The Constitution of Yohimbine and Related Alkaloids. Part VII. Synthesis of* 5 : 6 : 7 : 8-*Tetrahydroisoquinoline*-3-*carboxylic Acid.*

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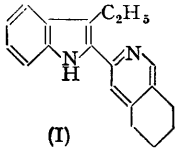
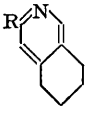
5 : 6 : 7 : 8-Tetrahydro*iso*quinoline-3-carboxylic acid, a degradation product of yohimbine, has been synthesised and converted into 3-acetyl-5 : 6 : 7 : 8-tetrahydro*iso*quinoline.

SELENIUM dehydrogenation of yohimbine gives yobyrine, " tetrahydroyobyrine " (I), and ketoyobyrine (Barger and Scholz, *Helv. Chim. Acta*, 1933, **16**, 1343; Scholz, *ibid.*, 1935, **18**, 923). Ozonolysis of " tetrahydroyobyrine " and subsequent hydrolysis of the intermediate amide yields *o*-aminopropiophenone and 5 : 6 : 7 : 8-tetrahydro*iso*quinoline-3-carboxylic acid (II; R = CO_2H).



(I)



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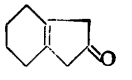


(III)

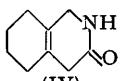
Chuang and Ma (*Ber.*, 1935, **68**, 871), by dehydration of diethyl 1-hydroxy*cyclo*hexane-1 : 2-diacetate obtained a product which may be diethyl *cyclo*hexene-1 : 2-diacetate, the isomer with an exocyclic double bond, or a mixture of the two. Dieckmann cyclisation of this product and subsequent hydrolysis could give either the hitherto undescribed 4 : 5 : 6 : 7-tetrahydroindan-2-one (III), or the isomer with the double bond in the five-membered ring. The latter was synthesised by Islam and Raphael (*J.*, 1952, 4086) and gives a red 2 : 4-dinitrophenylhydrazone, m. p. 200°, whereas our ketone forms a pale orange 2 : 4-dinitrophenylhydrazone, m. p. 183°, and has therefore structure (III). The same ketone is obtained by heating the barium salt of the *cyclo*hexene-1 : 2-diacetic acid.

All attempts to convert the oxime of (III) by the Beckmann reaction into 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-3-oxo*iso*quinoline (IV) failed.

The synthesis of the *iso*quinoline (IV) was investigated by another route. *N*-Acetyl-2-

* Part VI, *J.*, 1952, 650.

hydroxy*cyclo*hexylmethylamine (V) was oxidised to the corresponding ketone which with ethyl bromoacetate gave ethyl 2-acetamidomethyl-1-hydroxy*cyclo*hexylacetate (VI) which on dehydration and cyclisation gave (IV) or an isomer but the yield was too low for use in the preparation of (II; R = CO_2H).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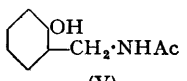
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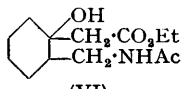
(VI)

Attempts to prepare the acid (II; R = CO_2H) or its ethyl ester by condensation of 2-aminomethylene*cyclo*hexanone with pyruvic acid or ethyl pyruvate respectively were unsuccessful, starting material being recovered.

It was finally found that 3-chloro-5 : 6 : 7 : 8-tetrahydro*iso*quinoline (Schlittler and Merian, *Helv. Chim. Acta*, 1947, **30**, 1339) could be converted into (II; R = CO_2H) identical with the acid obtained from yohimbine, by treatment with cuprous cyanide in aqueous potassium cyanide.

Whilst 3-chloro-5 : 6 : 7 : 8-tetrahydro*iso*quinoline did not form a Grignard reagent with magnesium, it formed a lithium derivative which with acetonitrile gave 3-acetyl-5 : 6 : 7 : 8-tetrahydro*iso*quinoline (II; R = Ac) in low yield. Claisen condensation of the ester (II; R = CO_2Et) with ethyl acetate and subsequent hydrolysis afforded a better yield of the ketone.

Experimental

Ultra-violet absorption measurements were made in ethanol with a Hilger "Uvispec" spectrophotometer.

