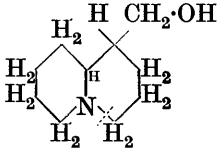
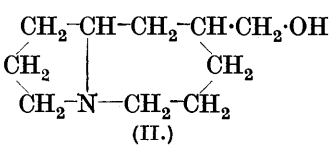
LIX.—*The Lupin Alkaloids. Part IV. The Synthesis of Octahydropyridocoline.*

By GEORGE ROGER CLEMO and GEORGE ROWNTREE RAMAGE.

THE development of the work in these laboratories on the lupin alkaloids (compare J., 1928, 1811; 1929, 1927; preceding paper), combined with the fact that Karrer and co-workers (*Helv. Chim. Acta*, 1928, **11**, 1062) advanced structure (I) in preference to (II) for lupinine on the evidence furnished by degradation, made it necessary to synthesise octahydropyridocoline (III) and certain of its derivatives. The first part of this work was accomplished some time ago and it


(I.)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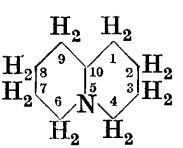
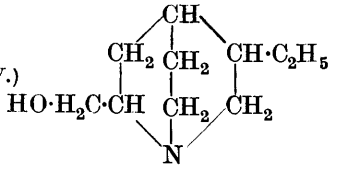
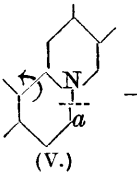

(III.)

had been intended to compare (III) with degradation products obtained from lupinine and also to synthesise structure (I) itself, but in view of the statement by Winterfeld and Holschneider (*Ber.*, 1931, **64**, 137) that they intend to synthesise (III) it is desirable to record the results so far obtained, even though the work in connexion with the latter objective is still incomplete. If lupinine is represented by (I), the elimination of carbon dioxide from lupininic acid (Willstätter and Fourneau, *Ber.*, 1902, **35**, 1917) should give octahydropyridocoline. Schöpf and co-workers (*Annalen*, 1928, **465**, 121) attempted to decide whether lupinine was the quinuclidine derivative (IV) by the soda–lime distillation of lupininic acid, but failed thus to obtain 3-ethylquinuclidine (Koenigs and Bernhart, *Ber.*, 1905,

38, 3049) or any other recognisable product. It has now been found that in addition to non-basic compounds—not fully investigated as yet—this reaction produces a basic mixture from which, after reduction with palladium and hydrogen, an inactive base, A, having the composition $C_9H_{17}N$ can be readily isolated. This base has an intense odour resembling that of oil of fennel, but the pure *base* regenerated from the picrate has a strong non-terpene-like basic odour. The *picrate*, *methiodide*, and *chloroaurate* of A are all highly crystalline and different from the corresponding derivatives of octahydropyridocoline. Further, the derivatives of A show that it is not 3-ethylquinuclidine. It appears, therefore, that either lupinine is not represented by (I) or structural changes have occurred in the production of A. Such possible changes were mentioned in Part II (*loc. cit.*), and Winterfeld and Holschneider have now repeated the same idea. The statement by Bruchhausen and Bersch (*Ber.*, 1930, **63**, 2520) that chelidonine may be derived from the berberine alkaloids by the change represented by the partial formulæ (V) and (VI) may have its counterpart in the lupinine molecule, whereby a structure such as (I), by fission at ¦ and subsequent ring closure, would give one of reduced quinoline type (VII). Such a change would account for the isolation of 2 : 3-disubstituted pyridines from lupinine by Winterfeld and Holschneider (*loc. cit.*).

(IV.)





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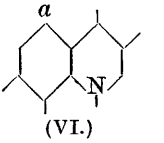
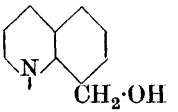
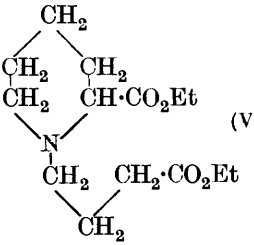


(VI.)

