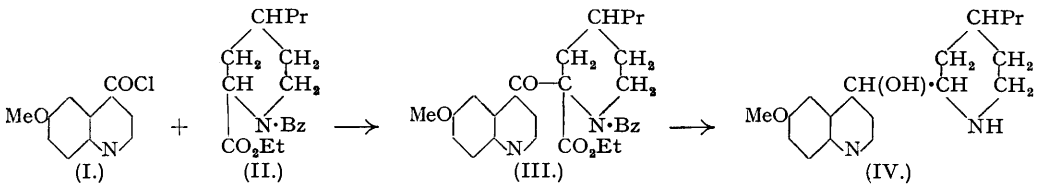
51. *The Synthesis of Antimalarial Compounds related to Niquidine. Part III. Alternative Synthesis of Dihydro-x-niquidine.*

By T. S. Work.

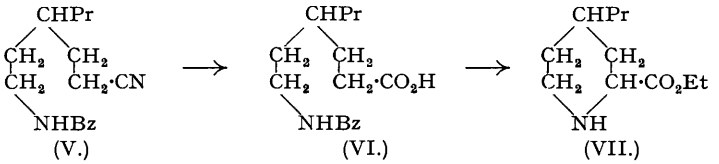
The reaction of quininic acid chloride with ethyl *N*-benzoyl-4-propylpiperidine-2-carboxylate was effected using sodium triphenylmethyl as condensing agent. The resultant keto-ester (III) was decarboxylated and reduced to give a small yield of dihydro-*x*-niquidine.

In the hope of improving upon the synthesis of dihydro-*x*-niquidine already described (Part II, *J.*, 1946, 197) trials were undertaken of the condensation of ethyl quininate with *ethyl* 3-(2-*benzamidoethyl*)*hexane*-1-*carboxylate* by the method of Ainley and King (*Proc. Roy. Soc.*, 1938, *B*, **125**, 60), but results were not encouraging.

As an alternative method the condensation of *ethyl* N-*benzoyl*-4-*propylpiperidine*-2-*carboxylate* (II) with quininic acid chloride (I) was studied (cf. Hudson and Hauser, *J. Amer. Chem. Soc.*, 1941, **65**, 3163). 4-Propylpiperidine was used as starting material for the synthesis of the desired α-carboxylate.



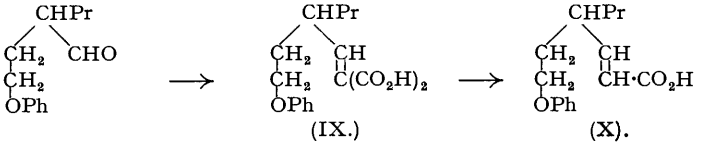
The nitrogen ring of N-*benzoyl*-4-*propylpiperidine* was opened by treatment with phosphorus pentachloride (von Braun, *Ber.*, 1906, **37**, 2916) to give benz-3-(2-chloroethyl)hexylamide. This amide was not purified but was allowed to react with potassium cyanide to yield 3-(2-*benzamidoethyl*)*hexyl cyanide* (V). The cyanide was converted into the *ester* and hydrolysed to the corresponding acid (VI) which was brominated in the α-position to the carboxyl group. Removal of the benzoyl group and cyclisation gave 4-propylpiperidine-2-carboxylic acid, isolated as the ester (VII). Benzoylation of this ester gave (II).



Ethyl *N*-benzoyl-4-propylpiperidine-2-carboxylate (II) with quininic acid chloride (I) and sodium triphenylmethyl in boiling anisole gave the keto-ester (III). This could not be purified, but on hydrolysis with dilute acid carbon dioxide was evolved and benzoic acid liberated. The resultant keto-amine was highly unstable so that it was necessary to handle it only as the hydrochloride and to reduce it as soon as possible to dihydroniquidine (IV). Despite various modifications of the conditions it was not found possible to isolate more than a trace of dihydroniquidine, and in several experiments no crystalline material was isolated.

