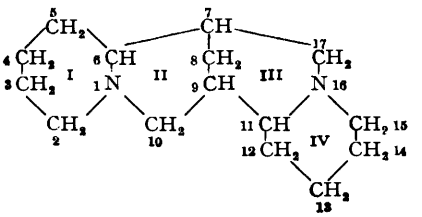
142. *The Lupin Alkaloids. Part XIV.*

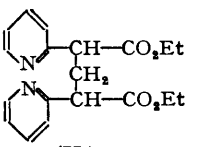
By G. R. Clemo, R. Raper, and W. S. Short.

Attempts to synthesise sparteine, and a successful reduction of oxysparteine using lithium aluminium hydride, are described. The structure (I) for sparteine is now regarded as completely proved.

In Part VII (*J.*, 1933, 644) structure (I) was suggested for sparteine, and the synthesis of oxysparteine (*J.*, 1936, 1025) confirmed this and demonstrated that in the latter the carbonyl group is at C_{10}.



(I.)

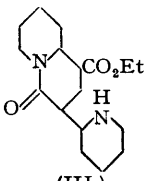


(II.)

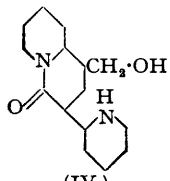
The failure of repeated attempts to reduce oxysparteine, however, made it desirable to synthesise sparteine itself. We therefore proposed to condense two molecules of the potassium

derivative of ethyl pyridyl-2-acetate with methylene iodide to form *ethyl αα'-di-(2-pyridyl)-glutarate* (II) and to reduce this to the dipiperidyl compound, which by a Bouveault reduction and subsequent treatment with phosphorus pentabromide followed by ring closure would be expected to yield sparteine.

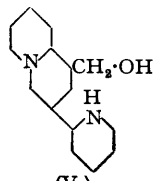
The first stage was satisfactorily carried out but on attempting to distil the product from the catalytic reduction, gummy mixtures of, probably, 4-*keto*-1-*carbethoxy*- 3-(2'-*piperidyl*)*octahydropyridocoline* (III) and 10 : 17-dioxysparteine were formed by ring closure. Bouveault reduction of the crude product from the catalytic reduction yielded a resinous product from which 4-*keto*-3-(2'-*piperidyl*)-1-*hydroxymethyloctahydropyridocoline* (IV) was isolated in very poor yield.



(III.)



(IV.)

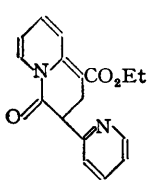


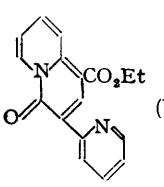
(V.)

Simultaneous reduction of both the pyridine rings and the carbethoxy-groups of (II) also gave a resinous product from which small amounts of 3-(2'-*piperidyl*)-1-*hydroxymethyloctahydropyridocoline* (V) were isolated. Many modifications were made of the conditions of this reaction without success, and treatment of 3-(2'-piperidyl)-1-hydroxymethyloctahydropyridocoline with phosphorus pentabromide resulted in only a very small amount of impure material containing halogen.

A yellow crystalline solid, 4-*keto*-1-*carbethoxy*-3-(2'-*pyridyl*)-2 : 3-*dihydropyridocoline* (VI) is formed as a by-product in the preparation of (II). Attempted catalytic reduction of this under the conditions used by Galinowsky and Stern (*Ber.*, 1943, **76**, 1034; 1944, **77**, 132) yielded a syrup which slowly crystallised and analysed satisfactorily for 10 : 17-dioxysparteine. Galinowsky and Kainz (*Sitzungsber. Öst. Akad. Wiss.*, 1947, **156**, 137) synthesised this compound and found that it could be readily reduced to oxysparteine, so presumably, in our case it was formed by ring closure of (III) on distillation.