4 : 5 : 6 : 7-*Tetrahydroindan-2-one* (III).—Diethyl *cyclo*hexene-1 : 2-diacetate (6·0 g.) was added slowly to a suspension of sodium ethoxide (from sodium, 1·4 g.) in dry benzene (50 ml.), and the mixture was refluxed for 12 hr. The dark red mixture was cooled, concentrated hydrochloric acid (100 ml.) added, and the whole refluxed for 12 hr. After dilution with water, the aqueous layer was separated and extracted with ether, and the extract washed with dilute sodium hydroxide and then water and dried (Na_2SO_4). Distillation afforded the crude ketone (1·3 g.) as a pale yellow oil, b. p. 98—105°/2 mm. The *semicarbazone* separated from aqueous ethanol in colourless needles, m. p. 231—232° (Found: C, 62·4; H, 8·1. $C_{10}H_{15}ON_3$ requires C, 62·2; H, 7·8%), and on hydrolysis by aqueous oxalic acid gave the pure *ketone*, a colourless oil, b. p. 110°/3 mm. (Found: C, 79·3; H, 9·1. $C_9H_{12}O$ requires C, 79·4; H, 8·8%). The 2 : 4-*dinitrophenylhydrazone* formed pale orange needles (from ethanol), m. p. 183° (Found: C, 57·0; H, 5·4. $C_{15}H_{16}O_4N_4$ requires C, 57·0; H, 5·1%); light absorption: max. at 2700 and 3880 Å (log ε 3·86 and 4·12 respectively); min. at 3160 Å (log ε 2·70). The *oxime* crystallised from aqueous ethanol in almost colourless needles, m. p. 108—110° (decomp.) (Found: C, 71·0; H, 8·9. $C_9H_{13}ON$ requires C, 71·5; H, 8·6%).

N-*Acetyl*-2-*hydroxy*cyclo*hexylmethylamine* (V).—A suspension of 2-hydroxy*cyclo*hexyl-1-methylamine (cf. Godchot and Mousseron, *Compt. rend.*, 1933, **196**, 621) (2·0 g.) in water (10 ml.) was shaken 2 hr. at room temperature with acetic anhydride (0·887 ml.), the solution extracted with chloroform, the extract dried (Na_2SO_4), and the chloroform removed, yielding the N-*acetyl* derivative (0·84 g.) as a gum which solidified on cooling and crystallised from benzene in small, colourless prisms, m. p. 108—109° (Found: C, 63·2; H, 10·1. $C_9H_{17}O_2N$ requires C, 63·2; H, 9·9%).

N-*Acetyl*-2-*oxo*cyclo*hexylmethylamine*.—A solution of the hydroxyamine (V) (5·0 g.) in acetic acid (22 ml.) was cooled in ice and chromic anhydride (2·4 g.) in water (8 ml.) and acetic acid (32 ml.) was added dropwise with stirring at 0°. The whole was kept for a further 3 hr. at 0°, then at room temperature overnight, and at 40—50° for 1 hr. The solvents were removed under reduced pressure at 50—60°, and the residue was dissolved in warm methanol (4 ml.) and shaken vigorously with ether (100 ml.). The ether solution was decanted from the chromium salts, the residue was extracted with ether, and the combined ether extracts were boiled to coagulate chromium salts, and filtered. Distillation gave the *ketone* (2·9 g.) as a colourless, viscous oil, b. p. 146—149°/2 mm. (Found: C, 63·7; H, 9·2. $C_9H_{15}O_2N$ requires C, 63·9; H, 8·9%). The *semicarbazone* separated from water in almost colourless prisms, m. p. 214—215° (Found: C, 53·3; H, 7·9. $C_{10}H_{18}O_2N_4$ requires C, 53·1; H, 8·0%).

Ethyl 2-*Acetamidomethyl*-1-*hydroxy*cyclo*hexylacetate* (VI).—A mixture of the above ketone

(5 g.), ethyl bromoacetate (5·4 g.), anhydrous benzene (20 ml.), freshly cleaned zinc wool (2·9 g.), and a trace of iodine was stirred and heated under reflux on the water-bath for 2 hr. The mixture was cooled, sufficient 10% sulphuric acid added to dissolve residual zinc, the benzene layer separated, and the aqueous layer extracted with ether. The ether extract was washed with dilute sodium hydrogen carbonate solution, then with water, and dried (Na_2SO_4). Distillation gave a pale yellow, viscous oil (1·7 g.), b. p. 160—165°/0·2 mm., which solidified on the addition of dry ether. Recrystallisation from dry ether gave the *ester* as colourless prisms, m. p. 75° (Found: C, 60·3; H, 9·1. $C_{13}H_{23}O_4N$ requires C, 60·7; H, 9·0%).

