307. *The Lupin Alkaloids. Part XI. The Octahydropyridocoline–norLupinane Relationship.*

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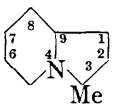
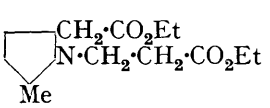
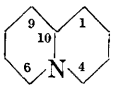
In Part VIII (J., 1935, 1743) we reported the synthesis of 3-methyloctahydropyrrocoline (I).*



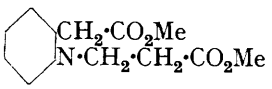
(I.)



(II.)



(III.)



(IV.)

Only one of the four possible stereoisomers was produced by the method there employed, and in an attempt to prepare others, and in order to gain further knowledge on the isomerism displayed by octahydropyridocoline and *nor*lupinane, we have built up the piperidine ring on the pyrrolidine ring by condensing ethyl 2-methylpyrrolidine-5-acetate (this vol., p. 607) with ethyl β-chloropropionate, giving *ethyl 2-methylpyrrolidine-5-acetate-1-β-propionate* (II). Ring closure of this by the Dieckmann method gave *7-keto-3-methyloctahydropyrrocoline*. The Clemmensen reduction of this ketone was not as satisfactory as reduction by the Wolff method. The 3-methyloctahydropyrrocoline obtained, however, was identical with the compound obtained in Part VIII. A by-product of higher boiling point was also produced in the Wolff reduction, but it has not yet been fully investigated.

* This was there erroneously called the 2-methyl derivative. The 3-hydroxy- and 3-keto-derivatives should be designated the 2-hydroxy- and 2-keto- respectively.

In previous papers (J., 1932, 2959; 1935, 1743) the synthesis of *nor*lupinane (III) has been described and it has also been shown (J., 1931, 437) that the Clemmensen reduction of 1-keto-octahydropyridocoline gives an isomeric octahydropyridocoline.

In order to gain a deeper insight into this question we have now ring-closed the *ester* (IV) to give the only hitherto undescribed keto-octahydropyridocoline, *viz.*, the 2-*compound*, and this on reduction also gives *nor*lupinane.

Of all the ring-closure methods used, therefore, to synthesise the system (III) it is remarkable that the only one leading to the isomeric octahydropyridocoline is the Clemmensen reduction of 1-keto-octahydropyridocoline. It was accordingly of interest to examine the Wolff reduction of this keto-compound, and, surprisingly enough, this leads to the production of pure *nor*lupinane together with some much higher boiling basic material.

These two reduction results obtained with the 1-keto-derivative of (III), which alone can enolise by migration of the hydrogen atom attached to the tertiary carbon atom 10, may be taken to support the *cis-trans* formulation of octahydropyridocoline and *nor*lupinane advanced in Part VI (J., 1932, 2959). At present we know little of the actual mechanism of these reduction processes, but it is worth noting that in two recent cases (J., 1935, 1743; this vol., p. 606) the Clemmensen reduction has ended at the hydroxy-stage.

Experimental.

Ethyl 2-Methylpyrrolidine-5-acetate-1-β-propionate.—Ethyl 2-methylpyrrolidine-5-acetate (2·2 g.), ethyl β-chloropropionate (2 g.), and sodium acetate (2 g.) were heated together for 5 hours on the water-bath. Water was added, then potassium hydroxide solution (50%) till strongly alkaline, and the oil was extracted with ether, dried, and distilled (2·6 g., b. p. 168—169°/14 mm.) (Found: C, 61·7; H, 9·4. $C_{14}H_{25}O_4N$ requires C, 62·0; H, 9·2%).

7-Keto-3-methyloctahydropyrrocoline.—The above ester (3·5 g.) was added to potassium (1 g.) powdered under xylene (10 c.c.). After the first vigorous reaction had abated, the whole was heated for 3 hours on the water-bath, alcohol added to dissolve unused potassium, then water (7 c.c.) and concentrated hydrochloric acid (30 c.c.), and the solution was heated for 14 hours in the water-bath. After evaporation to dryness the residue was basified with potassium hydroxide solution (50%), and the *ketone* extracted with ether; it distilled as a colourless unstable oil (1·2 g., b. p. 72—75°/1 mm.) (Found: C, 70·5; H, 10·2. $C_9H_{15}ON$ requires C, 70·6; H, 9·8%). The *picrate* formed yellow prisms, m. p. 204° (Found: C, 47·4; H, 4·9. $C_9H_{15}ON,C_6H_3O_7N_3$ requires C, 47·1; H, 4·7%), and the picrolonate dull yellow prisms, m. p. 203°.

