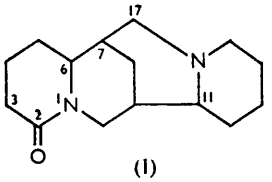
658. *The Lupin Alkaloids. Part XVI.* The Synthesis of Externally Compensated Lupanine.*

By G. R. Clemo, R. Raper, and J. C. Seaton.

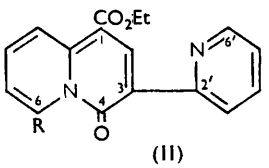
2 : 3-Dehydro-2-methylsparteine (VII) has been synthesised from 1-ethoxycarbonyl-6-methyl-4-oxo-3-2′-pyridylpyridocoline [1] (II; R = Me). The former, prepared from (±)-lupanine by a variation of Winterfeld's method,[2] has been used as a relay in the total synthesis of the alkaloid itself.

Of the major lupin alkaloids, lupanine, lupinine, and sparteine, the last two have already been synthesised.[3] Structure (I) was ascribed to the first of these alkaloids by two of us [4] and it is probable [5] that in it the hydrogen atom at position 6 is *cis*, and that at position 11 *trans*, with respect to the methylene bridge between positions 7 and 9.

We have now synthesised this alkaloid by the following method. 1-Ethoxycarbonyl-4-oxo-3-2′-pyridylpyridocoline-6-carboxylic acid (II; R = CO_2H), prepared by heating 1-ethoxycarbonyl-6-methyl-4-oxo-3-2′-pyridylpyridocoline [1] (II; R = Me) to its melting point with selenium dioxide, was esterified by treating it successively with thionyl chloride



(I)



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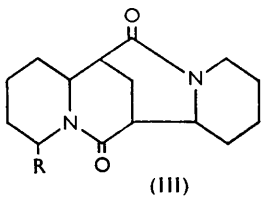
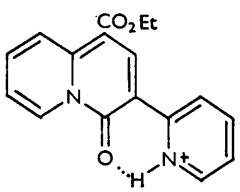


(III)

and ethanol, and the resulting diethyl ester was freed from selenium by refluxing in ethanol solution over stirred mercury.[6] This starting material was chosen rather than the isomeric 6′-methyl compound because, when Galinowsky and Kainz [7] hydrogenated 1-ethoxycarbonyl-4-oxo-3-2′-pyridylpyridocoline over platinum in ethanolic hydrogen chloride and cyclised the product, only the dioxosparteine (III; R = H) with the *cis-trans*-configuration was obtained. This is explicable if hydrogenation takes place from one side only of the molecules which is hydrogen-bonded (IV).

We therefore expected that when the diester (II; R = CO_2Et) was hydrogenated under



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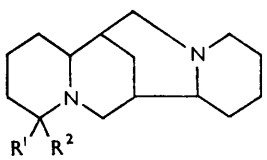

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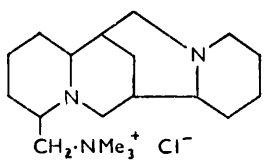


(VI)

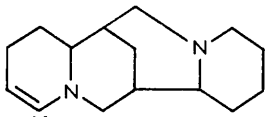
similar conditions and then cyclised, the *cis-trans*-isomers would predominate in the product. The viscous gum so obtained was washed in chloroform solution with dilute hydrochloric acid to remove basic unsaturated and uncyclised materials, after which distillation gave a product which partially crystallised, and was separated by chromatography on alumina

* Part XV, *J.*, 1954, 2693.

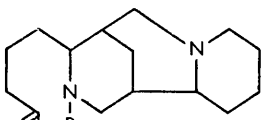
[1] Clemo, Fox, and Raper, *J.*, 1954. 2693.
[2] Winterfeld and Hoffmann. *Arch. Pharm.*, 1937, **275**, 5.
[3] Clemo, Morgan, and Raper, *J.*, 1938, 1574; Clemo, Raper, and Short, *J.*, 1949. 663.
[4] Clemo and Raper, *J.*, 1933. 644.
[5] Leonard and Beyler. *J. Amer. Chem. Soc.*, 1950. **72**. 1316: Marion and Leonard, *Canad. J. Chem.*, 1951. **29**. 355: Marion. *Bull. Soc. chim. France*, 1954. 1189.
[6] Jacques, *ibid.*, 1955. 1293.
[7] Galinovsky and Kainz, *Monatsh.*, 1947. **77**. 137.

into four crystalline 2-ethoxycarbonyl-10 : 17-dioxosparteines (III; R = CO_2Et), two of which appeared to predominate in the mixture.

