# 409. *The Lupin Alkaloids. Part VIII.*

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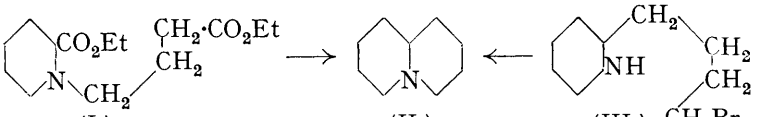
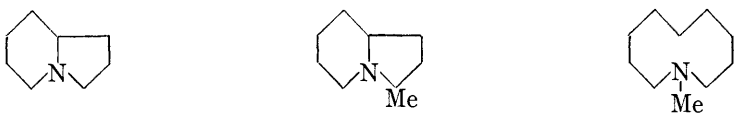
In J., 1931, 437, 3190, we reported the preparation of norlupinane (A) by the elimination of carbon dioxide from lupininic acid, and, on the basis of Karrer's formula for lupinine (*Helv. Chim. Acta*, 1928, **11**, 1062), this should have the structure (II). Our first synthesis



(I.) (II.) (III.)

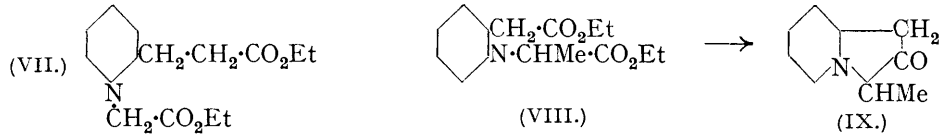
(J., 1931, 437), depending on the ring closure of (I) by the Dieckmann method, led to an isomeric base (B), but a later method (J., 1932, 2959), involving cyclisation of (III), led to (A). The suggestion was made that (A) and (B) might be stereoisomerides of the *cis*- and *trans*-decalin type. This view is strengthened by the fact that Clemo and Ramage (J., 1932, 2969) showed that octahydropyrrocoline (IV) occurs in two forms; further, (II) should give *cis*- and *trans*-methiodides. The fact that (A) and (B) each give one only supports the above view. In the preparation of (III), however, a Bouveault reduction was used, and there is a possibility that this reaction might have caused ring crumpling, resulting in (A) being (V), which could, like (II), give 1-methyl-2-*n*-butylpiperidine (C)



(IV.) (V.) (VI.)

among the products resulting from its Hofmann degradation and subsequent reduction (J., 1932, 2959). If (A) is (V), however, it is difficult to see why (B) also does not give (C) on this treatment; instead, it gives two other isomeric bases, (D) and (E), which are also obtained from (A). Further work on (E) (*loc. cit.*) suggests it is 1-methyl*cyclo*azadecane (VI). (D) was never obtained in sufficient quantity to enable its structure to be investigated, but, judging from a study of models, (VI) may well exist in more than one stereoisomeric form, the extremely tight packing of the atoms preventing the free rotations necessary for their interconversion, and the stresses introduced by thermal agitation resulting in the isomerisation to an open-chain base when the methochloride is distilled (compare Ruzicka, *Chem. and Ind.*, 1935, **54**, 2).

It was clearly desirable to synthesise (A) by a method not involving the use of the sodium and alcohol reduction common to the synthesis referred to above and that of Winterfeld and Holschneider (*Annalen*, 1932, **499**, 109). This has now been accomplished by reducing the quaternary salt formed from *ethyl pyridyl*-2-β-*propionate* and ethyl bromoacetate to *ethyl piperidyl*-1-*acetate*-2-β-*propionate* (VII), performing the Dieckmann ring closure on this, and reducing the resulting 3-*keto-octahydropyridocoline* by the Clemmensen method. The resulting base gave a picrate and picrolonate identical with the corresponding derivatives of norlupinane obtained from lupinine. The yield of the ring closure was much less than in the case of the analogous reaction leading to the formation of (B), and there are indications that some of this compound is also produced, since several recrystallisations of the derivatives are necessary before the melting points attain constant values.



(VII.) (VIII.) (IX.)

Structure (V) should, if the above views are correct, occur in four stereoisomeric forms, and we have been able to prepare one of them. *Ethyl pyridyl*-2-*acetate* is reduced to the

*piperidyl* ester. This can be condensed with ethyl α-bromopropionate, giving *ethyl piperidyl-2-acetate-1-α-propionate* (VIII). The Dieckmann ring closure of this gave an excellent yield of *3-keto-2-methyloctahydropyrrocoline* (IX), but attempts to reduce this by the Clemmensen method ended at the 3-hydroxy stage; the Wolff reduction, however (*Annalen*, 1912, **394**, 86), gives *2-methyloctahydropyrrocoline* (V). Its crystalline derivatives differ from those of either of the forms of octahydropyridocoline, and the base itself is more stable, showing no sign of decoloration after several days.

