# 137. *The Synthesis of α-Picolylisoquinolines as Possible Antimalarials. Part I.*

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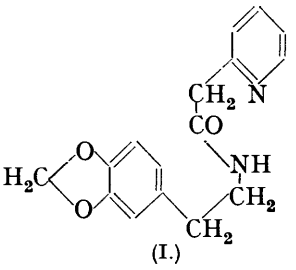
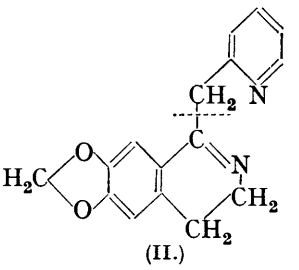
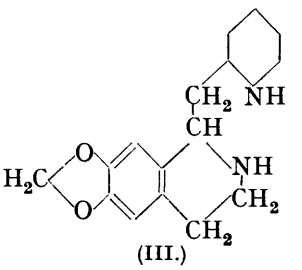
It is well known that a large number of *iso*quinoline compounds possess physiological action and that some, such as emetine, have a specific action on protozoa. In the present search for compounds of antimalarial value, it was therefore decided to prepare compounds intermediate in structure between the quinine and the *iso*quinoline alkaloids, such as (II). This compound has a part of the " second half " of the quinine molecule attached in the 1-position to the nitrogen of an *iso*quinoline nucleus, whereas in quinine it is in the 4-position to the quinoline nitrogen atom, and such compounds might be expected to exhibit interesting physiological properties even if they do not act as antimalarials.


(I.)


(II.)


(III.)

Pyridyl-2-acetic ester condenses readily with β-3 : 4-methylenedioxyphenylethylamine, yielding the *amide* (I), which (compare Decker, *Ber.*, 1909, **42**, 2075) undergoes ring closure with phosphorus oxychloride to 6 : 7-*methylenedioxy*-1-α-*picolyl*-3 : 4-*dihydro*isoquinoline (II). This is a yellow crystalline solid which forms a *monopicrate* and a stable water-soluble *dihydrochloride*. It is reduced smoothly to the 1 : 2 : 3 : 4-*tetrahydro*-compound by means of zinc in sulphuric acid and completely to 6 : 7-methylenedioxy-1-α-pipecolyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline (III) by hydrogen in the presence of platinum. These two compounds have been obtained as viscous distillable liquids, forming *dipicrates* and colourless water-soluble *dihydrochlorides*.

It has not been found possible to obtain 6 : 7-methylenedioxy-1-α-picolyl*iso*quinoline from the dihydro- or the tetrahydro-compound by the usual methods of dehydrogenation, the only isolable products being α-picoline and 6 : 7-methylenedioxy*iso*quinoline formed by the fission indicated in (II).

## Experimental.

*Pyridyl-2-aceto-3′ : 4′-methylenedioxy-β-phenylethylamide.*—Ethylpyridyl-2-acetate (2·5 g.) and 3 : 4-methylenedioxy-β-phenylethylamine (Haworth, Perkin, and Rankin, J., 1924, **125**, 1694) (2·5 g.) were heated under reflux at 200° for 1 hour; alcohol and a little α-picoline were evolved, leaving a brown viscous liquid, which was extracted with light petroleum. The solvent was concentrated; the *amide* then separated in colourless needles (3·5 g.), m. p. 89° (Found : C, 67·9; H, 5·8. $C_{16}H_{16}O_3N_2$ requires C, 67·6; H, 5·6%), very soluble in the commoner organic solvents except light petroleum.

6 : 7-*Methylenedioxy*-1-α-*picolyl*-3 : 4-*dihydro*isoquinoline.—The above amide (6·0 g.) was refluxed with phosphorus oxychloride (30 c.c.) for 40 minutes; the solution, originally straw-coloured, became red and was then poured gradually on ice, and the whole basified with sodium carbonate and extracted with ether. After removal of the ether the *dihydro*isoquinoline crystallised from alcohol in yellow needles (3·0 g.), m. p. 105° (Found : C, 72·4; H, 5·4. $C_{16}H_{14}O_2N_2$ requires C, 72·2; H, 5·3%). The compound is soluble in organic solvents but insoluble in water; its salts with the mineral acids are very soluble in water. A red compound (2·0 g.) obtained as a by-product in this reaction can be extracted with chloroform from its aqueous suspension after the ether extraction. Attempted ring closures under milder conditions (with phosphorus oxychloride or pentachloride in toluene or chloroform) did not give better results.