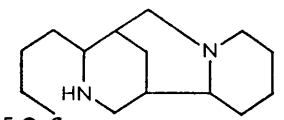
This separation was, however, very tedious, and, since the number of diastereoisomers is halved at later stages of the synthesis, we reduced the unseparated mixture by means of lithium aluminium hydride, obtaining a mixture of 2-hydroxymethylsparteines (V; R^1 = H, R^2 = CH_2·OH) which did not crystallise. Chlorination of this with thionyl chloride gave a product which again could not be crystallised and which decomposed on attempted distillation, possibly because of quaternisation, since water-soluble materials were formed. The crude product was therefore condensed with trimethylamine, giving an ether-insoluble highly deliquescent solid (VI). Hofmann degradation of this would be expected to yield a mixture containing (V; R^1R^2 = CH_2:). Acid would convert this into a 1 : 2-dehydro-2-methyl-1-sparteinium salt, which on basification would give 2 : 3-dehydro-



(VII)



(VIII)



(IX)

2-methylsparteine (VII) through a *pseudo*-base. Treating the chloride (VI) in this way we obtained an unsaturated gum, which, on fractionation on alumina, gave the base (VII) as an unstable oil, characterised as its mono- and di-picrate and dihydriodide, all of which were crystalline.

Winterfeld *et al.*[2] prepared this base by the action of methylmagnesium iodide on lupanine, and described it as an oil unstable even in the absence of air. Using slightly different conditions we obtained it from lupanine in improved yield as a colourless solid, m. p. 34°, whose mono- and di-picrate and dihydriodide were identical with those obtained from our synthetic material. Although our platinichloride had a different decomposition point from that recorded by Winterfeld *et al.*, the dihydrobromide and dihydro-derivative have physical constants agreeing with those recorded by him. The failure of our synthetic material to crystallise is probably to be ascribed to the presence in it of diastereoisomers.

This base was then used as a relay. With benzoyl chloride in aqueous alkaline solution it yielded the ketone (VIII) as a stiff gum, which was purified through its crystalline monopicrate. It gave the iodoform reaction and a crystalline 2 : 4-dinitrophenylhydrazone hydrochloride. Analogous compounds have been prepared.[2,8] The ketone (VIII) was shaken with sodium hypobromite in dioxan, and the amino-acid resulting was simultaneously esterified and debenzoylated by ethanolic hydrogen chloride. The product, when heated, gave colourless prismatic plates identical with (±)-lupanine obtained from the seeds of *Lupinus termis*. The picrate and thiocyanate were also identical. A trace of another substance richer in oxygen was also obtained, which may be an externally compensated hydroxylupanine.

The ester (IX) obtained by hydrolysis of lupanine (cf. Winterfeld *et al.*[9]) cyclised spontaneously to lupanine. We find, however, that the decomposition point of the platinichloride of this ester differs from that recorded by him, and we have obtained in addition a crystalline dihydrochloride.