Dehydration of the Ester (VI).—The above ester (0·7 g.) was dissolved in benzene (5 ml.), freshly distilled pyridine (0·85 ml.) was added, and the mixture cooled in ice. Freshly distilled thionyl chloride (0·23 ml.) was added dropwise, below 5°. The mixture was kept at room temperature overnight, then poured with stirring on crushed ice, and the benzene layer separated. The aqueous layer was extracted with benzene. The combined benzene extracts were washed with dilute hydrochloric acid, then with dilute sodium carbonate solution, and finally with water, and dried (Na_2SO_4). Distillation gave a pale yellow, viscous oil (0·4 g.), b. p. 145—150°/0·2 mm. (Found: C, 65·6; H, 9·0. Calc. for $C_{13}H_{21}O_3N$: C, 65·3; H, 8·8%).

Cyclisation of the Dehydration Product.—The above product (0·2 g.) was refluxed with 10% ethanolic potassium hydroxide (2 ml.) for 2·5 hr. The ethanol was removed under reduced pressure and the residue dissolved in a little water, cooled in ice, and treated with excess of 10% sulphuric acid. A slight excess of sodium carbonate was then added, the solution evaporated to dryness under reduced pressure, and the residue extracted with boiling anhydrous benzene. The benzene extract was filtered, and the benzene removed, giving the *iso*quinolone (IV or its isomer) as a white solid (10 mg.) which crystallised from anhydrous benzene in colourless, rectangular plates, m. p. (Kofler block) 135—138° (Found: C, 71·4; H, 8·9. Calc. for $C_9H_{13}ON$: C, 71·5; H, 8·6%), and gave a red colour with ethanolic ferric chloride.

5 : 6 : 7 : 8-*Tetrahydroisoquinoline*-3-*carboxylic Acid.*—3-Chloro-5 : 6 : 7 : 8-tetrahydro*iso*quinoline formed a *picrate* (yellow needles from ethanol), m. p. 103—105° (Found: C, 45·2; H, 3·6. $C_9H_{10}NCl,C_6H_3O_7N_3$ requires C, 45·4; H, 3·3%).

The above chloro-base (1 g.) in ethanol (1 ml.) was added to freshly prepared cuprous cyanide (0·6 g.) in potassium cyanide (1·5 g.) and water (5 ml.). The mixture was heated at 180—190° for 10 hr., cooled, and filtered. The pH of the filtrate was adjusted to 4, the precipitated cuprous salts were filtered off, and the clear yellow filtrate was continuously extracted with ether for 48 hr. Removal of the ether from the dried (Na_2SO_4) extract gave the *acid* (0·19 g.) which separated from water in colourless needles, m. p. 209—210° (Found: C, 67·7; H, 6·4. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·2%). Light absorption: max. at 2250 and 2660 Å (log ε 3·83 and 3·50); min. at 2500 Å (log. ε 3·40).

The acid (II; R = CO_2H) from yohimbine had m. p. 208°, mixed m. p. with our synthetic acid 208—209°, and light absorption max. at 2260 and 2660 Å (log ε 3·80 and 3·50 respectively), min. at 2510 Å (log ε 3·38).

The synthetic acid (0·3 g.) in anhydrous ethanol (15 ml.) was saturated at 0° with dry hydrogen chloride, gently warmed for 2 hr., refluxed for 2 hr., and kept at room temperature overnight. Removal of the ethanol in a vacuum and working up as usual gave the *ester* (0·2 g.), b. p. 115°/2 mm. (Found: C, 70·4; H, 7·5. $C_{12}H_{15}O_2N$ requires C, 70·2; H, 7·3%). The *picrate* crystallised from methanol in yellow plates, m. p. 150—151° (Found: C, 50·0; H, 4·4. $C_{12}H_{15}O_2N,C_6H_3O_7N_3$ requires C, 49·8; H, 4·15%).

3-*Acetyl*-5 : 6 : 7 : 8-*tetrahydroisoquinoline*.—To a suspension of potassium ethoxide (from potassium, 0·2 g.) in dry benzene (8 ml.) was added the above ester (0·2 g.) and ethyl acetate (0·5 g., 2 mols.) The mixture immediately became brown and was refluxed for 5 hr., cooled, treated with hydrochloric acid (2 : 1; 10 ml.), and heated under reflux on the water-bath for a further 12 hr. It was evaporated to dryness in a vacuum, and the residue was dissolved in water, basified with saturated K_2CO_3, and extracted with ether. Distillation of the dried (K_2CO_3) extract gave the ketone (0·1 g.) as a pale yellow, viscous oil, b. p. (bath-temp.) 150°/2 mm. The *picrate* separated from ethanol in yellow plates, m. p. 146—147° (decomp.) (Found: C, 50·3; H, 4·2. $C_{11}H_{13}ON,C_6H_3O_7N_3$ requires C, 50·5; H, 4·0%).

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