6 : 7-*Methylenedioxy*-1-α-*picolyl*-3 : 4-*dihydro*isoquinoline *dihydrochloride* was prepared by adding excess of alcoholic hydrogen chloride to an ethereal solution of the base (0·8 g.); the

bright yellow precipitate (1·0 g.), recrystallised from alcohol–ether, formed bright yellow prisms, m. p. 210° (Found: C, 56·0; H, 5·7. $C_{16}H_{14}O_2N_2,2HCl,C_2H_6O$ requires C, 56·0; H, 5·7%). The *picrate* (yellow plates, m. p. 210° after softening at 205°, from alcohol) was prepared by mixing alcoholic solutions of the base and picric acid (Found: C, 52·9; H, 3·5. $C_{16}H_{14}O_2N_2,C_6H_3O_7N_3$ requires C, 53·3; H, 3·5%).

6 : 7-*Methylenedioxy*-1-α-*picolyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline.—The above dihydro-compound (1·0 g.), zinc dust (3·0 g.), copper sulphate (0·05 g.), and water (30 c.c.) were warmed on the water-bath, and concentrated sulphuric acid (2·5 c.c.) added gradually with occasional shaking during 1 hour, so that hydrogen was only slowly evolved. The originally yellow solution became almost colourless, and was filtered, basified with sodium carbonate solution, and extracted with ether. Removal of this left the *tetrahydro*-compound as a pale yellow oil (0·8 g.), b. p. 215°/1 mm. (Found: C, 71·7; H, 6·4. $C_{16}H_{16}O_2N_2$ requires C, 71·7; H, 6·0%). The *picrate*, prepared as above, crystallised from alcohol in bright yellow prisms, m. p. 175° (Found: C, 46·1; H, 3·3. $C_{16}H_{16}O_2N_2,2C_6H_3O_7N_3$ requires C, 46·3; H, 3·1%). The *hydrochloride* was made by the addition of alcoholic hydrogen chloride to a solution of the base in alcohol; it crystallised from aqueous alcohol in fine colourless plates, m. p. 205° with softening above 200° (Found: C, 53·7; H, 5·6. $C_{16}H_{16}O_2N_2,2HCl,H_2O$ requires C, 53·4; H, 5·6%).

6 : 7-*Methylenedioxy*-1-α-*pipecolyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline.—The dihydroisoquinoline (II) as its dihydrochloride (0·25 g.), absolute alcohol (5 c.c.), and platinum oxide (0·05 g.) were shaken in hydrogen at 100 lb./sq. in. for 20 hours; the originally yellow material became white. A little water was added to dissolve the salt produced, the solution filtered from platinum, the alcohol removed, excess of sodium hydroxide solution (20%) added, and the liberated base extracted with ether. Removal of the solvent left the pipecolyl compound as an almost colourless oil (0·2 g.), b. p. 210°/1 mm. The *picrate*, prepared as above, crystallised from alcohol in fine matted needles, m. p. 236° (Found: C, 46·0; H, 4·3. $C_{16}H_{22}O_2N_2,2C_6H_3O_7N_3$ requires C, 45·9; H, 3·9%). The *hydrochloride*, prepared as was the tetrahydro-salt, crystallised from nearly absolute alcohol in colourless prisms, m. p. 293° (Found: C, 55·0; H, 7·1. $C_{16}H_{22}O_2N_2,2HCl$ requires C, 55·3; H, 6·9%).

*Attempted Dehydrogenation of* 6 : 7-*Methylenedioxy*-1-α-*picolyl*-3 : 4-*dihydro*isoquinoline.—The base (0·25 g.) and palladised charcoal (0·1 g.) were heated in an evacuated sealed tube at 200° for ½ hour. A liquid of pyridine-like odour condensed in the upper part of the tube, and yielded a picrate (0·1 g., m. p. 164° alone or mixed with α-picoline picrate). Extraction of the residue with ether yielded a solid (0·1 g., m. p. 118°) which formed a picrate, m. p. 206° (Found: C, 47·7; H, 2·9. $C_{10}H_7O_2N,C_6H_3O_7N_3$ requires C, 47·7; H, 2·5%). This analysis and the mode of production indicate that it is 6 : 7-*methylenedioxyisoquinoline picrate*.

Several other attempted dehydrogenations using mercuric acetate (Tafel, *Ber.*, **1892**, **25**, 1622) and iodine (Buck, Haworth, and Perkin, J., 1924, **125**, 2180) failed to yield a separable product, and similar results were obtained with the 1 : 2 : 3 : 4-tetrahydro-compound.

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