1874) converted this nitrile in rather poor yield into *$\alpha(\beta'$ -ethoxyethyl)valeraldehyde* (X) isolated as its 2 : 4-dinitrophenylhydrazone.



In the hope of obtaining a better overall yield of the desired aldehyde, ethyl propylmalonate was allowed to react in the same way with β -ethoxyethyl bromide to give *ethyl $\alpha(\beta'$ -ethoxyethyl)propylmalonate* which on hydrolysis gave crystalline *$\alpha(\beta'$ -ethoxyethyl)propylmalonic acid*; this decarboxylated on heating to give *$\alpha(\beta'$ -ethoxyethyl)valeric acid*. The acid was converted into the acid chloride with the intention of obtaining the aldehyde by the method of Sonn and Muller (*Ber.*, 1919, 52, 1927) but the acid chloride was found to rearrange spontaneously to give ethyl $\alpha(\beta'$ -chloroethyl)valerate.

Both these methods were repeated using β -phenoxyethyl bromide in place of β -ethoxyethyl bromide. *Ethyl $\alpha(\beta'$ -phenoxyethyl)propylcyanoacetate* hydrolysed and decarboxylated gave *$\alpha(\beta'$ -phenoxyethyl)valeronitrile* which was converted by Stephen's method to *$\alpha(\beta'$ -phenoxyethyl)valeraldehyde* in fair yield. The aldehyde was identified as crystalline *2:4-dinitrophenylhydrazone*. Better yields were obtained starting from *ethyl $\alpha(\beta'$ -phenoxyethyl)propylmalonate* and on decarboxylation gave *$\alpha(\beta'$ -phenoxyethyl)valeric acid*. The acid was converted to the corresponding *anilide* and, by the application of the method of Sonn and Muller (*loc. cit.*), to *$\alpha(\beta'$ -phenoxyethyl)valeraldehyde*. This aldehyde condensed with 6-methoxy-4-quinolyl methyl ketone, but the product could not in spite of repeated attempts be obtained analytically pure. The aldehyde was eventually utilised (Work, unpublished) for the synthesis of 4-propylpiperidine and ethyl 4-propylpiperidine-2-carboxylate.

For the synthesis of 5-bromo-1-nitro-3-propylpentane (V), $\alpha(\beta'$ -phenoxyethyl)valeric acid was used as starting material. The acid was converted into the acid chloride (XI) and allowed to react with diazomethane to give *phenyl 3-diazoacetohexyl ether* (XII) in nearly quantitative yield. The diazoketone rearranged quantitatively by the Arndt-Eistert process to give ethyl $\beta(\beta'$ -phenoxyethyl)hexoate (XIII). This ester reduced by the method of Bouveault and Blanc gave a good yield of *$\gamma(\beta'$ -phenoxyethyl)hexyl alcohol* (XIV). The acetate of this alcohol heated with hydrobromic acid and acetic acid gave 1:5-dibromo-3-propylpentane (XV). Treatment of this dibromide with silver nitrite gave 5-bromo-1-nitro-3-propylpentane (V).



5-Bromo-1-nitro-3-propylpentane condensed readily with 6-methoxyquinoline-4-aldehyde by the method worked out in Part I (*loc. cit.*) but the nitrocarbinol (VI) could not be crystallised; it was reduced catalytically without purification, cyclisation taking place spontaneously. As might be expected owing to the possible formation of 4 racemates, the product was difficult to purify, but eventually a pure *hydrobromide* of dihydro- α -niquidine (VII) was obtained in small yield. There was obviously at least one other isomeride present but it could not be obtained in a pure state. *Dihydro- α -niquidine monohydrate* was obtained crystalline from the hydrobromide.

The synthetic material was tested biologically by Miss Ann Bishop, D.Sc., of the Molteno Institute, Cambridge, who reported that it was at least as active as quinine against *Plasmodium relictum* in canaries and about half as toxic.