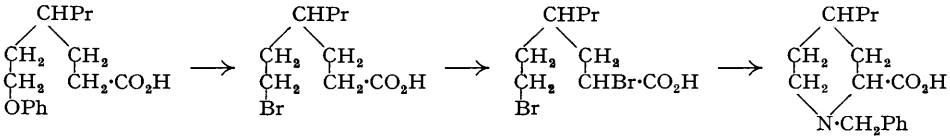
As the small yield appeared to be associated with considerable decomposition during hydrolysis of the benzamido-group, it was thought worth while to replace this by a benzyl group which could be removed by catalytic hydrogenation simultaneously with the reduction of the keto-group to a carbinol.

Phenoxyethylvaleraldehyde (Part II, *loc. cit.*) reacted readily with malonic acid to give (IX) which was decarboxylated to give 3-(2-*phenoxyethyl*)*hex*-1-*en*-1-*carboxylic acid* (X). This acid was



reduced catalytically to 3-(2-*phenoxyethyl*)*hexane*-1-*carboxylic acid* which gave a crystalline S-*benzylthiouronium* salt. Treatment of 3-(2-phenoxyethyl)hexane-1-carboxylic acid with

hydrobromic acid in acetic acid split the ether linkage, and the resultant 3-(2-*bromoethyl*)*hexane*-1-*carboxylic acid* (XII) was brominated in the α-position by treatment with bromine and phosphorus tribromide to give 1-*bromo*-3-(2-*bromoethyl*)*hexane*-1-*carboxylic acid*



(XI.) (XII.) (XIII.) (XIV.)

(XIII). The dibromo-acid reacted in the cold with benzylamine, and the resultant acid (XIV) was esterified to give the desired *ethyl* N-*benzyl*-4-*propylpiperidine*-2-*carboxylate*. The *N*-benzyl group was found to be readily removed by catalytic hydrogenation with platinum oxide at 70°.

The use of ethyl *N*-benzyl-4-propylpiperidine-2-carboxylate in place of the *N*-benzoyl ester in the sodium triphenylmethyl-catalysed reaction with quininic acid chloride did not achieve the hoped for improvement in yield in the synthesis of dihydroniquidine.

Experimental.

N-*Benzoyl*-4-*propylpiperidine*.—Propylpiperidine (43 g.) in a solution of sodium hydroxide (21 g.) was stirred vigorously and benzoyl chloride (55 g.) added slowly. The temperature was maintained below 40°. One hour after addition of benzoyl chloride the *compound* was extracted with benzene, dried, and distilled. The fraction (76·2 g.), b. p. 164—168°/0·8 mm., was collected (Found : C, 77·9; H, 9·1; N, 6·4. $C_{15}H_{21}ON$ requires C, 77·9; H, 9·1; N, 6·1%).

3-(2-*Benzamidoethyl*)*hexyl Cyanide*.—*N*-Benzoylpropylpiperidine (94 g.) was mixed with phosphorus pentachloride (78 g.) and heated cautiously under reflux until reaction commenced. When the initial vigorous reaction had subsided the mixture was refluxed for 45 minutes. After cooling, ice was added followed by sodium hydroxide until the solution was just acid to Congo-red paper. The product was steam distilled to remove volatile by-products, and the benz-3-(2-chloroethyl)hexylamide extracted with ether. This oil (82 g.) would not crystallise and was converted into the *cyanide* without purification by heating for 14 hours with potassium cyanide (90 g.) in 75% alcohol (250 c.c.). After removal of solvent the product was extracted with ether and fractionally distilled at 0·7 mm., the fraction (67 g.), b. p. 224—226°, being collected (Found : C, 74·9; H, 8·9. $C_{16}H_{22}ON_2$ requires C, 74·4; H, 8·5%).

Ethyl 3-(2-*Benzamidoethyl*)*hexane*-1-*carboxylate*.—The cyanide from the previous experiment (67 g.) in alcohol (350 c.c.) was saturated with dry hydrogen chloride at room temperature and then boiled for 6 hours. The solvent was removed, the residue diluted with water, and the *product* extracted with ether. The oil was purified by fractional distillation, the fraction (50 g.), b. p. 214—216°/0·7 mm., being collected (Found : C, 70·8; H, 9·0; N, 4·6. $C_{18}H_{27}O_3N$ requires C, 70·8; H, 8·8; N, 4·6%).