## Experimental.

*Ethyl pyridyl-2-β-propionate*, obtained by stirring a glacial acetic acid solution of ethyl pyridylacrylate (5 g.) and palladised charcoal (0·2 g.) in an atmosphere of hydrogen, boiled at 95°/1 mm. (Found: C, 66·5; H, 7·2. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·3%), and formed a *picrolonate*, m. p. 141° (Found: C, 54·2; H, 4·85; N, 15·6. $C_{10}H_{13}O_2N,C_{10}H_8O_5N_4$ requires C, 54·2; H, 4·7; N, 15·8%), and a *picrate*, large, yellow, lozenge-shaped prisms, m. p. 84° (Found: C, 47·35; H, 4·3. $C_{10}H_{13}O_2N,C_6H_3O_7N_3$ requires C, 47·1; H, 3·9%).

*Ethyl pyridinium-1-acetate-2-β-propionate bromide* was formed by refluxing the above ester (5 g.) and ethyl bromoacetate (5 g.) in acetone (25 c.c.) for 6 hours. It formed colourless plates (5 g., m. p. 159°) from acetone containing a little alcohol (Found: C, 48·1, 48·8; H, 6·0, 6·2. $C_{14}H_{20}O_4NBr$ requires C, 48·5; H, 5·8%).

*Ethyl Piperidyl-1-acetate-2-β-propionate.*—The quaternary bromide (10 g.) in water (60 c.c.) and glacial acetic acid (10 c.c.) was shaken with platinum oxide (0·1 g.) in hydrogen at 100 lb./sq. in. for 18 hours. After filtration and removal of solvents the residue was basified (potassium carbonate) and extracted with ether. On fractionation the *ester* was obtained as a colourless oil (6 g., b. p. 138—140°/1 mm.) (Found: C, 62·1; H, 9·4. $C_{14}H_{25}O_4N$ requires C, 62·1; H, 9·2%).

*3-Keto-octahydropyridocoline.*—The reduced ester (5 g.) was added in small portions to potassium (1·4 g.) powdered under toluene (15 c.c.). After 2 hours' heating on the water-bath, alcohol was added to dissolve unused potassium, then water (10 c.c.) and concentrated hydrochloric acid (40 c.c.), the whole was refluxed for 18 hours and evaporated to dryness, and the residue basified (50% potassium hydroxide solution); the *keto*-compound, extracted with ether, was a colourless oil (0·6 g., b. p. 74—76°/1 mm.) (Found: C, 70·2, 70·8; H, 9·7, 10·2. $C_9H_{15}ON$ requires C, 70·6; H, 9·8%). The *picrate* formed yellow needles, m. p. 185°, very soluble in alcohol (Found: C, 47·4; H, 5·2. $C_9H_{15}ON,C_6H_3O_7N_3$ requires C, 47·1; H, 4·7%).

*Norlupinane* (*Octahydropyridocoline A*).—The ketone (1·3 g.) in concentrated hydrochloric acid (25 c.c.) was refluxed for 18 hours with amalgamated zinc (15 g.). From the product, worked up in the usual way, norlupinane (0·5 g., b. p. 74—76°/14 mm.) was obtained (Found: N, 10·2. Calc. for $C_9H_{17}N$: N, 10·1%). The picrate melted at 194° alone or mixed with a specimen obtained from the alkaloid (Found: C, 48·9; H, 5·4. Calc. for $C_9H_{17}N,C_6H_3O_7N_3$: C, 48·9; H, 5·4%), and the picrolonate at 245° alone or mixed with a specimen from the same source (Found: C, 56·6; H, 5·7. Calc. for $C_9H_{17}N,C_{10}H_8O_5N_4$: C, 56·6; H, 6·2%).

*Ethyl pyridyl-2-acetate*, prepared in the same way as the methyl ester (Oparina, *Chem. Zentr.*, 1935, I, 2536), was a pale greenish-yellow oil, b. p. 134—135°/21 mm. (Found: C, 65·6; H, 6·75. $C_9H_{11}O_2N$ requires C, 65·4; H, 6·7%). The *picrate* formed yellow acicular prisms with oblique ends, m. p. 136—137° (Found: C, 46·1; H, 3·6. $C_9H_{11}O_2N,C_6H_3O_7N_3$ requires C, 45·7; H, 3·5%).