EXPERIMENTAL.

Ethyl $\alpha(\beta'$ -Ethoxyethyl)propylcyanoacetate.—To sodium ethoxide (5.3 g. Na) in dry alcohol was added ethyl propylcyanoacetate (36.6 g.). β -Bromoethyl ether (36.5 g.) was added to the boiling mixture during 15 minutes. After five hours the alcohol was allowed to distil slowly until no more came over. The residual oil was diluted with water and the product collected. The ester was purified by repeated fractional distillation at reduced pressure and the fraction, b. p. 157—161°/19 mm., was finally collected (Found: C, 63.5; H, 9.1. $\text{C}_{12}\text{H}_{21}\text{O}_3\text{N}$ requires C, 63.4; H, 9.3%).

$\alpha(\beta'$ -Ethoxyethyl)propylcyanoacetic Acid.—Ethyl ethoxyethylpropylcyanoacetate (15 g.) was hydrolysed by heating on a steam-bath with aqueous alcoholic potassium hydroxide (1 part 50% KOH, 4 parts alcohol) for 4 hours. The alcohol was removed and the ethoxyethylpropylcyanoacetic acid liberated by cautious addition of sulphuric acid to the cooled sodium salt. The product was purified by distillation and the fraction, b. p. 154—155°/0.2 mm. (10.8 g.), collected (Found: C, 60.9; H, 8.7. $\text{C}_{10}\text{H}_{17}\text{O}_3\text{N}$ requires C, 60.3; H, 8.5%).

$\alpha(\beta'$ -Ethoxyethyl)valeronitrile.—The cyanoacetic acid (10.5 g.) was decarboxylated by distilling slowly at 750 mm. The fraction, b. p. 214—220°, was redistilled when practically the whole (5.73 g.) distilled between 214° and 216° (Found: C, 70.0; H, 10.9. $\text{C}_9\text{H}_{17}\text{ON}$ requires C, 69.7; H, 11.0%).

$\alpha(\beta'$ -Ethoxyethyl)valeraldehyde.—Ethoxyethylvaleronitrile (10 g.) was added to a solution of dry stannous chloride (30 g.) in ether saturated with dry hydrogen chloride. The mixture was shaken overnight and then refluxed gently for seven hours. The heavy oil which settled at the bottom was washed thrice with ether by decantation and then dissolved in 3N-HCl. The acid solution was extracted with ether and the ether extract dried. The residual oil (3.6 g.) after removal of ether was distilled and the fraction, b. p. 180—220°/760 mm. (2 g.), was collected. This gave a crystalline *2:4-dinitrophenylhydrazone*, m. p. 88° (Found: C, 52.6; H, 6.3; N, 17.2. $\text{C}_{15}\text{H}_{22}\text{O}_5\text{N}_4$ requires C, 53.2; H, 6.5; N, 16.6%).

Ethyl $\alpha(\beta'$ -Ethoxyethyl)propylmalonate.—To a mixture of diethyl propylmalonate (82.5 g.) and sodium ethoxide (9.2 g. Na) β -bromoethyl ether (60.7 g.) was added slowly enough to avoid an uncontrollable reaction. The mixture was boiled until neutral to litmus, excess of alcohol removed under reduced pressure, and the product diluted with water. The oil which separated was fractionally distilled and the compound, b. p. 158—162°/17 mm. (48 g.), collected (Found: C, 61.2; H, 9.3. $\text{C}_{14}\text{H}_{26}\text{O}_5$ requires C, 61.3; H, 9.5%).

$\alpha(\beta'$ -Ethoxyethyl)propylmalonic Acid.—The ester (48 g.) was hydrolysed by boiling aqueous potassium hydroxide

The acid (36.9 g.), m. p. 104—105°, liberated by careful acidification, crystallised from ether–ligroin (Found: C, 54.9; H, 8.1. $C_{10}H_{18}O_5$ requires C, 55.0; H, 8.3%).

