THE PAPILIONACEOUS ALKALOIDS
XIX. THE STRUCTURE OF LUPANOLINE[1]

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ABSTRACT

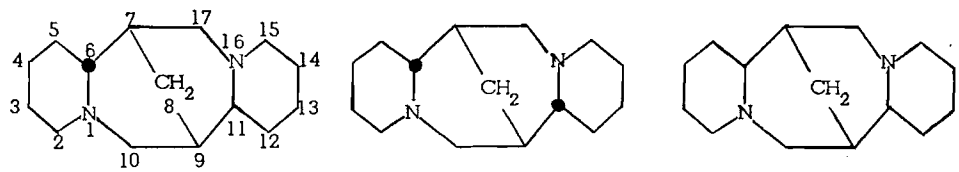
Lupanoline which contains both a carbonyl and a hydroxyl group was reduced by lithium aluminum hydride to β-isosparteine. The identity of β-isosparteine was established by its conversion into sparteine by dehydrogenation and subsequent rehydrogenation. Attempts to acylate lupanoline resulted in the formation of anhydrolupanoline which was hydrogenated to dihydroanhydrolupanoline, a compound also obtained by the direct oxidation of β-isosparteine. It is concluded that lupanoline is 2-hydroxy-17-oxo-β-isosparteine.

The alkaloid lupanoline, the occurrence of which has been reported recently (4), is an isomer of hydroxylupanine, $C_{15}H_{24}O_2N_2$. It behaves as a monoacidic base, giving rise to a monohydrochloride and a monomethiodide so that one of its two nitrogens is neutral. The infrared absorption spectrum of lupanoline shows absorption peaks at 3591 cm.$^{-1}$ and 1624 cm.$^{-1}$ corresponding to a hydroxyl group and a carbonyl respectively, and thus accounting for both oxygen atoms.

The carbonyl group of lupanoline is inert towards the usual ketone reagents and is apparently lactamic in character. The presence of a nonbasic nitrogen in the molecule and the location of the carbonyl absorption band in the infrared spectrum support this conclusion. The hydroxyl group could not be acylated. Under the wide variety of conditions investigated, the group was invariably eliminated with the formation of anhydrolupanoline, $C_{15}H_{22}ON_2$, a substance which regenerated lupanoline on treatment with mineral acids. This characteristic behavior of the hydroxyl group of lupanoline is noteworthy.

Reduction of lupanoline with lithium aluminum hydride in dioxane proceeded smoothly, leading to the complete removal of oxygen from the molecule with the production of an oily base, $C_{15}H_{26}N_2$. Hence the reaction involved not only the conversion of the carbonyl to a methylene group thus confirming its lactamic nature, but also involved the reductive elimination of the hydroxyl. The reduction product was identical neither with sparteine nor with α-isosparteine although isomeric with them, and it appeared possible that it might be the so far unknown β-isosparteine.

It has already been shown (2, 3) that of the three possible stereoisomeric forms I, II, and III of the sparteine structure two represent sparteine and



I II III

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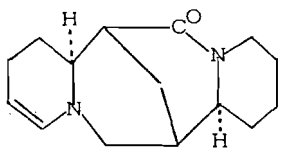
α-isosparteine. In formula I which represents sparteine the C_6-hydrogen is *cis* to the 7,9-methylene bridge whereas the C_{11}-hydrogen is *trans*. In α-isosparteine (II) both the C_6-hydrogen and the C_{11}-hydrogen are *cis* to the 7,9-methylene bridge (3). This structure which was assigned to α-isosparteine on the basis of hydrogenation results (3) has since been confirmed by a detailed X-ray crystallographic examination (5). β-Isosparteine should then be represented by III in which both the C_6-hydrogen and the C_{11}-hydrogen are *trans* to the 7,9-methylene bridge. Winterfeld and Rauch (6) converted sparteine into α-isosparteine by dehydrogenation with mercuric acetate, which removed two moles of hydrogen, and subsequent rehydrogenation. This conversion must therefore have resulted from the elimination of the *cis* C_6-hydrogen and the *trans* C_{11}-hydrogen, and their replacement both in the *cis* position. The same reaction should convert β-isosparteine to α-isosparteine if it removed two moles of hydrogen, or to sparteine if it removed only one mole. The reduction product of lupanoline was therefore oxidized with mercuric acetate and immediately rehydrogenated catalytically. The quantity of precipitated mercurous acetate corresponded to one mole of hydrogen, and the base obtained after rehydrogenation was identical with *l*-sparteine. Hence, the reduction product is β-isosparteine and lupanoline is an hydroxy-oxo-β-isosparteine.