Leonard and Beyler (*J. Amer. Chem. Soc.*, 1948, **70**, 2298) have recently synthesised (±)-sparteine by the catalytic reduction of (VII), using a copper chromite catalyst. We had already attempted the reduction of the corresponding dihydro-compound (VI) by the same method but at a rather lower temperature, and obtained a very small amount of a colourless liquid (b. p. 95—110°/4 mm.) the composition of which is still uncertain.

(VI.) 



(VII.)

It appeared therefore that reduction of the carbethoxy-groups of (II) followed by catalytic reduction might be the most satisfactory approach, as it would eliminate the formation of compounds such as (III). No satisfactory method of carrying out such a reduction was available until the recent publication of the use of lithium aluminium hydride (Finholt, Schlesinger, and Bond, *J. Amer. Chem. Soc.*, 1947, **69**, 1199; Nystrom and Brown, *ibid.*, pp. 1197, 2548). Trial experiments using this reagent on ethyl pyridyl-2-acetate were successful, and its action on (II) is promising.

While this work was in progress we also investigated the action of lithium aluminium hydride on oxysparteine, and found that it was reduced smoothly to sparteine. As in previous papers in this series (*J.*, 1928, 1811; 1929, 1927; 1931, 429; 1936, 1025) we have reduced (+)-lupanine to (−)-sparteine, (±)-lupanine to (±)-sparteine, and oxidised the last to (±)-oxysparteine, which has also been obtained synthetically, the structure of sparteine can now be regarded as completely proved.

Experimental.

Ethyl αα'-Di-(2-pyridyl)glutarate (II) *and Ethyl* 4-*Keto*-3-(2'-*pyridyl*)-2 : 3-*dihydropyridocoline*-1-*carboxylate* (VI).—Ethyl pyridyl-2-acetate (4·5 c.c.), powdered potassium (1·2 g.), and dry ether (90 c.c.)

were kept for 2 days at room temperature, moisture being excluded. Methylene iodide (4·05 g.) was added, the mixture heated under reflux for 24 hours, water added to dissolved potassium iodide, and the aqueous layer extracted with ether. The combined extracts were shaken with excess of dilute hydrochloric acid, the latter basified (K_2CO_3), and the bases extracted with ether, dried, and distilled, yielding (i) the *ethyl* ester (II) as a reddish oil (b. p. 215°/2 mm., 2·4 g., 50—55%) (Found : C, 66·5; H, 6·8. $C_{19}H_{22}O_4N_2$ requires C, 66·7; H, 6·43%) (*picrate*, yellow needles from alcohol, m. p. 154°. Found : C, 46·3; H, 3·7. $C_{19}H_{22}O_4N_2,2C_6H_3O_7N_3$ requires C, 46·5; H, 3·5%), and (ii) a brown gum which on crystallising from light petroleum (b. p. 60—80°) yielded yellow needles of the *keto*-ester (VI) (0·5 g.), m. p. 122° [Found : C, 69·1; H, 5·1; N, 9·2; *M* (Rast), 299, 302. $C_{17}H_{16}O_3N_2$ requires C, 68·9; H, 5·4; N, 9·5%; *M*, 296] (*picrate*, from ethanol, orange needles, m. p. 215—216°. Found : C, 53·3; H, 3·4. $C_{17}H_{16}O_3N_2,C_6H_3O_7N_3$ requires C, 52·6; H, 3·6%).

Catalytic Reduction of Ethyl αα′-Di-(2-pyridyl)glutarate.—The ester (II) (0·4 g.) in glacial acetic acid (6 c.c.) and platinum oxide (0·05 g.) were shaken in hydrogen at 100 lb./sq. in. for 18 hours. On working up, a trace of a colourless liquid and a yellow basic gum (0·2 g.), b. p. 210—220°/2 mm., believed to be 4-*keto*-1-*carbethoxy*-3-(2′-*piperidyl*)*octahydropyridocoline* (III), were obtained (Found : C, 65·35; H, 9·3. $C_{17}H_{26}O_3N_2$ requires C, 66·2; H, 9·1%). No crystalline derivatives of this gum could be prepared.