Ethyl N-*Benzoyl*-4-*propylpiperidine*-2-*carboxylate*.—3-(2-Benzamidoethyl)hexane-1-carboxylic acid (10 g.) was obtained from the above ester (12 g.) by controlled hydrolysis with potassium hydroxide (2·6 g.) in 60% methyl alcohol (50 c.c.) at 40°. The acid, a colourless gum, was not purified but was dried over phosphoric oxide and brominated by slow addition of dry bromine (22·1 g.) to a stirred mixture of the acid and red phosphorus (1·43 g.). The flask was heated to 100° for 30 minutes to complete the reaction and the product poured on ice. The 1-bromo-3-(2-benzamidoethyl)hexane-1-carboxylic acid obtained in this way was hydrolysed by heating in a sealed tube with concentrated hydrochloric acid (25 c.c.) for 18 hours at 150°. The contents of the tube were diluted with water and benzoic acid extracted with ether. The aqueous solution of 1-bromo-3-(2-aminoethyl)hexane-1-carboxylic acid was concentrated, dried, and esterified with alcohol and dry hydrogen chloride. The acid alcohol was removed under reduced pressure and excess of sodium bicarbonate and ether were added. The solution was shaken for 1 hour to allow time for the cyclisation, and the ether was then separated and dried, and the ether-soluble oil distilled. The ethyl 4-propylpiperidine-2-carboxylate, b. p. 140—144°/18 mm. (3·3 g.), was benzoylated by the method used earlier for benzoyl-4-propylpiperidine, and the benzoate was distilled. The fraction, b. p. 190—194°/1 mm. (3·2 g.), analysed satisfactorily for *ethyl* N-*benzoyl*-4-*propylpiperidine*-2-*carboxylate* (Found : C, 71·3; H, 7·9; N, 4·8. $C_{18}H_{25}O_3N$ requires C, 71·3; H, 8·2; N, 4·6%).

Dihydro-x-*niquidine*.—The above ester (3·2 g.) in dry anisole (5 c.c.) in a dry nitrogen atmosphere was treated with a solution of one equivalent of sodium triphenylmethyl in ether. The colour of the sodium salt disappeared rapidly. Quininic acid chloride (2·3 g.) in anisole (10 c.c.) was added, and ether distilled off. The anisole solution was refluxed in a dry nitrogen atmosphere for 4 hours. The anisole was removed under reduced pressure and the residue dissolved in concentrated hydrochloric acid. Triphenylmethane was removed by extraction with ether, an equal volume of water was added to the hydrochloric acid solution, and the mixture was heated on the water-bath for 4 hours. Benzoic acid was then extracted with ether, and the hydrochloric acid solution filtered through charcoal. The acid was removed at reduced pressure below 60° and the residue dissolved in methyl alcohol and reduced catalytically using palladium–charcoal catalyst. Reduction ceased when approximately 100 c.c. of hydrogen had been adsorbed. The catalyst was removed, the solution concentrated, and the product liberated by addition of aqueous sodium carbonate. The base was extracted with chloroform, and after prolonged manipulation a small quantity of crystalline hydrobromide melting at 224° was isolated. This compound did not depress the m. p. of dihydro-*x*-niquidine (m. p. 229°) prepared by an alternative method (Part II, *loc. cit.*).

3-(2-*Phenoxyethyl*)*hexane*-1-*carboxylic Acid*.—To a solution of malonic acid (9·5 g.) and phenoxyethylvaleraldehyde (18·5 g.) (Part II, *loc. cit.*) in pyridine (40 c.c.), piperidine (0·5 g.) was added as catalyst and after 3 hours the mixture was heated on a boiling water-bath for 2 hours and finally boiled under reflux for 30 minutes. Most of the pyridine was removed under reduced pressure, the residual oil diluted with water, and excess of sodium carbonate added. Unreacted aldehyde (11·0 g.) was recovered by extraction with ether, and the unsaturated acid liberated by addition of hydrochloric acid to the alkaline solution. The acid was decarboxylated and distilled, and the fraction, b. p. 178—180°/0·7 mm., collected. The distillate (8·6 g.) was dissolved in one equivalent of 2N-sodium carbonate and reduced catalytically using palladium–strontium carbonate catalyst. The *product* was purified by distillation, and the fraction (6·3 g.), b. p. 186—188°/1 mm., collected (Found: C, 71·8; H, 8·7. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%). The S-*benzylthiouronium* salt of the acid crystallised from acetone melted at 117° (Found: C, 66·9; H, 7·4; N, 6·4. $C_{15}H_{21}O_3,C_8H_{11}N_2S$ requires C, 66·4; H, 7·7; N, 6·7%). The *ethyl* ester boiled at 204°/12 mm. (Found: C, 73·8; H, 9·2. $C_{17}H_{26}O_3$ requires C, 73·4; H, 9·3%).