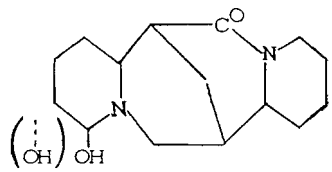
Information as to the positions of the substituents in lupanoline has been derived from a study of anhydrolupanoline and its derivatives. Anhydrolupanoline was readily hydrogenated over Adams' catalyst to yield the saturated dihydroanhydrolupanoline, $C_{15}H_{24}ON_2$, which had the composition of an oxosparteine, and could be prepared by the direct oxidation of β-isosparteine with alkaline potassium ferricyanide. By analogy with the similar oxidation of sparteine to oxosparteine, it is reasonable to assume oxidation to have occurred at the 17-position (or equivalent 10-position) in β-isosparteine (III). Dihydroanhydrolupanoline could also be obtained directly from lupanoline by catalytic hydrogenation in acid solution. The failure of the carbonyl to reduce under these conditions also militates in favor of its occupying the 17-position.

On reduction with lithium aluminum hydride, anhydrolupanoline afforded an unstable oily dehydro-base which was readily converted to β-isosparteine on catalytic hydrogenation. No stereochemical inversion, therefore, is involved in the series: lupanoline $\rightarrow$ anhydrolupanoline $\rightarrow$ dehydro-β-isosparteine $\rightarrow$ β-isosparteine. Thus it is clear that, if the possibility of migration be discounted, the double bond of anhydrolupanoline and the hydroxyl group of lupanoline itself cannot involve an angular position. The characteristic properties of the hydroxyl group (ready elimination and reduction) suggest association with a basic center in the form of an aldehyde-ammonia. The reductive elimination of the hydroxyl by lithium aluminum hydride particularly is indicative of such a grouping. The formulation of lupanoline as an aldehyde-ammonia is supported by the facile rehydration of anhydrolupanoline to the parent alkaloid under the influence of mineral acid. Thus anhydrolupanoline would appear to be best formulated as IV and lupanoline as 2-hydroxy-17-oxo-β-

isosparteine (V). An alternative formulation with a 10-hydroxyl group is



IV



V

considered unlikely as the preparation of an anhydro-base from such a system would require the formation of a double bond at a bridge head, in violation of Bredt's rule. Whether the hydroxyl group at the 2-position is *cis* or *trans* is not yet known.

Lupanoline is thus the first alkaloid known to be derived from β-isosparteine. The hitherto unknown β-isosparteine prepared from it is an oil which like sparteine discolors on standing in air. It has not yet been possible to induce its picrate to crystallize, but like its two other stereoisomers it forms a crystalline perchlorate. For the infrared absorption spectrum of β-isosparteine and the spectra of its two stereoisomers see Fig. 3, Ref. (1).

Anhydrolupanoline and its hydrogenation product are isomers of monspessulanine and dihydromonspessulanine, and their melting points are about the same. However, admixture with authentic samples of these two bases caused depressions in the melting points, and the infrared absorption spectra were quite distinct from those of the two derivatives of lupanoline. The sample of monspessulanine was kindly given to us by Dr. E. P. White.

EXPERIMENTAL[3]

Lupanoline has been described previously (4). It melts at 174–176° and has $[\alpha]_D^{26} + 64.4° \pm 0.8$ (*c*, 0.88 in water). It forms a monohydrochloride, m.p. 275–276°, and a methiodide, $C_{15}H_{24}O_2N_2.CH_3I$, m.p. 230–231°. Its infrared absorption spectrum showed absorption peaks at 1624 cm.$^{-1}$ and 3593 cm.$^{-1}$ indicating the presence of a lactam carbonyl and a hydroxyl group respectively.

