THE STRUCTURE OF RETAMINE AND THE PARTIAL SYNTHESIS OF THE (−)-ENANTIOMORPH[1]

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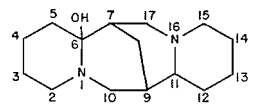
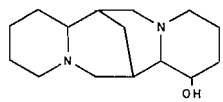
ABSTRACT

Previous work by many authors has led to the assumption that retamine might be (+)-12-hydroxysparteine. A partial synthesis of the enantiomorph of this compound has been effected by dehydration of (+)-13-hydroxylupanine and hydroboration of the product. The dehydration product consisted of two components that were separated by thin-layer chromatography and identified by the characteristics of their nuclear magnetic resonance (n.m.r.) spectra as $\Delta^{12,13}$- and $\Delta^{13,14}$-dehydrolupanine. Hydroboration of the $\Delta^{12,13}$-isomer gave rise to (−)-12-hydroxysparteine having, in thin-layer chromatography, the same R_f value as natural retamine and the same optical rotation numerically, although of opposite sign. The synthetic base had the same infrared and n.m.r. spectra as the alkaloid and the two had superimposable Debye–Scherrer patterns. Evidence is given showing the hydroxyl to be equatorial.

The lupin alkaloid retamine, $C_{15}H_{26}ON_2$, m.p. 168°, $[\alpha]_D$ +46.2°, was first isolated by Battandier and Malosse (1). It was suggested by White (2) that it was probably a hydroxysparteine, and by Ribas, Sanchez, and Primo (3) that it was likely 6-hydroxysparteine (I). Later Ribas and Fraga (4) recognized that the properties of retamine could not be accommodated by a 6-hydroxy structure and, since the base could not be oxidized to a ketone, they suggested that it was either a 7- or a 9-hydroxy-(+)-sparteine. More recently, in the light of new evidence, Ribas and his co-workers (5) abandoned the 7- or 9-hydroxy structure in favor of 8-hydroxy-(+)-sparteine, notwithstanding the fact that retamine did not produce a ketone on oxidation. Finally, Bohlmann and his co-workers (6, 7) synthesized both epimers of each 7-hydroxy and 9-hydroxy-(+)-sparteine as well as the two epimers of 8-hydroxy-(+)-sparteine and established that none of these was identical with retamine.



I



II

From the results of Ribas *et al.* (5) the hydroxyl in retamine can be present only in ring A or ring D. Since, however, anhydroretamine obtained by the dehydration of the base at high temperature gives rise on catalytic hydrogenation to a mixture of sparteine and α-isosparteine, it must be concluded that the hydroxyl is located in ring D. Furthermore, retamine is not a carbinolamine and, therefore, the hydroxyl cannot occupy positions 11 or 15. Also both epimers of 13-hydroxysparteine are known (8) and neither is identical with the alkaloid. Consequently, Bohlmann *et al.* (7) have suggested that retamine was either 12-hydroxysparteine II or 14-hydroxysparteine. It was assumed that the dehydration of 12-hydroxysparteine would give rise to $\Delta^{11,12}$-dehydrosparteine, and since this product on catalytic hydrogenation should form α-isosparteine exclusively (9, 10) whereas the dehydration product of retamine, depending on the temperature at which it was

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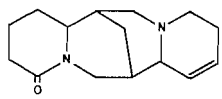
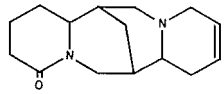
formed (5), produced on hydrogenation either sparteine or a mixture of sparteine and α-isosparteine, Bohlmann (8) considered 14-hydroxysparteine as the more likely structure for retamine.



III



IV

From a consideration of the optical activity, the possibility that retamine could be a hydroxy-α-isosparteine can be discarded. The molecular rotation of retamine is +115 and, on the assumption that it is a hydroxysparteine, the calculated molecular rotation of its hydroxy epimer, isoretamine, should be −35° in agreement with the found value (5). Were retamine a hydroxy-α-isosparteine, the molecular rotation of its hydroxy epimer should be +145.

In an attempt to establish the structure of retamine we have sought to synthesize its (−)-enantiomorph from naturally occurring (+)-13-hydroxylupanine. The dehydration of this hydroxy base would be expected to give a mixture of $\Delta^{12,13}$-dehydrolupanine III and the $\Delta^{13,14}$-isomer. In fact when 13-hydroxylupanine was dehydrated by heating at 170° with phosphoric anhydride the product showed two main spots in thin-layer chromatography.