The crude product (A) before distillation was assumed to be chiefly ethyl αα′-di-(2-piperidyl)glutarate and was used unpurified in subsequent work.

4-*Keto*-3-(2′-*piperidyl*)-1-*hydroxymethyloctahydropyridocoline* (IV).—The above crude reduction product (A) (1·75 g.), dissolved in absolute ethanol (30 c.c.), was heated under reflux while sodium (2·25 g.) was added in small pieces. After the reaction was complete, water was added, the solution acidified (acetic acid), basified (K_2CO_3), evaporated, and extracted with chloroform, and the extract dried. Removal of the chloroform left a brown hygroscopic resin (1·2 g.) which on distillation yielded the *keto*-compound (IV) as a pale yellow basic gum (0·32 g.), b. p. 250°/2 mm. (Found : C, 67·3; H, 9·5. $C_{15}H_{26}O_2N_2$ requires C, 67·7; H, 9·8%).

3-(2′-*Piperidyl*)-1-*hydroxymethyloctahydropyridocoline* (V).—The crude product (A) (1·1 g.) was dissolved in absolute ethanol and heated under reflux while sodium (3·5 g.) was added in small pieces together with more ethanol as required to keep everything in solution. The cooled solution was acidified (concentrated hydrochloric acid), filtered, and the filtrate evaporated to dryness, the residue basified (K_2CO_3), and extracted with chloroform, and the extract dried. After removal of chloroform the residue was distilled, yielding the *piperidyl* derivative (V) as a pale greenish-yellow liquid (30 mg., b. p. 130—140°/2 mm.) (Found : C, 70·1, 72·7; H, 10·9, 11·1. $C_{15}H_{28}ON_2$ requires C, 71·4; H, 11·1%).

10 : 17-*Dioxysparteine.*—Ethyl 4-keto-3-(2′-pyridyl)-2 : 3-dihydropyridocoline-1-carboxylate (0·13 g.), platinum oxide (0·13 g.), and dilute hydrochloric acid (20 c.c., 1·25%) were shaken in hydrogen at atmospheric pressure and room temperature for 70 hours. The solution was filtered, evaporated to dryness, basified (K_2CO_3), extracted with chloroform, and dried. Removal of the chloroform left a whitish resin which on distillation yielded a trace of liquid and a pale yellow gum, b. p. 220—235°/2 mm., which solidified on long standing to a white crystalline solid, m. p. 113° (Found : C, 68·9; H, 8·55. Calc. for $C_{15}H_{22}O_2N_2$: C, 68·7; H, 8·4%).

(−)-*Sparteine.*—(−)-Oxysparteine (1 g.) in ether (8 c.c.) was added to a solution of lithium aluminium hydride (0·1 g.) in ether (7 c.c.), the mixture being protected from access of atmospheric moisture and carbon dioxide. After standing for 3 days at room temperature, a copious white precipitate formed. Excess of lithium aluminium hydride was decomposed by water, and the product acidified (10% H_2SO_4, 18 c.c.). Basification with potassium carbonate precipitated a solid consisting presumably of the base and lithium carbonate from which nothing could be extracted with ether or chloroform. On acidification (dilute HCl) followed by basification (10% NaOH), an oil was obtained; this was extracted with ether, dried, and distilled, giving three fractions : (1) a colourless liquid (0·35 g., b. p. 110—130°/4 mm.), (2) a yellow oil (b. p. 140—160°/4 mm.), (3) a viscous yellow oil (b. p. 170—190°/4 mm.). Fractions (2) and (3) were obviously not pure and rapidly turned red. Fraction (1) (Found : C, 76·9; H, 11·6. Calc. for $C_{15}H_{26}N_2$: C, 76·9; H, 11·1%) gave a picrate, yellow needles from ethanol, m. p. 205—206° not depressed by admixture with the picrate of (−)-sparteine, and a hydriodide, m. p. 230°, also not depressed by admixture with the monohydriodide of (−)-sparteine.

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