323. *Synthesis of Possible Antimalarials. Part II.* Compounds with the* iso*Quinoline Ring attached to the Quinuclidine System.*

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In view of the special interest, both chemical and physiological, attaching to the quinine structure (I) and also to many groups of alkaloids containing the *iso*quinoline system, the synthesis of compounds (II) containing the *iso*quinoline ring attached to the quinuclidine ring of the quinine alkaloids has been attempted.

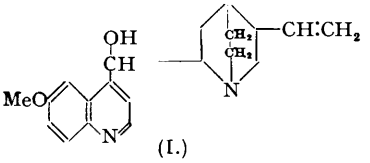
Preliminary experiments showed that ethyl *iso*quinoline-3-carboxylate (III) underwent a normal Claisen reaction with ethyl acetate, although 1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylic ester reacted in poor yield; (III) condensed smoothly with ethyl β-(1-benzoyl-4-piperidyl)propionate. On hydrolysis and decarboxylation of the β-keto-ester, 2-4′-piperidylethyl 3-*iso*quinolyl ketone (V) was obtained which, on cyclisation by Rabe's method (*Ber.*, 1931, **64**, 2487), gave 3-*iso*quinolyl 2-quinuclidyl ketone (VI).

Since the formulation of the structure of quinine (I) by Rabe (*Ber.*, 1908, **71**, 62) synthetic work has culminated in the syntheses of dihydroquinone (Rabe, Huntenberg, Schulze, and Volger, *Ber.*, 1931, **64**, 2487) and of quinine itself (I) by Woodward and Doering (*J. Amer. Chem. Soc.*, 1944, **66**, 849; 1945, **67**, 860).

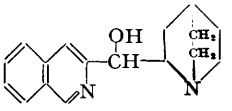
In view of the vast amount of work done in this field and the considerable physiological activity of *iso*quinoline compounds, some of which, *e.g.*, emetine, have a specific action on protozoa, it appeared to be of interest to synthesise and study the antimalarial activity of similar compounds in which the quinoline nucleus was replaced by *iso*quinoline, the simplest of this type being (II). This small variation in structure, while retaining factors which influence

* Part I, *J.*, 1936, 160.

antimalarial activity, should throw some light on the rôle of the quinoline system in the cinchona alkaloids (cf. Work, *J.*, 1940, 1315; 1942, 426) and also the effect of its replacement by *iso*quinoline.



(I.)



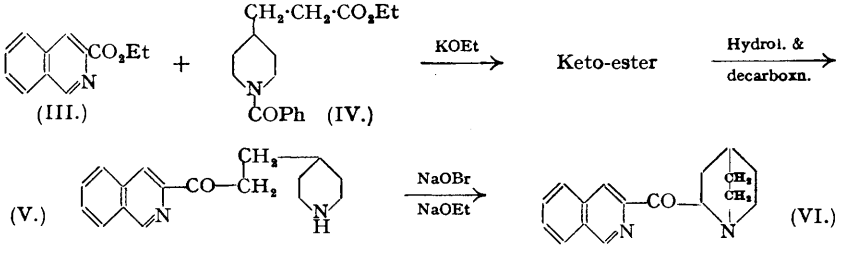
(II.)

Preliminary experiments to this end involved a study of the Claisen condensation on *iso*quinoline-3-carboxylic ester and related compounds. Padbury and Lindwall (*J. Amer. Chem. Soc.*, 1945, **67**, 1268) have prepared methyl 1(and 4)-*iso*quinolyl ketones by a Claisen condensation of *iso*quinoline-1(and 4)-carboxylic esters with ethyl acetate, but no instance of a similar reaction of *iso*quinoline-3-carboxylic ester appears to have been recorded. In view of their observation, which was supported by the independent work of Koelsch (*J. Org. Chem.*, 1945, **10**, 34), who showed that the carbethoxy-group in the 4-position in *iso*quinoline was less active than that in the 1-position, as shown by the respective yields of methyl *iso*quinolyl ketones, and the fact that 1-methyl*iso*quinoline readily condenses with benzaldehyde, whereas 3-methyl*iso*quinoline does not (Mills and Smith, *J.*, 1922, **121**, 2724), it was decided to study the behaviour of ethyl *iso*quinoline-3-carboxylate under comparable conditions. This was prepared from phenylalanine by condensation with formaldehyde by a modification of Pictet and Spengler's method (*Ber.*, 1911, **44**, 2030) and subsequent dehydrogenation of the tetrahydro-ester so obtained with sulphur in tetralin. Palladised charcoal, or choranil (Campbell and Soffer, *J. Amer. Chem. Soc.*, 1942, **64**, 423), was less satisfactory, and although palladium-black gave higher yields, the quantity required would have been prohibitive for large-scale preparative work.