Hydroboration of the mixed dehydrolupanines produced a mixture, one of the components of which, after purification by chromatography and sublimation, corresponded to the (−)-enantiomorph of retamine. It melted at 166–167° and depressed the melting point of the alkaloid when the two were mixed, but its infrared and n.m.r. spectra were identical, respectively, with those of retamine. It can be concluded from this result that retamine must be either 12-hydroxy- or 14-hydroxysparteine. It had been ascertained in a preliminary experiment that diborane reduced the lactamic carbonyl and converted (+)-lupanine to (−)-sparteine. Brown and Heim (11) have since shown that amides generally are reduced by diborane.

In $\Delta^{12,13}$-dehydrolupanine III the system $\rangle CH \cdot CH{=}CH \cdot CH_2-$ is present while in $\Delta^{13,14}$-dehydrolupanine IV there is the sequence $-CH_2 \cdot CH{=}CH \cdot CH_2-$. The n.m.r. spectrum of the mixture of the two dehydrolupanines isolated from the product of the dehydration of 13-hydroxylupanine contains in the ethylenic region a symmetrical quartet centered at δ 5.07 which should be assigned to the protons of the symmetrically substituted ethylenic system of $\Delta^{13,14}$-dehydrolupanine, and an unsymmetrical signal at σ 5.64, 5.48 assignable to $\Delta^{12,13}$-dehydrolupanine. The mixture of dehydrolupanines was separated into its two components by preparative scale chromatography. The component with R_f 0.49 which, in the n.m.r., showed an unsymmetrical signal (δ 5.72, 5.53, 5.32), but no symmetrical quartet, was taken to be $\Delta^{12,13}$-dehydrolupanine III while the component with R_f 0.55 containing a symmetrical quartet in its n.m.r. spectrum was considered to be $\Delta^{13,14}$-dehydrolupanine IV.[3] Hydroxylation of $\Delta^{12,13}$-dehydrolupanine by treatment with diborane yielded a product showing in thin-layer chromatography three main spots (R_f 0.64, 0.47, and 0.33), of which the intermediate one corresponded to retamine, plus four other weak spots.

[3]*Such an assignment is not always reliable, particularly when dealing with a single compound. With a mixture of two compounds, however, representing both systems and giving the coupling patterns expected of each, the assignment becomes much more reliable, especially since after separation one component gives only the unsymmetrical pattern and the other component produces exclusively the symmetrical pattern.*

The components of the reaction mixture were separated by preparative scale thin-layer chromatography with developing solvent No. 3. The band corresponding to retamine was eluted and the product after distillation *in vacuo* crystallized spontaneously. The crystals, washed with acetone and dried, melted at 166–167°. In admixture with the synthetic retamine enantiomorph described above, the melting point was unaltered, but in admixture with naturally occurring (+)-retamine (m.p. 168°)[4] it melted at 146–147.5°. The synthetic base had $[\alpha]_D^{24}$ −47.3°, which is in good agreement numerically, but of opposite sign, with the optical rotation of authentic retamine. The infrared and n.m.r. spectra and the X-ray powder pattern of synthetic (−)-12-hydroxysparteine III were identical, respectively, with those of authentic retamine, and the mobilities of the two in thin-layer chromatography were the same. It can be concluded that retamine is (+)-12-hydroxysparteine.

The direction of elimination in the dehydration of retamine is temperature dependent. If the temperature of the reaction is kept below 170° the dehydro derivative formed gives rise to sparteine on hydrogenation. When the dehydration is carried out at 200° the product gives rise to α-isosparteine on hydrogenation so that in this case the double bond must be in the $\Delta^{11,12}$ position. It is most unlikely that a 14-hydroxysparteine could give rise to $\Delta^{11,12}$-dehydrosparteine and therefore on chemical grounds can be rejected.

Since an axial hydroxyl would be expected to give $\Delta^{11,12}$-dehydrosparteine readily on dehydration, the experimental results of Ribas (5) showing that this isomer is formed only under drastic conditions and is still accompanied by the $\Delta^{12,13}$-isomer militate in favor of an equatorial hydroxyl in retamine. Such a configuration of 12-hydroxy-(+)-sparteine would favor acid-catalyzed elimination of trans-diequatorial hydroxyl and hydrogen and formation of $\Delta^{12,13}$-dehydrosparteine, whereas an axial hydroxyl would not favor the formation of this compound.

Furthermore, hydroboration proceeds preferentially from the less hindered side of cyclic or bicyclic olefins (12). An examination of a Dreiding model shows that a C-12 equatorial hydroxyl is less hindered than an axial hydroxyl, so that in accordance with the foregoing generalization the former would be favored.