3-Methyloctahydropyrrocoline.—The ketone (1·4 g.) and hydrazine hydrate (0·8 g. of 95%) were refluxed for 10 hours, the hydrazone dried in ethereal solution, and the ether removed. The residual oil (1·3 g.) was heated at 160—170° for 12 hours in a sealed tube with sodium ethoxide, from sodium (0·8 g.) and absolute alcohol (15 c.c.). Water (10 c.c.) and excess of hydrochloric acid were added, and the solution evaporated to dryness. The base was liberated by potassium hydroxide solution (50%), extracted with ether, dried, and distilled (0·1 g., b. p. 27°/1 mm.) (Found: C, 77·4; H, 12·4. Calc. for $C_9H_{17}N$: C, 77·7; H, 12·2%). The picrate formed bright yellow prisms, m. p. 197°, not depressed by admixture with the picrate, m. p. 197°, described in Part VIII (Found: C, 49·2; H, 5·7. Calc. for $C_9H_{17}N,C_6H_3O_7N_3$: C, 48·9; H, 5·4%), and the picrolonate, reddish-brown prisms, m. p. 208°, not depressed by the picrolonate obtained in Part VIII (Found: C, 56·65; H, 6·5. Calc. for $C_9H_{17}N,C_{10}H_8O_5N_4$: C, 56·6; H, 6·2%). A viscous colourless liquid was also produced (0·4 g.), b. p. 95°/1 mm. (Found: C, 68·6; H, 10·7%); the picrate separated in bright yellow prisms, m. p. 143°, from alcohol, in which it was very soluble; and the *picrolonate* as reddish-brown prisms, m. p. 245° (decomp.) (Found: C, 54·9; H, 6·2%).

Methyl Piperidine-2-acetate-1-β-propionate.—Methyl piperidine-2-acetate (1·6 g.), methyl β-chloropropionate (1·4 g.), and anhydrous sodium acetate (1·6 g.) were heated for 2 hours in a loosely corked tube in the water-bath. Water and excess of potassium carbonate solution were added and the *oil* was taken up in ether, dried with sodium sulphate, and fractionated, giving 1·1 g., b. p. 170—175°/1 mm. The latter redistilled at 170—172°/1 mm. (Found: C, 58·8, 59·0; H, 8·3, 8·6. $C_{12}H_{21}O_4N$ requires C, 59·2; H, 8·6%).

2-Keto-octahydropyridocoline.—The above ester (3·5 g.) was added to potassium (1 g.) powdered under toluene. After the vigorous reaction subsided, the mixture was heated for

1½ hours on the water-bath, alcohol (2 c.c.) added to dissolve unused potassium, and the whole evaporated. The residue was taken up in water (3 c.c.), concentrated hydrochloric acid (10 c.c.) added, and the heating continued for another 7 hours. After evaporation to dryness, and basification (50% potassium hydroxide solution) the *ketone* was taken up in ether, dried, and distilled (0·8 g., b. p. 70—75°/1 mm.). It redistilled at 70—72°/1 mm., and rapidly turned brown in the air (Found : C, 70·4; H, 9·8. $C_9H_{15}ON$ requires C, 70·6; H, 9·8%). The *picrate* formed old-gold prisms, m. p. 211° (Found : C, 47·6; H, 4·7. $C_9H_{15}ON,C_6H_3O_7N_3$ requires C, 47·6; H, 4·8%).

nor*Lupinane*.—The ketone (0·5 g.) in concentrated hydrochloric acid (10 c.c.) was refluxed with amalgamated zinc (5 g.) for 18 hours. From the product, worked up in the usual way, *nor*lupinane (0·15 g., b. p. 38—40°/1 mm.) was obtained. The picrate had m. p. 194°, and the picrolonate, m. p. 245°, not depressed by admixture with specimens prepared from lupinine.

Reduction of 1-*Keto-octahydropyridocoline to Octahydropyridocoline and* nor*Lupinane*.—The Clemmensen reduction of the keto-compound (0·5 g.) was carried out as described in J., 1931, 437, and gave the base (0·15 g.), picrate (m. p. 213°), picrolonate (m. p. 189°), and methiodide (m. p. 281°) as recorded for octahydropyridocoline. A further portion of the ketone (0·95 g.) was reduced by the Wolff method, giving 0·14 g., b. p. 40°/1 mm., and 0·15 g., b. p. 95°/1 mm. The former fraction gave a picrate, m. p. 194°, picrolonate (prisms from acetic acid), m. p. 245°, and methiodide, m. p. 321°, thus being proved to be pure *nor*lupinane.

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