Experimental

1-Ethoxycarbonyl-4-oxo-3-2′-pyridylpyridocoline-6-carboxylic Acid (II; R = CO_2H).—A finely ground mixture of 1-ethoxycarbonyl-6-methyl-4-oxo-3-2′-pyridylpyridocoline (II: R = Me) (10 g.) and freshly sublimed selenium dioxide (8 g.) was stirred and heated to 150°: the mass melted. After cooling to 130° during 3—4 min. a vigorous reaction took place with evolution of steam. The temperature was raised to 150° for 15 min.. whereupon the melt solidified. The cooled mass was dissolved in hot hydrochloric acid. and the solution filtered and cooled: the acid separated and recrystallised from water as its *hexahydrate* (9·4 g.). orange needles

[8] Winterfeld and Petkow, *Ber.*, 1949. **82**. 156; Petkow. *Scientia Pharmaceutica*, 1948. **16**. 57.
[9] Winterfeld, Hoffmann, and Holschneider, *Arch. Pharm.*, 1937. **275**. 65.

softening at 160—165°, m. p. 220° (decomp.) (Found: C, 48·55; H, 5·7. $C_{18}H_{14}O_5N_2,6H_2O$ requires C, 48·4: H, 5·8%). The *anhydrous acid* obtained by drying at 150°/1 mm. had m. p. 220° (decomp.) (Found: C, 64·0; H, 4·4; N, 8·2. $C_{18}H_{14}O_5N_2$ requires C, 63·9: H, 4·1; N. 8·3%).

1 : 6-*Diethoxycarbonyl*-4-*oxo*-3-2′-*pyridylpyridocoline* (II; R = CO_2Et).—The anhydrous acid (30 g.) and thionyl chloride (250 ml.) were refluxed for 1 hr.. the excess of thionyl chloride was removed under reduced pressure, benzene (20 ml.) added. and the whole again evaporated. Ethanol (250 ml.) was added to the cooled residue and the whole refluxed for 1 hr. The excess of ethanol was removed and the diester liberated with potassium carbonate and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated. leaving the *diester*, which solidified and was recrystallised from light petroleum (b. p. 100—120°) or ethanol. Its ethanol solution was refluxed overnight over stirred mercury, and when filtered and cooled deposited pale yellow needles (12·5 g.), m. p. 141° (Found: C, 65·75: H. 5·15; N. 7·6. $C_{20}H_{18}O_5N_2$ requires C, 65·6; H. 4·9; N, 7·6%).

2-*Ethoxycarbonyl*-10 : 17-*dioxosparteine* (III; R = CO_2Et).—The diester (30 g.) in ethanolic hydrogen chloride (200 ml. of 2%) was shaken with platinum oxide (0·5 g.) under hydrogen at 105 lb./in.^{2} at room temperature for 48 hr. Platinum oxide (0·5 g.) was then added and shaking continued for a further 72 hr. The solution became colourless with absorption of 7 mols. of hydrogen. The catalyst and solvent were removed, and the thick gum remaining was basified with potassium carbonate and extracted with chloroform. The solvent was removed from the dried extract, and the residual gum heated for 2 hr. at 200°/8 mm.. the liquid becoming quiescent. A chloroform solution of the cooled material was washed with dilute hydrochloric acid, and removal of the solvent from the dried solution left a mixture of stereoisomeric 2-ethoxycarbonyl-10 : 17-dioxosparteines (19 g.) which distilled at 210—224°/0·2 mm. (Found: C. 65·1; H, 8·0. Calc. for $C_{18}H_{26}O_4N_2$: C, 64·7: H, 7·8%). When kept it partly solidified. The distillate (3·5 g.) was adsorbed from light petroleum (b. p. 60—80°) on a column of alumina (100 g.). Elution with light petroleum–benzene (1 : 1) gave a pale gum which partly solidified and was recrystallised from ether, yielding a *stereoisomer* as large colourless prismatic needles (0·6 g.), m. p. 146—147° (Found: C, 64·7; H, 7·9; N, 8·6. $C_{18}H_{26}O_4N_2$ requires N. 8·4%). Benzene–chloroform (9 : 1) then eluted a different *form* as a gum, which crystallised from its ethereal solution in large, colourless. hexagonal prisms (0·6 g.). m. p. 146° (Found: C, 64·7; H, 7·6; N. 8·5%). Concentration of the mother-liquor gave colourless rhombs (0·05 g.) of a third *form*, m. p. 138° (Found: C, 64·5; H, 8·5%). Finally chloroform eluted a gum, the ethereal solution of which deposited a fourth *form* as large prismatic needles (0·07 g.), m. p. 172° (Found: C, 64·5: H, 8·5%). Each of these four substances depressed the m. p.'s of the other three, all were soluble in water, and none formed a picrate.