Ethyl *iso*quinoline-3-carboxylate condensed readily with ethyl acetate in the presence of potassium ethoxide in toluene to give the corresponding β-keto-ester. The latter on hydrolysis followed by decarboxylation gave methyl 3-*iso*quinolyl ketone (semicarbazone and phenylhydrazone picrate) in an overall yield of 60%.

A similar condensation of ethyl 1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylate with ethyl acetate gave poor yields, which were not improved by using the *N*-benzoyl derivative of the former. In view of this, and the observation that in the cinchona alkaloid series reduction of the quinoline ring increases the toxicity and reduces the antimalarial activity (Boyd, *Amer. J. Hyg.*, 1926, **6**, 173), it was decided to proceed with the dehydrogenated product. Thus, ethyl *iso*quinoline-3-carboxylate behaved similarly to ethyl quininate and related quinoline-carboxylic esters, and from it, therefore, a synthesis of a compound like (II) by Rabe's method appeared possible.

The ethyl β-4-piperidylpropionate required was obtained by catalytic reduction of ethyl pyridine-4-acrylate (Rabe, *Ber.*, 1919, **52**, 1850) with Adams's catalyst in acetic–hydrochloric acid or with Raney nickel at 150°/180 atm. in alcohol, and was then converted into its *N*-benzoyl derivative (IV), which was purified by distillation in a molecular still.



Condensation of (III) and (IV) was effected by heating the mixture of the reactants in toluene with dry potassium ethoxide, the crude intermediate β-keto-ester giving, on hydrolysis with boiling 8N-hydrochloric acid, 2-4′-piperidylethyl 3-*iso*quinolyl ketone (V). This was characterised as its 2 : 4-dinitrophenylhydrazone, dipicrate, and phenylhydrazone dipicrate, and was converted by the action of sodium hypobromite into its *N*-bromo-derivative, which was

cyclised by sodium ethoxide in alcoholic solution to give 3-*iso*quinolyl 2-quinuclidyl ketone (VI). This compound (compare Rabe *et al.*, *loc. cit.*) bears a close resemblance to quininone.

The replacement of the quinoline by the *iso*quinoline residue makes it desirable to test the antimalarial potentialities of (V) and (VI), and the reduction product of the latter in which a secondary alcoholic group unites the *iso*quinoline and the quinuclidine system. This might not only indicate the changes obtained in pharmacological properties by the interchange of the quinoline and *iso*quinoline nuclei, but might also throw some light on the effect of other groups present (*e.g.*, the quinuclidine ring) on the antimalarial activity.

This work is being continued.

Experimental.

Ethyl 1 : 2 : 3 : 4-*Tetrahydro*iso*quinoline*-3-*carboxylate*.—A mixture of phenylalanine (27·0 g.), methylal (30 ml.), and hydrochloric acid (300 ml.) was left overnight at room temperature and then heated on a steam-bath for 5 hours with occasional shaking, and cooled, and methylal (30 ml.) added. After being kept for another 10 hours at room temperature, the mixture was again heated on a steam-bath for 5 hours and evaporated to dryness under reduced pressure, and the last traces of moisture were removed by adding and distilling off absolute alcohol (25 ml.). Absolute alcohol (150 ml.) was then added, the whole saturated at 0° with hydrogen chloride, left overnight, and refluxed for 3 hours, and the alcohol removed. The residue was basified (K_2CO_3), and extracted thrice with ether, the extract was dried (Na_2SO_4), the solvent removed, and the residue distilled, giving ethyl 1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylate as a liquid (12·8 g., b. p. 144—145°/15 mm., 97—98°/0·1 mm.) (Found : C, 70·2; H, 7·7. Calc. for $C_{12}H_{15}O_2N$: C, 70·2; H, 7·3%). Its picrate separated from alcohol as yellow crystals, m. p. 204°.