$\alpha(\beta'$ -Ethoxyethyl)valeric Acid.—The substituted malonic acid (35 g.) decarboxylated and distilled in the usual way gave $\alpha(\beta'$ -ethoxyethyl)valeric acid (23.5 g.), b. p. 132—134°/4 mm. (Found: C, 61.8; H, 10.3. $C_9H_{18}O_3$ requires C, 62.1; H, 10.3%).

Ethyl $\alpha(\beta'$ -Chloroethyl)valerate.—With the intention of preparing the acid chloride from ethoxyethylvaleric acid this acid in dry chloroform was treated with thionyl chloride. The product was distilled and an 84% yield obtained of an oil, b. p. 170°/165 mm. This oil was found to have the reactions of an ester and to contain an unreactive halogen. There appeared to have been interchange of the Cl and OEt groups (Found: C, 56.3; H, 8.9. Calc. for $C_9H_{17}O_2Cl$: C, 56.1; H, 8.8%).

Ethyl $\alpha(\beta'$ -Phenoxyethyl)propylcyanoacetate.—To a boiling solution of ethyl propylcyanoacetate (62 g.) in alcoholic sodium ethoxide (8.6 g. Na) phenoxyethyl bromide (75 g.) was added at such a rate that the reaction did not get out of hand. Heating was continued for a further 45 minutes. The product (58.3 g.) isolated in the usual way had b. p. 155—158°/1.5 mm. (Found: C, 69.4; H, 7.5. $C_{18}H_{21}O_5N$ requires C, 69.8; H, 7.6%).

$\alpha(\beta'$ -Phenoxyethyl)valeronitrile.—The cyanoacetic ester was hydrolysed and decarboxylated in the same way as the corresponding ethoxyethylcyanoacetic ester. The product distilled at 200°/18 mm. (Found: C, 76.8; H, 8.5. $C_{13}H_{17}ON$ requires C, 76.8; H, 8.4%). The intermediate phenoxyethylcyanoacetic acid, crystallised from benzene, had m. p. 112° (Found: C, 68.4; H, 7.0. $C_{14}H_{17}O_3N$ requires C, 68.0; H, 6.9%).

$\alpha(\beta'$ -Phenoxyethyl)valeraldehyde.—Phenoxyethylvaleronitrile (30 g.) was added to an ethereal solution of dry stannous chloride previously saturated with dry hydrogen chloride and the mixture shaken for 12 hours, boiled gently for 1 hour, and re-saturated with dry hydrogen chloride. This process was repeated and finally the ether was separated from the heavy oil. The oil was shaken with dilute hydrochloric acid and the ether soluble fraction extracted. It was found advantageous to add a small quantity of copper bronze to the extracted oil (13.8 g.) to prevent polymerisation; the oil could then be distilled under reduced pressure and the fraction, b. p. 186—189°/18 mm. (11.5 g.), collected. The aldehyde was identified by conversion to the 2:4-dinitrophenylhydrazone, which crystallised from ethanol as needles, m. p. 86° (Found: C, 58.8; H, 5.6; N, 14.3. $C_{15}H_{22}O_5N_4$ requires C, 59.1; H, 5.7; N, 14.5%).

Ethyl $\alpha(\beta'$ -Phenoxyethyl)propylmalonate.—Slow addition of phenoxyethyl bromide (280 g.) to a hot solution of diethyl propylmalonate (280 g.) in alcoholic sodium ethoxide (32 g. Na) followed by boiling of the resultant mixture for five hours gave after separation and fractional distillation in the usual way an oil (219 g.), b. p. 228—230°/18 mm. (Found: C, 67.6; H, 7.9. $C_{18}H_{26}O_5$ requires C, 67.1; H, 8.1%).