2-*Hydroxymethylsparteine* (V; R^1 = H, R^2 = CH_2·OH).—The mixture of isomeric ethoxycarbonyldioxosparteines (12 g.) in dry ether (240 ml.) was added slowly with stirring to a refluxing solution of lithium aluminium hydride in ether (240 ml. of 80-vol.). A yellow precipitate was formed and the mixture was refluxed for 6 hr. and left overnight. The excess of lithium aluminium hydride was decomposed with water, and concentrated sodium hydroxide solution was added. The resulting paste was extracted several times with ether, the extract dried (Na_2SO_4), and the solvent removed, leaving the *alcohol* which distilled as a pale yellow oil (4·5 g.), b. p. 135—140°/0·2 mm. (Found: C, 72·6; H, 10·9. $C_{16}H_{28}ON_2$ requires C, 72·7; H, 10·6%). The *dipicrate*, from ethanol, was yellow and microcrystalline, m. p. 110—116° (Found: C, 46·7: H. 5·0. $C_{16}H_{28}ON_2.2C_6H_3O_7N_3$ requires C, 46·5; H, 4·7%).

2 : 3-*Dehydro*-2-*methylsparteine* (VII).—(*a*) A solution of the above alcohol (6 g.) in ether (300 ml.) was cooled and stirred while thionyl chloride (24 ml.) was added slowly. A precipitate was formed and the mixture was refluxed for 2 hr., after which the solvent and excess of thionyl chloride were removed under reduced pressure. The residue was cooled. basified with potassium carbonate solution, and extracted with ether. The extract was dried (Na_2SO_4) and the solvent removed, leaving a pale oil (6 g.) which decomposed when heated and did not give a crystalline picrate or picrolonate. This oil (6 g.) was heated with trimethylamine (12 g.) in ethanol (50 ml.) at 100° for 7 hr. Removal of the solvent left a thick, light red gum which solidified when it was extracted several times with boiling ether. This solid was very deliquescent and gave a positive test for ionic chlorine. A solution of it (3 g.) in water (20 ml.) was shaken with excess of freshly prepared silver oxide for 1 hr., the solids were filtered off, and the filtrate was evaporated in a vacuum below 45°. The residue was heated to 200°/0·2 mm., the distillate being collected in a trap cooled in liquid air and dissolved in dilute hydrochloric acid. After basification with potassium carbonate and extraction with ether the extract was dried (Na_2SO_4), the ether was

removed, and the residue distilled as a pale yellow oil (0·4 g.), b. p. 100—150°/0·2 mm. The ether distillate with picric acid gave trimethylamine picrate (0·4 g.), m. p. and mixed m. p. 219°. The oil was adsorbed from light petroleum (b. p. 60—80°) on alumina [12 g., Savory and Moore, " For chromatographic analysis," deactivated with water (0·4 g.)] and eluted with successive 10 ml. quantities of the same solvent. Fractions 4—10. when united and evaporated, left a colourless oily *base* (0·1 g.), b. p. 130—140° (bath-temp.)/0·2 mm. (Found : C, 77·8; H, 10·9. $C_{16}H_{26}N_2$ requires C, 78·0; H, 10·6%. Winterfeld *et al.* give no analysis of this compound). The *monopicrate* crystallised from ethanol in orange needles, m. p. 148° (Found : C, 55·2; H. 6·15. $C_{16}H_{26}N_2,C_6H_3O_7N_3$ requires C, 55·6: H. 6·1%). The *dipicrate* crystallised from ethanol in yellow diamond-shaped prisms. m. p. 199—200° (Found : C. 47·55; H, 4·55. $C_{16}H_{26}N_2,2C_6H_3O_7N_3$ requires C, 47·7; H, 4·5%). The *dihydriodide* formed large prisms (from ethanol), m. p. 254° (Found : C, 38·35; H, 5·8. $C_{16}H_{26}N_2,2HI$ requires C, 38·2; H, 5·6%). The m. p.s of these derivatives were not depressed on admixture with specimens prepared from the base obtained as described below. Further elution of the alumina column gave oils which neither crystallised nor gave crystalline derivatives.