Reduction of Lupanoline with Lithium Aluminum Hydride

A solution of lupanoline (250 mgm.) in pure, dry dioxane (5 ml.) was treated with an ethereal solution of lithium aluminum hydride (3 ml., 0.016 gm. per mole, 1.3 moles) and the mixture refluxed in an atmosphere of nitrogen for four hours (the ether being allowed to escape). The mixture was cooled, treated with a little ethanol to destroy excess hydride, and then acidified with dilute hydrochloric acid. The solution was freed from nonbasic impurities by extraction with ether and alkalized with aqueous potassium hydroxide. The liberated base was extracted with ether and after evaporation of the extract was distilled *in vacuo*. The main fraction afforded β-isosparteine as a colorless oil, b.p. 110–120° (air bath) at 1 mm., which gave a crystalline diperchlorate crystallizing from methanol as colorless prisms, m.p. 255° (dec.). Calcd. for

[3] *All melting points are corrected.*

$C_{15}H_{26}N_2.2HClO_4$: C, 41.38; H, 6.48; N, 6.43. Found: C, 41.36, 41.22; H, 6.28, 6.55; N, 5.95%.

Conversion of β-Isosparteine to Sparteine

A mixture of β-isosparteine (234 mgm., 1 mM.), 5% aqueous acetic acid (35 ml.), and mercuric acetate (2.5 gm., 8 mM.) was stirred under an atmosphere of nitrogen and heated on a water bath for three hours. The mixture was cooled and the crystalline mercurous acetate collected by filtration (1 mM. obtained ≡ 2H). The clear aqueous solution was saturated with hydrogen sulphide and the precipitated mercuric sulphide filtered off. The aqueous filtrate was evaporated *in vacuo* to a small bulk, diluted with water, and evaporated again in order to ensure complete removal of hydrogen sulphide. The concentrated liquor was alkalized with aqueous sodium hydroxide and extracted with chloroform. The washed chloroform extract was dried rapidly over anhydrous potassium carbonate, filtered, added to glacial acetic acid (7 ml.), and the resulting solution heated on a steam bath until all the chloroform had evaporated. Since the dehydro-base thus obtained was not stable it was not isolated from the acetic acid concentrate, but was hydrogenated directly over fresh Adams' catalyst for 12 hr. The hydrogen uptake (ca. 40 ml.) corresponded approximately to 2H. After filtration the solution was alkalized with aqueous sodium hydroxide and extracted with chloroform. Evaporation of the chloroform extract yielded a base which was distilled; it consisted of a colorless oil (80 mgm.), boiling at 0.4 mm. at an air bath temperature of 95–105°, which did not crystallize. The dipicrate of this base, which crystallized from a solution of the components in methanol, was recrystallized from methanol. It consisted of bright yellow needles, m.p. 209°, undepressed in admixture with authentic *l*-sparteine dipicrate. The infrared absorption spectrum taken as a Nujol mull was identical with that of *l*-sparteine dipicrate measured under the same conditions.

Anhydrolupanoline

A solution of lupanoline (500 mgm.) in purified acetic anhydride (3 ml.) was refluxed for one hour, cooled, and treated with cold water. It was extracted twice with ether and alkalized with aqueous sodium hydroxide. The liberated base was extracted with ether, recovered from the extract by evaporation of the solvent, and distilled *in vacuo*. Anhydrolupanoline was thus obtained as a colorless oil, b.p. 145–150° at 0.1 mm., which crystallized readily from ligroin (60–80°) in colorless prisms, m.p. 94–95°, yield 315 mgm. Recrystallization did not alter the melting point. $[\alpha]_D^{24} - 43.1° \pm 1$ (*c*, 0.58 in water). Calcd. for $C_{15}H_{22}ON_2$: C, 73.13; H, 9.01. Found: C, 73.15, 73.30; H, 9.03, 8.85%. In admixture with monspessulanine (m.p. 100°) of which it is an isomer it melted at 65–70°. Admixture with aphyllidine also caused a depression.

Anhydrolupanoline formed a perchlorate in the usual way which separated from methanol as colorless, elongated prisms, m.p. 252–253° (dec.). $[\alpha]_D^{26} - 57° \pm 1$ (*c*, 0.912 in water). Calcd. for $C_{15}H_{22}ON_2.HClO_4$: C, 51.94; H, 6.68; N, 8.08. Found: C, 51.77; H, 6.68; N, 7.71%.

