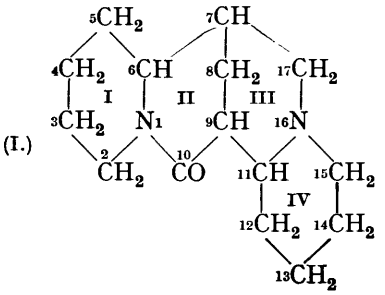
226. *The Lupin Alkaloids. Part X. The Synthesis of* dl-*Oxysparteine.*

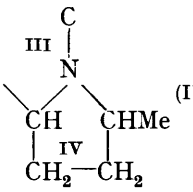
By G. R. CLEMO, W. McG. MORGAN, and R. RAPER.

IN Part VII (J., 1933, 644) we suggested arguments based on degradation evidence for formula (I) for oxysparteine,* which differed from the skeleton (II) favoured by Ing for

(I.)



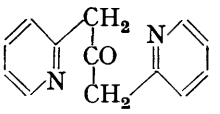
(II.)



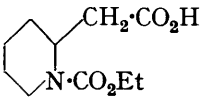
anagyrine in having ring IV six-membered. Since that time we have been engaged on synthetic work with the object of differentiating between these alternatives, and have recently succeeded in synthesising the structure (I).

One of our first schemes for accomplishing this was to bring about a Claisen condensation between two molecules of methyl pyridyl-2-acetate, followed by ketone hydrolysis, yielding (III). This was then to be submitted to catalytic reduction, and we hoped, by condensing

(III.)



(IV.)



the product with two molecules of formaldehyde, to obtain 8-ketosparteine, from which, by reduction, *dl*-sparteine (deoxylupanine; Part I, J., 1928, 1811) would be formed. It was, however, impossible to bring about the Claisen condensation satisfactorily, repeated

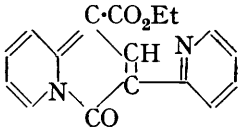
* In our original paper the carbonyl group of oxysparteine was placed at C_{17}. This is equivalent to the position C_{10}; this latter makes the numbering of the synthetic intermediates more straightforward.

attempts under widely varying conditions giving either no reaction or complex solid products of m. p. 177° or 295°. The same results were obtained with the ethyl ester. It was next attempted, but again without success, to bring about a Claisen condensation between two molecules of methyl piperidyl-2-acetate, and its 1-benzoyl derivative, and between two molecules of the 1-*carbethoxy*-derivative of the ethyl ester. In the first two cases no reaction took place, and in the last we obtained a solid which analysis indicates to be 1-*carbethoxypiperidyl-2-acetic acid* (IV) (compare Schotten, *Ber.*, 1882, **15**, 425; 1883, **16**, 643).

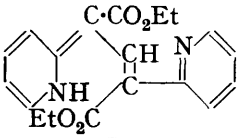
Distillation of the barium salt of pyridyl-2-acetic acid gave only 2-picoline, and the corresponding hexahydro-derivative gave a mixture of indefinite boiling point from which no recognisable product has been isolated.

As none of these methods seemed likely to lead to the accomplishment of our object, we have not yet fully examined the products.

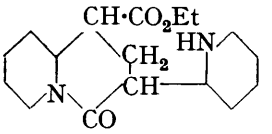
Finally, taking advantage of the fact that the methylene group of ethyl pyridyl-2-acetate has many of the properties of that of a 1 : 3-diketone, we condensed this ester with ethyl orthoformate in the presence of acetic anhydride; 1-*carbethoxy*-4-*keto*-3-(2′-*pyridyl*)-



(V.)



(VI.)



(VII.)

pyridocoline (V) was obtained as a yellow crystalline compound whose solutions exhibit an intense green fluorescence. This substance was doubtless formed by ring closure of the tautomeric form of the bis-methenyl compound (VI) (compare Claisen, *Annalen*, 1897, **297**, 16). The electrolytic reduction of the carbonyl group 4 of (V) was then unsuccessfully attempted in the hope of obtaining *dl*-oxysparteine (*iso*lupanine; Part I, *loc. cit*) by amide formation between the carbethoxy-group 17 and the secondary nitrogen atom 16 of the fully reduced derivative. Finally (V) was reduced catalytically, giving 1-*carbethoxy*-4-*keto*-3-(2′-*piperidyl*)*octahydropyridocoline* (VII). By submitting this to the Bouveault reduction the corresponding 1-*carbinol* (VIII) was obtained, which, with phosphorus pentabromide, gave 1-*bromomethyl*-4-*keto*-3-(2′-*piperidyl*)*octahydropyridocoline* (IX).