(*b*) A solution of (±)-lupanine, m. p. 99° (10 g.), in ether (150 ml.) was added with stirring to a boiling Grignard reagent prepared from magnesium (3·5 g.), methyl iodide (17·4 g.), and ether (200 ml.). The mixture was stirred and refluxed for a further 3 hr. and then kept overnight. The excess of Grignard reagent was decomposed with water, and the solid complex with hydrochloric acid. The base was liberated with aqueous sodium hydroxide and extracted with ether, the extract dried (Na_2SO_4), the solvent removed, and the residue distilled, yielding a colourless oil (8·5 g.), b. p. 130°/0·2 mm.. which soon solidified and had then m. p. 34° (Found : C, 78·4; H, 10·7; N, 11·3. $C_{16}H_{26}N_2$ requires N, 11·4%). The solid was easily soluble in the commoner organic solvents, and on exposure to air it resinified. The platinichloride crystallised from dilute hydrochloric acid in orange prisms, decomp. 265° (Winterfeld *et al.* give 245—250°) (Found : C, 28·9: H, 4·6; Pt, 30·0. Calc. for $C_{16}H_{26}N_2,H_2PtCl_6$: C, 29·3; H, 4·5; Pt, 29·75%). The monopicrate crystallised in orange needles, m. p. 148° (Found : C, 55·4; H, 5·8%), the dipicrate in yellow prisms, m. p. 199—200° (Found : C, 47·8; H, 4·7%), and the dihydriodide in large colourless prisms, m. p. 254° (Found : C, 38·2: H, 5·9; N, 5·5%. Calc. for $C_{16}H_{26}N_2.2HI$: C, 38·2; H, 5·6; N, 5·6%). The dihydrobromide formed colourless prisms, m. p. 180°, from ethanol (Winterfeld *et al.* give 180°) (Found : N, 6·3. Calc. for $C_{16}H_{26}N_2,2HBr,H_2O$: N, 6·4%). 2-Methylsparteine, obtained from this base by hydrogenation, crystallised from light petroleum (b. p. 40—60°) in prismatic plates, m. p. 48—50° (Winterfeld *et al.*, 48—50°) (Found : C, 77·5; H, 11·35; N, 11·0. Calc. for $C_{16}H_{28}N_2$: C, 77·4; H, 11·3; N, 11·3%), and gave a monopicrate, m. p. 152° (Winterfeld *et al.*, 221° for hydrated material) (Found : C, 55·3; H, 6·3. Calc. for $C_{16}H_{28}N_2,C_6H_3O_7N_3$: C, 55·35; H, 6·5%), and a *dipicrate*, m. p. 213° (Found : C, 47·8; H, 5·1. $C_{16}H_{28}N_2.2C_6H_3O_7N_3$ requires C, 47·6; H, 4·8%).

3-Benzoyltetrahydrodeoxy-4-4′-oxopentylcytisine (VIII).—A mixture of 2 : 3-dehydro-2-methylsparteine (50 g.) and water (200 ml.) was kept alkaline with sodium hydroxide (8%) while benzoyl chloride (50 ml.) was added in small quantities during 1 hr. with continuous shaking. After a further 2 hours' shaking the thick yellow oil was extracted with ether, the extract dried (KOH), and the solvent removed. The residue was distilled and the fraction of b. p. 250°/0·2 mm. collected as a very viscous pale yellow oil which did not crystallise but gave a *picrate*; this, recrystallised three times from ethanol, formed large yellow rhombic prisms (26 g.), m. p. 136° (Found : C, 58·5; H, 6·1. $C_{23}H_{32}O_2N_2,C_6H_3O_7N_3$ requires C, 58·3; H, 5·9%). The picrate was decomposed with hydrochloric acid, the mixture basified with sodium hydroxide, and the base extracted with ether. The extract was dried (Na_2SO_4) and the solvent removed after which the residue distilled with slight decomposition. giving a pale yellow viscous oil (15 g.), b. p. 250°/0·2 mm. The 2 : 4-*dinitrophenylhydrazone hydrochloride* crystallised from water in yellow hydrated prisms, m. p. 145° (Found : C, 56·2; H, 7·1. $C_{29}H_{36}O_5N_6,HCl,2H_2O$ requires C, 56·1; H, 6·6%). Dehydration at 120°/0·2 mm. for 2 hr. gave the *anhydrous derivative* as a dark orange, viscous oil (Found : C, 59·0; H, 6·4. $C_{29}H_{36}O_5N_6,HCl$ requires C, 59·5; H, 6·3%).