Ethyl N-*Benzoyl*-1 : 2 : 3 : 4-*tetrahydro*iso*quinoline*-3-*carboxylate*.—A mixture of the foregoing ester (2·0 g., 0·01 mole) and potassium carbonate (2·8 g., 0·02 mole) in chloroform (10 ml.) was cooled to 0° and an ice-cold solution of benzoyl chloride (1·7 g., 0·012 mole) in chloroform (10 ml.) was added dropwise; the mixture was heated on a steam-bath for 8 hours, then cooled, and the solution filtered, the inorganic salts being washed with chloroform. The combined filtrate and washings were evaporated, the last traces of the solvent being removed in a vacuum, the residue transferred to the molecular still, and the fraction boiling at 150—160° (bath-temp.)/0·0001 mm. collected (2·5 g.) as an odourless, viscous liquid which, on being cooled and touched with ether, solidified; this *benzoyl* derivative had m. p. 79° (Found : C, 73·8; H, 5·9. $C_{19}H_{19}O_3N$ requires C, 73·8; H, 6·1%).

Ethyl iso*Quinoline*-3-*carboxylate*.—A mixture of ethyl 1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylate (above) (0·5 g.) and palladium-black (0·35 g.) was heated at 160—170°/25 mm. for ½ hour and distilled, ethyl *iso*quinoline-3-carboxylate (0·35 g.; b. p. 144—145°/0·5 mm.) being obtained (Found : C, 71·4; H, 5·7. Calc. for $C_{12}H_{11}O_2N$: C, 71·1; H, 5·5%). The picrate, m. p. 153°, crystallised from alcohol in yellow needles. Ethyl *iso*quinoline-3-carboxylate was also prepared by dehydrogenation with sulphur in tetralin at 160—165° for 4 hours (Swan, *J.*, 1950, 1536). The yields were, however, lower (25—33%).

Methyl 3-iso*Quinolyl Ketone*.—To a suspension of potassium ethoxide (0·4 g., 0·005 mole) in dry toluene (15 ml.) was added ethyl *iso*quinoline-3-carboxylate (0·65 g., 0·0033 mole), followed by ethyl acetate (0·90 g., 0·01 mole; 100% excess). The brown mixture was heated on a steam-bath for 5 hours and cooled, 8N-hydrochloric acid (15 ml.) was added, and the whole heated on a water-bath for 15 hours and taken to dryness under reduced pressure. The residue was basified (saturated potassium carbonate), extracted with ether, dried (K_2CO_3), and distilled, giving the *ketone* as a pale yellow liquid, which solidified on cooling, and crystallised from light petroleum (b. p. 40—60°) in rectangular plates, m. p. 88° (Found : C, 77·5; H, 5·2. $C_{11}H_9ON$ requires C, 77·2; H, 5·3%); it yielded a *semicarbazone*, rectangular rods, m. p. 216°, from aqueous ethanol (Found : C, 63·4; H, 5·1. $C_{12}H_{12}ON_4$ requires C, 63·2; H, 5·3%), and a *phenylhydrazone picrate*, orange-red needles, m. p. 209°, from ethanol (Found : C, 56·3; H, 3·9. $C_{23}H_{18}O_7N_6$ requires C, 56·3; H, 3·7%).

Ethyl β-4-Pyridylacrylate.—β-4-Pyridylacrylic acid (Rabe, *loc. cit.*) (13·5 g.) in absolute alcohol (120 ml.) was saturated with dry hydrogen chloride and warmed on a water-bath for 3 hours. The solvent was removed, and the residue basified (saturated potassium carbonate), extracted with ether, and dried. The residual *ester* solidified on cooling and was purified by sublimation (130°/15 mm.), giving a crystalline solid (11·6 g.), m. p. 64° (Found : C, 68·0; H, 5·9. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·2%).

Ethyl β-4-Piperidylpropionate.—(*a*) Ethyl β-4-pyridylacrylate (10·0 g.), platinum oxide (100 mg.), and glacial acetic acid (50 ml.) were shaken in hydrogen at 100 lb./sq. in. for 15 hours. The hydrogen was removed, and the catalyst regenerated by shaking with air for ½ hour. Platinum oxide (50 mg.) was added, and shaking continued in hydrogen for another 10 hours at 100 lb./sq. in., the platinum was filtered off, the solvent removed, and the residue basified (50% potassium hydroxide), extracted with ether, dried, and distilled, giving an oily ester (9·1 g.; b. p. 98°/0·1 mm.) (Found : C, 64·8; H, 10·1. Calc. for $C_{10}H_{19}O_2N$: C, 64·9; H, 10·3%); it formed a picrate (from ethanol), m. p. 115°.

(*b*) Ethyl β-4-pyridylacrylate (1·75 g.) and Raney nickel (1·0 g.) in absolute alcohol (75 ml.) were stirred with hydrogen at 150°/180 atm. for 5 hours and worked up as above, giving the reduced compound (1·65 g.).