In the light of the established structure of retamine the peculiarities of the dehydration of the alkaloid are readily explained. Dehydration at the lower temperature gives rise to $\Delta^{12,13}$-dehydrosparteine, which on hydrogenation produces sparteine. On the other hand at ca. 200° the predominant product is $\Delta^{11,12}$-dehydrosparteine accompanied by some of the $\Delta^{12,13}$-isomer, because of the partial rearrangement of the latter. Catalytic hydrogenation of the mixture would give rise to both α-isosparteine and sparteine.

NOTE ADDED IN PROOF: After this manuscript had been accepted for publication a paper on the structure and synthesis of retamine (F. Bohlmann, H. Overwien, and D. Schumann, Chem. Ber. 98, 659, 1965) received in Ottawa April 23 appeared in print. The constitution assigned to retamine in that paper is the same as that we have assigned, although the configuration is different. The interpretation of our evidence led us to the conclusion that the hydroxyl in retamine is equatorial.

EXPERIMENTAL

The distillations were carried out in glass bulbs blown in a tube and the temperatures cited were those of the air bath surrounding the end bulb. The n.m.r. spectra were obtained on an A-60 Varian spectrometer, in deutero-chloroform solution with tetramethylsilane as an internal indicator. For thin-layer chromatography, silica gel G was used with one of the following developing solvents: cyclohexane–chloroform–diethylamine

[4]*Very kindly sent by Professor I. Ribas, whom we thank cordially.*

7:2:1 (solvent No. 1); methanol–diethylamine 9:1 (solvent No. 2); heptane–methylethylketone–diethylamine 7.5:2:0.5 (solvent No. 3). The spots were brought out by spraying with modified Dragendorf's reagent.

Dehydration of (+)-13-Hydroxylupanine

Finely powdered (+)-13-hydroxylupanine (3.0 g) mixed with phosphorus pentoxide (17.0 g) was heated during 6 h in a metal bath at 170–175°. After cooling, cracked ice was added gradually, the reaction mixture was made strongly basic with potassium hydroxide and extracted with methylene chloride. The extract was dried over sodium sulfate and the solvent evaporated *in vacuo*. There was left a slightly colored residual oil (2.3 g). A small sample showed in thin-layer chromatography two quite close spots corresponding to the anhydrolupanines (R_f 0.49, solvent No. 1), one spot corresponding to the starting material (R_f 0.12) and three other spots that were very faint.

The residual oil was dissolved in benzene and chromatographed on neutral grade I alumina (70 g). The column was eluted and the eluate collected in 100 ml fractions. The results of the elution are given in the following table. Combined fractions 1–11 gave 1.360 g of the mixture of anhydrolupanines. This mixture

Fractions	Eluant	Residue, mg	Product
1–5	Benzene	105	Anhydrolupanines
6	Benzene–chloroform 9:1	15	,,
7	Benzene–chloroform 8:2	50	,,
8	Benzene–chloroform 7:3	75	,,
9	Benzene–chloroform 5:5	300	,,
10	Benzene–chloroform 4:6	400	,,
11	Benzene–chloroform 3:7	415	,,
12	Benzene–chloroform 2:8	50	,, and starting product
13–15	Chloroform	110	Starting product
16–18	Methanol	440	Starting product

contained in its n.m.r. spectrum in the ethylenic region a symmetrical quartet centered at δ 5.07 attributable to the protons of the symmetrically substituted ethylenic system of $\Delta^{13,14}$-anhydrolupanine and an unsymmetrical signal at δ 5.64, 5.48 assignable to $\Delta^{12,13}$-anhydrolupanine.

Synthesis of Retamine

A solution of diborane was first prepared by the addition of freshly distilled boron fluoride ethyl ether (5 ml) to a solution of sodium borohydride (5.9 g) in tetrahydrofurane (100 ml) kept magnetically stirred and cooled in an ice bath. The addition was carried out in the course of 20 min in a stream of nitrogen. The reaction mixture was then kept at room temperature for 16 h.

To the mixture of anhydrolupanines (900 mg) obtained by dehydration of (+)-13-hydroxylupanine dissolved in tetrahydrofurane (50 ml) and cooled in ice while magnetically stirred, the above solution of diborane was added in the course of 10 min in a stream of nitrogen. After 30 min the ice bath was removed and the stirring continued under an atmosphere of nitrogen for $2\frac{1}{2}$ h at room temperature. The reaction mixture was again cooled in an ice bath, made alkaline by the gradual addition of 20% aqueous sodium hydroxide, followed by the dropwise addition of 30% hydrogen peroxide (5 ml). The mixture was heated on the steam bath for 15 min, cooled, and decanted. The aqueous layer was extracted with benzene, the benzene extract combined with the tetrahydrofurane layer, dried over sodium sulfate, and evaporated to dryness under reduced pressure. The residue consisted of a slightly colored oil (900 mg) which, in thin-layer chromatography, showed two main spots (R_f 0.64 and 0.47, solvent No. 3), the second of which (R_f 0.47) was identical with that of retamine. There is also a spot (R_f 0.33) corresponding to an important quantity of unchanged starting material, and four other much weaker spots (R_f 0.54, 0.24, 0.18, 0.12).