Unfortunately we have not been able to obtain (VII), (VIII), or (IX) in a state of purity. They are thick oils, and on distillation, even in a high vacuum, partial ring closure appears to take place between positions 16 and 17, yielding inseparable mixtures which give indefinite analyses and from which we have not yet been able to obtain pure crystalline derivatives. If, however, the crude substance (IX) is heated in a sealed tube with anhydrous potassium carbonate, *dl*-oxysparteine (I) is obtained, identical with that obtained by the alkaline ferricyanide oxidation of *dl*-sparteine. The synthetic base, its hydriodide and monomethiodide, and those obtained from natural sources, give no depression in mixed melting point tests, and a crystallographic examination carried out for us by Mr. S. Tomkeieff revealed no essential differences.

The identity of the synthetic product with that obtained from the alkaloid establishes the ring structure (I) as fundamental for the C_{15} lupin alkaloids, and also for anagyrine and aphyllin. This nucleus can occur in many other stereoisomeric forms, which probably occur in matrin and the alkaloids of *Sophora tomentosa*, *S. lanceolata*, and *S. alopecuroides*.

This work is being actively followed up, with the intentinn of obtaining the optically active forms of the alkaloids themselves.

Experimental.

Attempted Claisen Condensation of Methyl Pyridyl-2-acetate.—Methyl pyridyl-2-acetate (6·5 g.) was added to sodium methoxide (from 0·5 g. of sodium) in benzene (20 c.c.), the whole refluxed for 4 hours, the solvent removed, ice-water added, and the solution acidified (acetic acid), then basified (sodium bicarbonate), and ether-extracted (*). On distillation, unchanged ester (2 g., b. p. 136°/25 mm.—identified as picrate) passed over, leaving a dark brown residue

which solidified, and formed yellow rectangular prisms (0·7 g., m. p. 177°) from methyl alcohol [Found : C, 69·6, 69·1; H, 4·95, 4·8; N, 9·7, 10·0; *M* (Rast), 266, 273, 271]. This solid (0·45 g.) in glacial acetic acid (6 c.c.) was shaken with platinum oxide (0·05 g.) for 21 hours in hydrogen at 100 lb./in.². On working up, a colourless solid (0·2 g., m. p. 129°) was obtained (Found : C, 69·5, 70·0; H, 5·6, 5·95%). The solid, m. p. 177°, was unchanged on prolonged heating with concentrated hydrochloric acid. The aqueous layer from the ethereal extract (*), diluted and filtered, gave a small amount of yellow solid which, recrystallised from benzene, formed pale yellow needles, m. p. 295° (Found : C, 71·4; H, 4·9%). Under various conditions, different proportions of these solids were obtained.

Ethyl 1-*Carbethoxypiperidyl*-2-*acetate*.—Ethyl piperidyl-2-acetate (J., 1935, 1744) (4 g.), ethyl chloroformate (2·5 g.), and anhydrous sodium carbonate (excess) were left for 18 hours in ether (80 c.c.); the filtered solution, on fractionation, gave *ethyl* 1-*carbethoxypiperidyl*-2-*acetate* (5 g.), b. p. 148—150°/9 mm. (Found : C, 59·3; H, 8·6. $C_{12}H_{21}O_4N$ requires C, 59·6; H, 8·6%).

1-*Carbethoxypiperidyl*-2-*acetic Acid*.—The above ester (2 g.) in benzene (2 c.c.) was added to sodium ethoxide (from sodium, 0·1 g.) in benzene (5 c.c.), and refluxed for 6 hours. The benzene was removed, water (2 c.c.) and concentrated hydrochloric acid (10 c.c.) added, and the whole heated for 12 hours on the water-bath. After evaporation to dryness, excess of potassium carbonate solution was added and the brown oil which was thrown out was separated, taken up in water, and acidified with hydrochloric acid. Ether-extraction gave an oil (0·17 g.), b. p. 165—170°/1 mm., which crystallised on standing, and gave colourless crystals, m. p. 65°, from light petroleum (b. p. 40—60°) (Found : C, 55·6; H, 7·9. $C_{10}H_{17}O_4N$ requires C, 55·8; H, 7·9%).

1-*Carbethoxy*-4-*keto*-3-(2′-*pyridyl*)*pyridocoline* (V).—Ethyl pyridyl-2-acetate (16 g.), ethyl orthoformate (15 g.), and acetic anhydride (19 c.c.) were refluxed for 2 hours, and the bulk of the acetic anhydride removed on the water-bath in a vacuum. The residue was distilled in a vacuum, giving 3·2 g. up to 140°/1 mm., 5·7 g. at about 160°/1 mm., and 10 g., b. p. 250—255°/1 mm. The last fraction rapidly solidified, and gave yellow prisms, m. p. 126°, from light petroleum (b. p. 80—100°) (Found : C, 69·5, 69·7; H, 4·7, 4·5; N, 9·8. $C_{17}H_{14}O_3N_2$ requires C, 69·4; H, 4·8; N, 9·5%). The *picrate* formed small yellow prisms, m. p. 216°, from alcohol (Found : C, 53·0; H, 3·5. $C_{17}H_{14}O_3N_2,C_6H_3O_7N_3$ requires C, 52·85; H, 3·25%).