$\alpha(\beta'$ -Phenoxyethyl)propylmalonic Acid.—The ester from the above preparation (219 g.) was refluxed with aqueous alcohol and potassium hydroxide (150 g. KOH; 150 c.c. H_2O ; 450 c.c. alcohol) for 1½ hours. The alcohol was removed under reduced pressure and the acid liberated from its sodium salt by slow addition of acid to a well cooled solution. The acid crystallised from ligroin–benzene as needles, m. p. 135° (Found: C, 63.3; H, 6.8. $C_{14}H_{18}O_5$ requires C, 63.2; H, 6.8%).

$\alpha(\beta'$ -Phenoxyethyl)valeric Acid.—Phenoxyethylpropylmalonic acid decarboxylated on warming above its m. p. The product distilled at 124°/20 mm. and solidified on standing. Crystallisation from light petroleum gave the compound as needles, m. p. 61° (Found: C, 70.2; H, 7.8. $C_{13}H_{18}O_3$ requires C, 70.3; H, 8.1%).

$\alpha(\beta'$ -Phenoxyethyl)valeraniide.—To phenoxyethylvaleric acid (107 g.) in benzene (135 c.c.) was added thionyl chloride (80.7 g.). The mixture was warmed for 30 minutes on a steam-bath and then solvent and excess thionyl chloride were removed under reduced pressure. The residual oil was mixed with benzene (270 c.c.) and added slowly to a mixture of aniline (107.5 g.) in benzene (270 c.c.) cooled in ice. After 1 hour the solution was washed free from aniline hydrochloride and the solvent removed. The product crystallised when triturated with ligroin and was recrystallised from a mixture of ligroin (500 c.c.) and benzene (10 c.c.). The aniide (124 g.), needles, had m. p. 103° (Found: C, 76.6; H, 7.6. $C_{19}H_{23}O_2N$ requires C, 76.8; H, 7.7%).

To phenoxyethylvaleraniide (50 g.) in benzene (100 c.c.) phosphorus pentachloride (42 g.) was added in small lots. When the vigorous reaction had subsided, benzene and phosphorus oxychloride were removed under reduced pressure. The residue was mixed with a solution of dry stannous chloride (140 g.) in dry ethereal hydrochloric acid (1000 c.c.). After shaking for 12 hours the mixture was boiled gently under reflux for 8 hours. The ether was decanted from the heavy oil which was dissolved in 2N-HCl (500 c.c.). Copper bronze (1 g.) and light petroleum (400 c.c.) were added to the acid solution and the whole shaken vigorously until on standing only two layers of liquid formed. The light petroleum was separated, washed, and dried. Before removing the solvent, fresh copper bronze was added to prevent polymerisation of the aldehyde (23 g.) which gave a 2:4-dinitrophenylhydrazone identical with that obtained from phenoxyethylvaleraldehyde prepared from the nitrile (see above).

Phenyl 3-Diazoacetohexyl Ether.—Phenoxyethylvaleric acid (46 g.) was converted into the acid chloride by treatment with thionyl chloride (1.25 mols.) in benzene. Excess of thionyl chloride was removed under reduced pressure and the acid chloride, dissolved in ether, was added to an ice cold ethereal solution of diazomethane (82 g. nitrosomethylurea). After twelve hours at room temperature most of the ether was removed under reduced pressure without raising the temperature. The diazoketone crystallised as pale yellow needles (44 g.), m. p. 50—51° (Found: C, 67.9; H, 7.2. $C_{14}H_{18}O_2N_2$ requires C, 68.3; H, 7.3%).

Ethyl $\beta(\beta'$ -Phenoxyethyl)hexoate.—The diazoketone (44 g.) was rearranged by adding freshly prepared silver oxide (5 g.) in small lots to its alcoholic solution warmed to 60°. After removal of solvent and silver the product (40.3 g.) distilled at 188—192°/14 mm. (Found: C, 73.1; H, 9.1. $C_{16}H_{24}O_2$ requires C, 72.7; H, 9.1%).