(±)-*Lupanine* (I).—A solution of the above ketone (15 g.) in dioxan (300 ml.) was cooled while a solution of sodium hypobromite [from bromine (20 g.), sodium hydroxide (17·5 g.), and water (350 ml.)] was added. After being shaken for 15 min. the mixture was evaporated. the residue dissolved in water (100 ml.), and the solution extracted with ether. The aqueous layer was acidified with hydrochloric acid and evaporated to dryness. After absolute ethanol (50 ml.) had been added and the whole again evaporated the residue was extracted thrice with boiling absolute ethanol (100 ml.). The combined extracts were saturated with dry hydrogen chloride,

set aside overnight, then refluxed for 6 hr. The solution was evaporated to dryness, the residue basified with potassium carbonate solution, and the liberated base extracted with ether. The extract was dried (Na_2SO_4), the solvent removed, and the residue heated at 200°/8 mm. for 1 hr. Distillation gave a colourless oil (2·5 g.), b. p. 160—180°/2 mm., a solution of which in light petroleum (b. p. 60—80°) deposited colourless needles (0·1 g.) of a (?)*hydroxylupanine*, m. p. 154° (Found: C, 67·8; H, 9·35. $C_{15}H_{24}O_2N_2$ requires C, 68·2; H, 9·1%). The *picrate* crystallised from ethanol–ether in yellow prisms, m. p. 244°. Concentration of the light petroleum mother-liquors gave (±)-lupanine which crystallised in prismatic plates (1·7 g.), m. p. 99° (Found: C, 72·4; H, 10·0. Calc. for $C_{15}H_{24}ON_2$: C, 72·6; H, 9·7%). The picrate crystallised from ethanol in yellow prisms, m. p. 229° (Found: C, 53·0; H, 5·7. Calc. for $C_{15}H_{24}ON_2.C_6H_3O_7N_3$: C, 52·8; H, 5·7%). The thiocyanate crystallised from water in colourless hydrated prisms, m. p. 124° (Found: C, 59·1; H, 8·5. Calc. for $C_{15}H_{24}ON_2.HCNS,H_2O$: C, 59·1; H. 8·3%). The m. p.s. of the base and these salts were not depressed by admixture with authentic specimens.

Hydrolysis of (±)-Lupanine with Hydrochloric Acid.—(±)-Lupanine (5 g.) was hydrolysed, by Winterfeld's procedure, the ethyl ester of the amino-acid being isolated as its *dihydrochloride* which crystallised from ethanol in colourless needles (3·0 g.), m. p. 208° (decomp.) (Found: Cl, 19·25. $C_{17}H_{30}O_2N_2,2HCl$ requires Cl, 19·3%). The platinichloride crystallised from dilute hydrochloric acid–ethanol in orange plates, decomp. 230° (Winterfeld *et al.*, 245°) (Found: Pt, 26·9. Calc. for $C_{17}H_{30}O_2N_2.H_2PtCl_6,H_2O$: Pt, 26·9%). The ester cyclised when kept or distilled, giving (±)-lupanine, m. p. 99° not depressed on admixture with an authentic specimen.

One of us (J. C. S.) thanks the D.S.I.R. for a maintenance grant.

UNIVERSITY OF DURHAM, KING'S COLLEGE,
NEWCASTLE UPON TYNE, 1.

[*Received, May 7th,* 1956.]