The synthesis of octahydropyridocoline has been effected by condensing ethyl piperidine-2-carboxylate (Willstätter, *Ber.*, 1896, **29**, 390) with γ-bromobutyronitrile (Gabriel, *Ber.*, 1889, **22**, 3336). Although ring closure of the product, *γ-2-carbethoxypiperidinobutyronitrile*, could not be effected by treatment with sodium in toluene, the *dicarboxylic ester* (VIII), prepared from the nitrile with ethyl-alcoholic hydrogen chloride, underwent the Dieckmann reaction quite smoothly, giving ethyl *1-keto-octahydropyridocoline-2-carboxylate*. Hydrolysis with dilute sulphuric acid readily gave *1-keto-octahydropyridocoline*, which, when reduced by the Clemmensen method and by sodium amalgam in ethyl alcohol gave *octahydropyridocoline* and *1-hydroxyoctahydropyridocoline* respectively. The yields throughout the foregoing operations are very satisfactory, 10 g. of commercial α-picoline—an improved and more convenient

method for the oxidation of which is described—giving, after the seven stages involved, 2·2 g. of 1-keto-octahydropyridocoline.

(VII.) 

(VIII.) 

Degradative and synthetic work, particularly with lupininic acid, the compound A, and 1-keto-octahydropyridocoline, is being actively pursued, as well as an examination of the Hofmann degradation products of octahydropyridocoline and its derivatives.

Experimental.

Methyl Lupininate and the Base A, $C_9H_{17}N$.—Lupinine (25 g.) was oxidised to lupininic acid and isolated as methyl lupininate (17·25 g.; b. p. 105—110°/1 mm. Found: N, 7·05. Calc. for $C_{11}H_{19}O_2N$: N, 7·1%) by the Willstätter and Fourneau method (*loc. cit.*) as modified by Schöpf and co-workers (*loc. cit.*). This ester (16·4 g.) was refluxed for 4 hours with concentrated hydrochloric acid (16 c.c.), the mixture evaporated to dryness under reduced pressure, and the resulting crystalline hydrochloride well mixed with soda-lime (45 g.) and carefully heated in three hard-glass tubes, a trap containing dilute hydrochloric acid being attached to the receiver. The distillate was made strongly acid with hydrochloric acid and steam-distilled; 0·4 g. of a colourless oil rapidly passed over. On fractionation, 0·2 g. distilled at 55—60°/15 mm. (Found: C, 74·5; H, 10·8%) and the remainder at 105—110°/25 mm. (Found: C, 80·3, 79·8; H, 10·4, 10·1%). The contents of the steam-distillation flask were made alkaline and again steam-distilled, and the colourless oil which quickly passed over was separated (2·5 g. approx.). As analysis subsequent to fractionation had shown some measure of unsaturation (Found for a fraction, b. p. 55—60°/0·5 mm.: C, 78·3, 78·0; H, 11·2, 11·0. $C_9H_{15}N$ requires C, 78·8; H, 11·1%) and as a crystalline picrate could not be obtained, the basic material (2·5 g.) was dissolved in glacial acetic acid (25 c.c.), palladised charcoal (0·25 g., prepared as described in Houben-Weyl's "Chemischen Methoden," 3rd. edn., vol. 2, p. 324) added, and the mixture stirred for 4 hours in an atmosphere of hydrogen. After 12 hours, a further quantity of catalyst (0·2 g.) was added, and the stirring continued for 8 hours. The reaction mixture was then filtered, a small piece

of granulated zinc added, and the bulk of the acetic acid distilled off. The residue was made strongly alkaline and steam-distilled and the volatile oil was extracted with ether, dried, and fractionated, giving the compound A (1 g.), b. p. 43—45°/0·5 mm., with an intense fennel oil odour, and a fraction B (0·35 g.), b. p. up to 60°/0·5 mm. (Found for A: C, 76·1; H, 11·8%). The base A and sulphur in ethereal solution give a light orange precipitate on treatment with hydrogen sulphide. The *picrate* of A (m. p. 186—188°), formed in alcohol and recrystallised from that solvent, formed bright yellow prisms with straight extinction and a basal cleavage and having dome-shaped ends; m. p. 193—194° (Found: C, 48·75, 49·15; H, 5·2, 5·4. $C_9H_{17}N,C_6H_3O_7N_3$ requires C, 48·9; H, 5·4%) (Found for the pure *base* regenerated from the picrate: C, 77·5, 77·5; H, 11·8, 12·2. $C_9H_{17}N$ requires C, 77·7; H, 12·2%). The *methiodide*, formed in acetone, in which it was practically insoluble, crystallised from a 5% ethyl alcohol–acetone mixture in square plates, m. p. 333—335° (decomp.) (Found: C, 42·9; H, 7·1. $C_9H_{17}N,MeI$ requires C, 42·7; H, 7·1%). The *chloroaurate* crystallised from alcohol, containing a little hydrogen chloride, in light yellow, acicular prisms, m. p. 166—167° [Found: C, 23·0; H, 3·6; Au, 41·9; *M* (for base), 131. $C_9H_{17}N,HAuCl_4$ requires C, 22·5; H, 3·8; Au, 41·2%; *M*, 139].