$\gamma(\beta'$ -Phenoxyethyl)hexyl Alcohol.—The ester from the above preparation (30 g.) reduced with sodium (17.6 g.) in alcohol (140 c.c.) gave after fractional distillation of the product an oil (22.7 g.), b. p. 190°/14 mm. (Found: C, 75.9; H, 10.0. $C_{14}H_{22}O_2$ requires C, 75.6; H, 10.0%). The alcohol gave a crystalline 3:5-dinitrobenzoate, m. p. 71°, needles from methanol (Found: C, 60.7; H, 5.9. $C_{21}H_{24}O_7N_2$ requires C, 60.6; H, 5.8%).

$\gamma(\beta'$ -Phenoxyethyl)hexyl Acetate.—A mixture of phenoxyethylhexyl alcohol (66.6 g.) and pyridine (60 c.c.) was cooled in ice and acetyl chloride (24 g.) added slowly. The reaction was completed by warming the mixture for 5 minutes on the steam-bath. The product was poured into water, and the oil which separated was washed with acid and alkali, dried, and fractionally distilled, the portion (72.4 g.), b. p. 191—193°/14 mm., being collected (Found: C, 73.0; H, 9.2. $C_{16}H_{24}O_2$ requires C, 72.7; H, 9.1%).

1:5-Dibromo-3-propylpentane.—Glacial acetic acid saturated at room temperature with dry hydrobromic acid (39 c.c.) and phenoxyethylhexyl acetate (15 g.) were heated together in a sealed tube at 100° for 9 hours and then at 145° for another 9 hours. The product was poured into water and extracted with ether. The ether was washed with alkali and the product distilled. The fraction (12.2 g.), b. p. 132—136°/16 mm., was collected (Found: Br, 58.0. $C_8H_{16}Br_2$ requires Br, 58.8%).

5-Bromo-1-nitro-3-propylpentane.—To dibromoisooctane (40 g.) in a flask fitted with a high speed stirrer and a nitrogen inlet freshly prepared silver nitrite (32 g.) was added in small lots during 6 hours. Nitrogen was bubbled slowly through the stirred solution for a further 36 hours. Silver bromide was removed and the product fractionally distilled. The

fraction, b. p. 104—108°/0.8 mm. (16 g.), was collected (Found: C, 40.3; H, 6.9; N, 6.1. $C_3H_{10}O_2NBr$ requires C, 40.3; H, 6.7; N, 5.9%).

Dihydro-x-niquidine.—To a suspension of the bisulphite compound of 6-methoxyquinoline-4-aldehyde (8.5 g.) in water (100 c.c.) warmed to 40° was added an ice-cold mixture of bromonitroisooctane (6.2 g.) and sodium methoxide (1.5 g. Na) in methyl alcohol (20 c.c.). The reactants were shaken vigorously for two minutes and then after another five minutes the supernatant liquid was decanted from the heavy gum which had separated. All efforts to crystallise this product failed. The gum was dissolved in methanol and hydrogenated in the presence of hydrogen and excess of carbon dioxide at room temperature and 5 atmospheres pressure using Raney nickel catalyst. After shaking for four hours the catalyst was removed and the product concentrated. When most of the alcohol had been removed acetone was added and after several hours the crystalline product (1.5 g.) was collected. This material appeared to contain more than one crystalline hydrobromide, but only one compound (0.4 g.) was obtained pure, m. p. 230—231°, after repeated fractional crystallisation from water and from methyl alcohol-acetone. Analytical results showed this to be the *monohydrobromide* of dihydro-x-niquidine (Found: C, 58.3; H, 6.9; N, 6.9. $C_{13}H_{20}O_2N_2, HBr$ requires C, 57.7; H, 6.8; N, 7.1%). The base isolated from the hydrobromide was obtained crystalline as a *monohydrate*, m. p. 98—100°, from aqueous acetone (Found: C, 68.5; H, 8.5. $C_{13}H_{24}O_2N_2, H_2O$ requires C, 68.6; H, 8.4%).

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