*Ethyl Piperidyl-2-acetate.*—The pyridyl ester (5 g.) in glacial acetic acid (15 c.c.) was shaken for 12 hours with platinum oxide (0·1 g.) in hydrogen at 100 lb./sq. in., and the acid removed under reduced pressure. After basification (potassium hydroxide and solid potassium carbonate) the *ester* was extracted with ether and distilled (3·8 g., b. p. 105°/14 mm.) (Found: C, 63·0; H, 9·8. $C_9H_{17}O_2N$ requires C, 63·2; H, 9·9%). The *picrate* formed clusters of square-ended prisms, m. p. 125° (Found: C, 45·3; H, 5·3. $C_9H_{17}O_2N,C_6H_3O_7N_3$ requires C, 45·0; H, 5·0%). In some cases a deliquescent solid, m. p. 68°, was obtained along with the ester: this has not yet been investigated (Found: C, 57·4; H, 9·2%).

*Ethyl piperidyl-2-acetate-1-α-propionate* was formed by heating ethyl piperidyl-2-acetate (3 g.), ethyl α-bromopropionate (3·4 g.), and potassium carbonate (6 g.) in a sealed tube in the water-bath for 18 hours. Water was added, and the oil taken up in ether, dried, and distilled (2·5 g., b. p. 135—140°/1 mm.) (Found: C, 62·0; H, 9·3. $C_{14}H_{25}O_4N$ requires C, 62·0; H, 9·2%).

*3-Keto-2-methyloctahydropyrrocoline.*—The ethyl ester (5 g.) was added to potassium (2 g.)

powdered under toluene (15 c.c.). After the first vigorous reaction had abated, the whole was heated for 4 hours on the water-bath, alcohol added to dissolve unused potassium, then water (10 c.c.) and concentrated hydrochloric acid (50 c.c.), and the solution heated for 18 hours on the water-bath. After evaporation to dryness, excess of potassium hydroxide solution (50%) was added, and the *ketone* extracted and distilled (1·9 g., b. p. 67—69°/1 mm.) (Found : C, 70·4; H, 9·7. $C_9H_{15}ON$ requires C, 70·6; H, 9·8%). The *picrate* formed yellow prisms, m. p. 162° (Found : C, 47·1; H, 4·9. $C_9H_{15}ON,C_6H_3O_7N_3$ requires C, 47·1; H, 4·7%).

3-*Hydroxy*-2-*methyloctahydropyrrocoline*.—The ketone (0·3 g.) was boiled with amalgamated zinc wool (3 g.) and concentrated hydrochloric acid (5 c.c.) for 18 hours, the liquid evaporated, fresh amalgamated zinc wool (3 g.) and fuming hydrochloric acid (5 c.c.) added, and the boiling continued for 24 hours. After evaporation to dryness and basification (50% potassium hydroxide solution), 0·15 g. of oil was obtained, b. p. 100—105°/16 mm. (Found : C, 69·7; H, 11·3; N, 9·2. $C_9H_{17}ON$ requires C, 69·7; H, 11·0; N, 9·0%). The *picrate* formed narrow elongated plates with one oblique end, m. p. 159°, depressed to 140° by admixture with the picrate of the above ketone (Found : C, 47·2; H, 5·5. $C_9H_{17}ON,C_6H_3O_7N_3$ requires C, 46·9; H, 5·2%), and the *picrolonate*, orange-yellow prisms, m. p. 181° (Found : C, 54·4; H, 6·1. $C_9H_{17}ON,C_{10}H_8O_5N_4$ requires C, 54·4; H, 6·0%).

2-*Methyloctahydropyrrocoline*.—The ketone (1·5 g.) and hydrazine hydrate (0·7 g., 95%) were refluxed for 8 hours, the hydrazone dried in ethereal solution with potassium carbonate, and the ether removed. The residue (1·2 g.) was heated at 160—170° for 16 hours in a sealed tube with sodium (0·8 g.) dissolved in alcohol (10 c.c.). After addition of water (10 c.c.), acidification (hydrochloric acid), evaporation to dryness, and basification (50% potassium hydroxide solution), the base was extracted with ether and distilled (0·42 g., b. p. 32—35°/1 mm.) (Found : C, 78·1; H, 12·3. $C_9H_{17}N$ requires C, 77·7; H, 12·2%). The *picrate* formed yellow dendritic clusters, m. p. 197°, depressed to 194°, after considerable softening, by admixture with norlupinane picrate of m. p. 195°, and to 191° in another experiment (Found : C, 49·0; H, 5·5. $C_9H_{17}N,C_6H_3O_7N_3$ requires C, 48·9; H, 5·4%). The *picrolonate* formed light brown prisms, m. p. 208° (Found : C, 56·75; H, 6·2. $C_9H_{17}N,C_{10}H_8O_5N_4$ requires C, 56·6; H, 6·2%).

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