Separation of Retamine

The above product (900 mg) obtained from the hydroboration reaction was distributed onto 10 plates (20 × 20 cm) covered with silica gel G of 0.5 mm thickness and the chromatograms were developed with solvent No. 3. The spots were brought out on strips of the chromatograms with Dragendorf's reagent and the parts corresponding to the retamine spot were scraped off, and eluted with methanol containing 5% of diethylamine. The substance obtained from this elution (200 mg) was again chromatographed on two plates (20 × 20 cm) exactly as before. It yielded on elution a crystalline residue (100 mg) that was further purified by two sublimations at 115° under 10^{-3} mm, wt. 60 mg. The substance then melted at 166–167° and in admixture with authentic (+)-retamine[4] melted at 144–148°, $[\alpha]_D^{21}$ −47.3° (c = 0.97 in 95% EtOH). Its infrared and n.m.r. spectra and X-ray powder pattern were identical, respectively, with those of (+)-retamine.

Separation of $\Delta^{12,13}$- and $\Delta^{13,14}$-Anhydrolupanine

The mixture of $\Delta^{12,13}$- and $\Delta^{13,14}$-anhydrolupanine (300 mg) was applied on five plates (20 × 20 cm) covered with silica gel and the chromatograms developed with solvent No. 1. Two fractions were obtained: fraction A ($\Delta^{13,14}$-anhydrolupanine), R_f 0.55, had a higher mobility than fraction B ($\Delta^{12,13}$-anhydrolupanine, R_f 0.49). Both fractions were located after spraying a strip on each plate with modified Dragendorf's reagent. Fraction B was scraped off and eluted with methylene chloride containing about 5% of diethyl amine. The eluate, evaporated *in vacuo*, left a residual, slightly yellow oil containing fraction B still contaminated with a very small quantity of fraction A. The separation by preparative scale thin-layer chromatography was repeated. It yielded pure $\Delta^{12,13}$-anhydrolupanine (fraction B), which produced a single spot in thin-layer chromatography. The product was distilled at 140° under 0.01 mm, wt. 102 mg. Its n.m.r. spectrum contained signals at δ 5.72, 5.53, 5.32.

Fraction A was also scraped off the plates, eluted with methylene chloride containing 5% of diethylamine. It was purified again by preparative scale thin-layer chromatography. The product thus obtained ($\Delta^{13,14}$-anhydrolupanine) showed a single spot in thin-layer chromatography and its n.m.r. spectrum contained a symmetrical quartet centered at δ 5.07.

Conversion of $\Delta^{12,13}$-Anhydrolupanine to (−)-Retamine

To a solution of $\Delta^{12,13}$-anhydrolupanine (102 mg) in tetrahydrofurane cooled in an ice-water bath and stirred under a nitrogen atmosphere, a diborane solution prepared as above (6 ml) was added in the course of 10 min. The reaction was completed exactly as described above, and the product isolated by the same procedure. It was purified by preparative scale chromatography, followed by distillation at 130° under 0.01 mm it crystallized spontaneously, m.p. 155–164°. The undistilled residue was dissolved in methylene chloride, chromatographed on grade III alumina, and eluted with chloroform. Evaporation of the eluate left a residue which was crystallized from acetone, m.p. 164–167°. Both crystalline fractions (m.p. 155–164° and 164–167°) were combined and distilled at 135° under 0.01 mm. The distillate crystallized spontaneously and was washed with a little acetone, m.p. 166–167°. The melting point was not depressed by admixture with the synthetic sample described above, but in admixture with authentic retamine, m.p. 146–147.5°. The synthetic product had the same mobility in thin-layer chromatography as authentic retamine; its infrared and n.m.r. spectra and X-ray powder pattern were identical, respectively, with those of the alkaloid.

Action of Diborane on (−)-Lupanine

(−)-Lupanine (380 mg) was dissolved in tetrahydrofurane (30 ml) and treated with diborane exactly as described above. The product, worked up as described for retamine and distilled at 150° under 0.01 mm, was an oil that formed a crystalline perchlorate. After recrystallization from methanol, the salt melted at 173° either alone or in admixture with an authentic sample of (+)-sparteine perchlorate.

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