Ethyl β-(1-Benzoyl-4-piperidyl)propionate (IV).—To an ice-cold solution of the piperidylpropionate (3·3 g.) in chloroform (10 ml.) were added anhydrous potassium carbonate (5·1 g.), and then gradually a solution of freshly distilled benzoyl chloride (2·2 ml.). The mixture was refluxed for 6 hours, the chloroform solution was decanted, the inorganic salts were washed with chloroform, and the combined chloroform solution and washings evaporated to a small volume and transferred to the molecular still.

The fraction, b. p. 145—155°/(bath-temp.)/0·0001 mm., was a thick, colourless, odourless liquid (Found : C, 70·2; H, 8·2. Calc. for $C_{17}H_{23}O_3N$: C, 70·6; H, 8·0%).

2-4′-*Piperidylethyl* 3-iso*Quinolyl Ketone* (V).—To a well-cooled suspension of potassium ethoxide (0·50 g., 0·006 mole) in dry benzene (20 ml.) was added a mixture of ethyl *iso*quinoline-3-carboxylate (1·0 g., 0·005 mole) and ethyl β-(1-benzoyl-4-piperidyl)propionate (1·45 g., 0·005 mole). The mixture was stirred thoroughly and then heated on a steam-bath for 5 hours and cooled, and hydrochloric acid (20 ml.; 4N.) added. The solution was heated on a water-bath for 16 hours and taken to dryness under reduced pressure, the residue basified (saturated potassium carbonate), extracted with ether, and dried, and the solvent removed. The viscous red residue was digested with light petroleum (b. p. 40—60°), and on concentration and cooling gave light cream-coloured crystals which were washed with ether and recrystallised from light petroleum (b. p. 40—60°), giving the *ketone* (150 mg.; m. p. 95°, not raised by further crystallisation) (Found : C, 71·1; H, 8·1. $C_{17}H_{20}ON_2,H_2O$ requires C, 71·3; H, 7·7%); it gave a *dipicrate*, yellow prisms, m. p. 178° (from ethanol) (Found : C, 48·3; H, 3·3. $C_{17}H_{20}ON_2,2C_6H_3O_7N_3$ requires C, 47·9; H, 3·6%), 2 : 4-*dinitrophenylhydrazone hydrogen sulphate*, yellowish-orange, m. p. 250° (decomp.), from alcohol (Found : C, 42·0; H, 4·6. $C_{23}H_{24}O_4N_6,2H_2SO_4,H_2O$ requires C, 41·7; H, 4·5%), and *phenylhydrazone dipicrate*, deep red plates, m. p. 215° (decomp.), from ethanol (Found : C, 51·7; H, 4·4. $C_{23}H_{26}N_4,2C_6H_3O_7N_3$ requires C, 51·7; H, 4·0%).

2-(1-*Bromo*-4-*piperidyl*)*ethyl* 3-iso*Quinolyl Ketone*—The above ketone (116 mg.) was dissolved in N-hydrochloric acid (0·5 ml.) and ether (3·0 ml.), and a solution of bromine (64 mg.) in 6% sodium hydroxide (0·8 g.) added in a fine stream with stirring. The mixture was left for 15 minutes, the ethereal layer separated, and the residue extracted twice with 3 ml. of ether. The combined ethereal extracts were dried (Na_2SO_4) and concentrated to a small volume, and on cooling gave the pure *bromo*-compound (56·0 mg.), m. p. 237° (decomp.) after darkening at 205° (Found : C, 58·6; H, 5·6. $C_{17}H_{19}ON_2Br$ requires C, 58·8; H, 5·5%). Unchanged ketone (22 mg.) was recovered from the sodium sulphate by extraction with boiling ethanol.

3-iso*Quinolyl* 2-*Quinuclidyl Ketone* (VI).—A boiling solution of the *N*-bromo-compound (50 mg.) in ethanol (4·0 ml.) was added to a cold solution of sodium (10 mg.) in ethanol (4 ml.). The brownish-red solution was heated on a water-bath for 30 minutes, allowed to cool, and made slightly acid (dilute hydrochloric acid). The alcohol was distilled off under reduced pressure, the residue basified with sodium hydroxide and extracted with ether, and the ethereal extract dried (Na_2SO_4); on removal of the solvent a viscous liquid was obtained which solidified on cooling. On recrystallisation from light petroleum (b. p. 40—60°), this *ketone* formed crystals (13 mg.), m. p. 85—86° (Found : C, 71·4; H, 7·2. $C_{17}H_{18}ON_2,H_2O$ requires C, 71·8; H, 7·0%).

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