When fraction B was redistilled, almost the whole passed over at 55—60°/0·5 mm.: it has not yet been possible to prepare a crystalline picrate.

Pyridine-2-carboxylic Acid.—Commercial α-picoline (20 g.) and potassium permanganate (36 g.) in water (900 c.c.) were heated in a water-bath and more permanganate (36 g.) in water (400 c.c.) was added as the colour was destroyed. The oxide was filtered off and well washed, and 200 c.c. were distilled from the filtrate and used in the next oxidation. The remainder was almost neutralised with dilute sulphuric acid, evaporated until crystals appeared, cooled, filtered from potassium sulphate (which was washed with a little aqueous alcohol), and made slightly acid. Excess of hot saturated copper sulphate solution was added and the precipitate was collected, washed, suspended in boiling water (150 c.c.), and decomposed with hydrogen sulphide. The filtered solution was evaporated to dryness, whereby pyridine-2-carboxylic acid (22 g. or 80%), m. p. 130—132°, was obtained: the distillate was used in the decomposition of the next batch of copper picolinate.

Ethyl Piperidine-2-carboxylate.—Pyridine-2-carboxylic acid (10 g.) was refluxed in dry amyl alcohol (400 c.c.), and sodium (32 g.) added. The resulting solution was poured into water (400 c.c.), the alcohol was separated and extracted twice with water, and the combined

aqueous solutions were acidified with hydrochloric acid and evaporated under reduced pressure. The residue was extracted three times with absolute alcohol (200 c.c. in all), the alcohol removed, and the residue refluxed with absolute alcohol (50 c.c.) and concentrated sulphuric acid (10 c.c.) for 10 hours. The alcohol was removed, the acid nearly neutralised with sodium hydroxide (15%), and the solution saturated with potassium carbonate and extracted with ether. The extract on fractionation gave ethyl piperidine-2-carboxylate (6·1 g. or 50%), b. p. 92°/12 mm. (Found: N, 8·8. Calc.: N, 8·9%).

γ-2-Carbethoxypiperidinobutyronitrile.—Ethyl piperidine-2-carboxylate (4·71 g.), γ-bromobutyronitrile (4·44 g.), and powdered anhydrous potassium carbonate (4·5 g.) were heated for 45 minutes on the water-bath with occasional stirring. Water was added, and the resulting oil extracted with ether and fractionated, giving *γ-2-carbethoxypiperidinobutyronitrile* (5·5 g.; almost 90%), b. p. 170°/12 mm. (Found: N, 12·6. $C_{12}H_{20}O_2N_2$ requires N, 12·5%).

When excess of γ-bromobutyronitrile was used, a *quaternary* salt (colourless plates, m. p. 184°, from acetone) was formed.

Ethyl γ-2-Carbethoxypiperidinobutyrate (VIII).—A solution of the above nitrile (7 g.) in absolute alcohol (30 c.c.) was cooled in ice, saturated with dry hydrogen chloride, warmed slightly for 2 hours, and refluxed gently for a further 2 hours. The ammonium chloride (1·6 g.) was filtered off, the filtrate evaporated under reduced pressure, and the residue dissolved in water (10 c.c.), made alkaline with sodium hydroxide (15%), and extracted immediately with ether. The extract on fractionation gave *ethyl γ-2-carbethoxypiperidinobutyrate* (6·4 g.; 75%), b. p. 169°/14 mm. (Found: N, 5·3. $C_{14}H_{25}O_4N$ requires N, 5·2%).