Dihydroanhydrolupanoline

Anhydrolupanoline (100 mgm.) was hydrogenated in ethanol (10 ml.) at room temperature and atmospheric pressure in the presence of freshly prepared Adams' catalyst (50 mgm.). Hydrogenation proceeded rapidly and was essentially complete within 15 min. After one hour (hydrogen uptake ca. 15 ml.) the mixture was filtered and the filtrate evaporated on a steam bath. The residual dihydroanhydrolupanoline crystallized readily from ligroin (60–80°) in colorless sheaves, m.p. 103–104° (yield 70 mgm.). Calcd. for $C_{15}H_{24}ON_2$: C, 72.51; H, 9.74; N, 11.28. Found: C, 72.56, 72.78; H, 9.59, 9.58; N, 11.15%. The infrared absorption spectrum of the base was not identical with that of the isomeric dihydromonspessulanine.[4]

A small quantity of the base was dissolved in methanol and the solution made just acid to Congo red by the dropwise addition of 67% perchloric acid. On standing the solution deposited a crystalline perchlorate which after several recrystallizations from methanol consisted of colorless prisms, m.p. 224–225°. Calcd. for $C_{15}H_{24}ON_2.HClO_4$: C, 51.65; H, 7.17. Found: C, 51.61, 51.72; H, 6.84, 6.75%.

Action of Mineral Acid on Anhydrolupanoline

A solution of anhydrolupanoline (100 mgm.) in *N* hydrochloric acid was heated to 100° for two hours, then cooled and alkalized with aqueous sodium hydroxide. The product, isolated by extraction with chloroform, crystallized from ligroin (60–80°) in colorless rhombs, m.p. 163–167° (65 mgm.). Two recrystallizations raised the melting point to 169–170° (with previous shrinking). The material gave no depression in melting point on admixture with pure lupanoline. Calcd. for $C_{15}H_{24}O_2N_2$: C, 68.14; H, 9.15; N, 10.60. Found: C, 67.53, 67.83; H, 9.27, 8.91; N, 10.50%. This base was converted by the action of lithium aluminum hydride into β-isosparteine which was identified as its perchlorate. It is thus identical with lupanoline but probably contains a trace of an isomer sufficient to cause the unsharp melting point behavior.

Reduction of Anhydrolupanoline with Lithium Aluminum Hydride

Anhydrolupanoline (100 mgm.) in dry ether (10 ml.) was treated with ethereal lithium aluminum hydride (1 ml., 0.015 gm. per ml.) and the mixture refluxed for four hours. Water was then added cautiously, followed by aqueous sodium hydroxide, and the product isolated with ether. A portion of the oily base thus obtained decomposed on attempted distillation *in vacuo* and formed an oily perchlorate. The remainder of the product was hydrogenated in acetic acid solution over fresh Adams' catalyst for 12 hr. The basic product, isolated in the usual way, distilled as an oil, b.p.110–120° (air bath) at 0.2 mm. The diperchlorate, m.p. 255° (dec.), proved to be identical with that of β-isosparteine.

Oxo-β-isosparteine

β-Isosparteine (freshly distilled, 130 mgm.) was shaken vigorously with

[4] *Dihydroanhydrolupanoline is also obtainable directly by catalytic hydrogenation of lupanoline. This experiment as well as the comparison with dihydromonspessulanine was carried out by Dr. Bryce Douglas.*

cold water (25 ml.), the resulting suspension treated with a solution of potassium ferricyanide (660 mgm.) and potassium hydroxide (60 mgm.) in water (10 ml.) and shaken mechanically for one hour. The resulting straw-colored solution was allowed to stand overnight at room temperature, and then extracted with chloroform. The crude base obtained by evaporation of the chloroform extract was distilled *in vacuo* and afforded a pale yellow oil (35 mgm.), b.p. 135–140° (air bath) at 0.5 mm., together with a considerable nonvolatile residue. The distillate was dissolved in ligroin (60–80°), the solution filtered, evaporated to a small bulk, and allowed to stand. Oxo-β-sparteine crystallized which after recrystallization from ligroin (60–80°) consisted of colorless sheaves, m.p. 103–104°, undepressed on admixture with a specimen of dihydroanhydrolupanoline.

ACKNOWLEDGMENT

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