3-(2-*Bromoethyl*)*hexane*-1-*carboxylic Acid*.—3-(2-Phenoxyethyl)hexane-1-carboxylic acid (50 g.) in a mixture of hydrobromic acid (200 c.c.; *d* 1·7) and glacial acetic acid (560 c.c.) was boiled under reflux for 7 hours. The solvent was removed under reduced pressure and the residue diluted with water. The *bromo-acid* was extracted with ether, extracted from the ether with sodium carbonate solution, and liberated by addition of excess of hydrochloric acid. It was purified by fractional distillation, the fraction (32 g.), b. p. 164—168°/3 mm., being collected (Found: Br, 33·1. $C_9H_{17}O_2Br$ requires Br, 33·7%).

1-*Bromo*-3-(2-*bromoethyl*)*hexane*-1-*carboxylic Acid*.—The above acid (32 g.) and phosphorus tribromide (0·5 c.c.) were mixed, and dry bromine (31·5 g.) was added slowly to the stirred solution under anhydrous conditions. When addition was complete the mixture was heated and maintained at 75° for 15 hours. The temperature was finally raised to 110° for 10 minutes and the product distilled, the fraction, b. p. 180—190°/3 mm., being collected. Redistillation gave the required *acid* (46 g.), b. p. 144—146°/0·6 mm. (Found: C, 34·4; H, 5·2; Br, 49·5. $C_9H_{16}O_2Br_2$ requires C, 34·2; H, 5·1; Br, 50·6%).

Ethyl N-*Benzyl*-4-*propylpiperidine*-2-*carboxylate*.—The bromo-acid from the above experiment (40 g.) was mixed with methyl alcohol (40 c.c.), cooled in ice, and benzylamine (40 g.) in methyl alcohol (40 c.c.) added slowly. After 2 hours at 0° and 24 hours at room temperature the mixture was heated for 3 hours at 90°. Methyl alcohol was removed and the product shaken with ether and excess of dilute sodium hydroxide. The sodium *N*-benzylpropylpiperidine-2-carboxylate was sparingly soluble in sodium hydroxide, but dissolved on adding sufficient water. The ether was separated and discarded. On addition of excess of 50% sodium hydroxide to the aqueous solution the sodium salt separated and was extracted with butyl alcohol. The butyl alcohol extract was concentrated and the residue esterified by treatment with alcohol and dry hydrogen chloride. The *ethyl* N-*benzyl*-4-*propylpiperidine*-2-*carboxylate* was fractionally distilled twice, and the fraction (9·4 g.), b. p. 174—176°/1 mm. collected (Found: C, 75·2; H, 9·2; N, 5·1. $C_{18}H_{27}O_2N$ requires C, 74·7; H, 9·3; N, 4·8%).

Ethyl 4-*Propylpiperidine*-2-*carboxylate*.—The distillate from the above preparation (6·0 g.) in glacial acetic acid (50 c.c.) was reduced catalytically at 70° and normal pressure with Adams's platinum oxide catalyst. Reduction was complete in 6 hours. The catalyst was removed, the solvent distilled at reduced pressure, and the base liberated by addition of saturated sodium carbonate solution. The *base* after fractional distillation had b. p. 140—142°/18 mm. (2·5 g.) (Found: C, 66·4; H, 10·4; N, 7·2. $C_{11}H_{21}O_2N$ requires C, 66·3; H, 10·5; N, 7·0%).

I wish to thank Mr. N. Schunman for valuable technical assistance. Dr. E. R. Buchman (private communication) has successfully applied the sodium triphenylmethyl method in similar condensations of ethyl *N*-benzoylpiperidine-2-carboxylate with aromatic esters and reports equally disappointing yields. I am greatly indebted to Mr. Solomon of the Wellcome Research Institution, who developed the same method independently, for advice on the experimental technique.

NATIONAL INSTITUTE FOR MEDICAL RESEARCH,
LONDON, N.W.3.

[*Received, June 4th,* 1946.]