Ethyl 1-Keto-octahydropyridocoline-2-carboxylate.—Sodium (0·9 g.) was finely powdered under toluene (8 c.c.), and heated on the water-bath while the above dicarboxylic ester (5·4 g.) was gradually added. The mixture turned dark brown and after 2 hours alcohol was added to dissolve any remaining sodium. Water (3 c.c.) was then added and the solution (C) was acidified with dilute hydrochloric acid, made alkaline with sodium bicarbonate, and extracted with ether. The extract on distillation gave *ethyl 1-keto-octahydropyridocoline-2-carboxylate*, an orange-coloured oil (2·3 g.; 50%), b. p. 155°/15 mm. (Found: N, 6·25. $C_{12}H_{19}O_3N$ requires N, 6·2%).

1-Keto-octahydropyridocoline.—The above solution (C) was neutralised, made up to 20% with sulphuric acid, heated for 3 hours on the water-bath, cooled, made alkaline with sodium hydroxide (30%), and extracted with ether. On fractionation of the extract, *1-keto-octahydropyridocoline* (2·1 g.; 70% calc. on the ester VIII) distilled as a yellowish oil, b. p. 107°/14 mm. (Found: C, 70·4; H, 9·7; N,

9·3. $C_9H_{15}ON$ requires C, 70·6; H, 9·8; N, 9·2%). The *semicarbazone* crystallised from alcohol in colourless plates, m. p. 215° (Found: C, 57·3; H, 8·6. $C_{10}H_{18}ON_4$ requires C, 57·1; H, 8·6%). The *methiodide* formed colourless plates, m. p. 210°, from glacial acetic acid (Found: C, 40·5; H, 6·3. $C_{10}H_{18}ONI$ requires C, 40·7; H, 6·1%).

Octahydropyridocoline (III).—A mixture of 1-keto-octahydropyridocoline (1 g.), amalgamated zinc (5 g.), and concentrated hydrochloric acid (7 c.c.) was kept for 2 hours and then refluxed for 24 hours. The decanted solution was made strongly alkaline and steam-distilled, and the distillate extracted with ether. The extract on fractionation gave *octahydropyridocoline* (0·55 g.; 60%), b. p. 43°/0·5 mm., 75°/14 mm. (Found: C, 77·5; H, 12·1. $C_9H_{17}N$ requires C, 77·7; H, 12·2%). The compound is slightly soluble in water, giving a solution alkaline to litmus, and has a paralysing action on the throat. It gives, together with sulphur in ethereal solution, an orange precipitate when it is treated with hydrogen sulphide. The *picrate* crystallised from alcohol in yellow prisms with flat rectangular ends; m. p. 213° (decomp.) alone and 195—200° when mixed with the picrate of A (Found: C, 49·0; H, 5·3. $C_9H_{17}N,C_6H_3O_7N_3$ requires C, 48·9; H, 5·4%). The *methiodide* crystallised from acetone in large prisms with pointed ends; m. p. 283° (Found: C, 43·0; H, 7·5. $C_{10}H_{20}NI$ requires C, 42·7; H, 7·1%). The *chloroaurate* formed old-gold plates, m. p. 170°, depressed to 155—160° by admixture with the chloroaurate of A [Found: C, 23·0; H, 3·5; Au, 41·5; *M* (for base), 135. $C_9H_{17}N,HAuCl_4$ requires C, 22·5; H, 3·8; Au, 41·2%; *M*, 139].

1-*Hydroxyoctahydropyridocoline*.—A mixture of 1-keto-octahydropyridocoline (0·5 g.), sodium amalgam (12 g., 4%), and absolute alcohol (5 c.c.) was refluxed over-night. The alcoholic solution was decanted and, after addition of water (6 c.c.), extracted with ether. The extract on fractionation gave 1-*hydroxyoctahydropyridocoline* (0·4 g.; 75%), b. p. 120°/13 mm., which solidified to a white solid, m. p. 65—68° (Found: N, 9·0. $C_9H_{17}ON$ requires N, 9·0%).

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