1-*Carbethoxy*-4-*keto*-3-(2′-*piperidyl*)*octahydropyridocoline* (VI).—The ester (V) (10 g.) in glacial acetic acid (100 c.c.) was shaken for 40 hours with platinum oxide (0·5 g.) in hydrogen at 100 lb./in.², the catalyst filtered off, and the acetic acid removed on the water-bath under reduced pressure. The residue was basified (saturated potassium carbonate solution) and extracted with ether, and the ether removed, leaving a thick gum (9·3 g.). From a preliminary experiment we obtained a similar gum, which gave, on distillation, a thick oil, b. p. 200—210°/1 mm. with some decomposition (Found : C, 66·9; H, 9·0. $C_{17}H_{28}O_3N_2$ requires C, 66·2; H, 9·1%).

dl-*Oxysparteine*.—The above gum (9·3 g.) in absolute ethyl alcohol (30 c.c.) was added to sodium (20 g.) kept at 170° in an oil-bath, more alcohol (300 c.c. in all) being added to dissolve the metal. Water was added, and then concentrated hydrochloric acid to produce an acid reaction (Congo-red). The solution was evaporated, basified (saturated potassium carbonate solution), and extracted ten times with ether (50 c.c.), and the ether dried and removed, leaving a light brown gum (4·85 g.), presumably (IX). Preliminary experiments having indicated that this could not be distilled without decomposition, it was dissolved in benzene (20 c.c.), phosphorus pentabromide (15·5 g.) added in three portions during 20 minutes, and the whole heated for 4 hours on the water-bath. The benzene was removed, and the residue ground with potassium hydroxide solution (50%) and extracted ten times with 50 c.c. of ether. Half the dried extract was evaporated in each of two tubes, leaving in all a brown gum (2·5 g.). Anhydrous potassium carbonate (6 g.) was added to each, the tubes sealed, heated for 18 hours in the water-bath, and opened, the contents treated with warm potassium hydroxide solution (50%), the cooled product extracted repeatedly with ether, and the extract dried and fractionated, giving a pale yellow gum (0·6 g., b. p. 165—170°/1 mm.), a darker gum (0·5 g., b. p. 180—190°/1 mm.), and a charred residue. After some days the first two fractions partly solidified, and were drained on porous tile, leaving a pale brown, pasty solid (0·2 g.). After four recrystallisations from light petroleum (b. p. 60—80°) this had m. p. 111°, not raised by two further crystallisations. Mixed with *iso*lupanine of m. p. 110°, the m. p. was 110—111° (Found : C, 72·7; H, 9·8. Calc. for $C_{15}H_{24}ON_2$: C, 72·6; H, 9·7%).

iso*Lupanine*.—Deoxylupanine (J., 1928, 1818) (0·7 g.) was shaken for 5 hours with a solution of potassium ferricyanide (6 g.) and sodium hydroxide (1·05 g.) in water (15 c.c.), and the whole

extracted with ether. After drying and removal of the solvent, 0·25 g. of an oil, b. p. 180—182°/1 mm., was obtained which rapidly solidified. Recrystallisation from light petroleum (b. p. 60—80°) gave colourless prisms, m. p. 110° (Found: C, 72·5; H, 9·9. Calc. for $C_{15}H_{24}ON_2$: C, 72·6; H, 9·7%). The methiodide, prepared by allowing the base (0·2 g.) and methyl iodide (0·2 c.c.) to stand over-night in acetone (0·4 c.c.), and twice crystallised from methyl alcohol–ether, formed colourless prisms, m. p. 203—204°, alone or mixed with the material from the synthetic base (in Part I this m. p. is given as 208°) (Found: C, 49·5; H, 6·85. Calc. for $C_{16}H_{27}ON_2I$: C, 49·2; H, 6·9%). The *hydriodide*, prepared from the base and pure hydriodic acid, and recrystallised from alcohol, formed clusters of prisms, m. p. 275°, decomp. 345°, alone or mixed with synthetic material (Found: C, 48·1; H, 7·1. $C_{15}H_{24}ON_2,HI$ requires C, 47·9; H, 6·65%). If the preparation of the methiodide is carried out by heating in a sealed tube, the hydriodide also is formed, presumably from hydriodic acid resulting from decomposition of the methyl iodide. By recrystallisation from acetone (2 parts) and alcohol (1 part) the hydriodide separates first, the methiodide being more soluble and only obtained pure by fractional precipitation from the mother-liquor with ether.

Our thanks are due to the Royal Society for a grant, and to the Department of Scientific and Industrial Reasearch for a maintenance grant (to W. McG. M.).

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[*Received, May 19th,* 1936.]