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The Aconite Alkaloids. XXXVII.[1] Anhydro-diacetyldelcosine (Anhydrodiacetyllucaconine) and Its Novel Hydrogenation[2]

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Delcosine (lucaconine) and its derivatives have all been shown to lose one mole of water, upon treatment with acetyl chloride, thus giving an anhydro compound. On the basis of the observation of the infrared spectra of anhydro-diacetyldelcosine, anhydro-oxodelcosine, and anhydro-1, 10-didehydro-oxodelcosine, it may be concluded that, in each compound, dehydration takes place between two tertiary hydroxyl groups, with a ketone carbonyl group being formed. Based on a tentative structure for delcosine proposed by Marion and his co-workers, structures for anhydro-diacetyldelcosine and anhydro-oxdelcosine are proposed. On hydrogenation over platinum in acetic acid, anhydro-diacetyldelcosine yielded anhydro-dihydro-diacetyldelcosine. Anhydro-oxodelcosine was inert under these reduction conditions. On the basis of these experimental results, a possible mechanism of this novel hydrogenation is proposed. The ultraviolet spectrum of anhydro-diacetyldelcosine, with a new type of chromophore, is also shown.

Lucaconine (I) ($C_{24}H_{39}O_7N$) is an alkaloid isolated from *Aconitum lucidusculum, Nakai.*[5] Recently this alkaloid was shown to be identical with a *Delphinium* alkaloid, delcosine.[1],[*1] On the basis

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[1] This is one of a series entitled "The Aconite Alkaloids," by H. Suginome; Part XXXVI; T. Amiya and T. Shima, This Bulletin, **35**, 740 (1962).

[2] Preliminary notes on part of the matter of this paper appeared in Refs. 4a, b.

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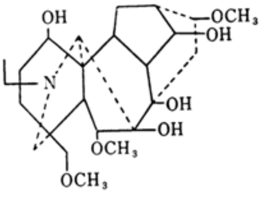
[4] a) T. Amiya and T. Shima, This Bulletin, **31**, 1083 (1958); b) T. Amiya and T. Shima, *J. Org. Chem.*, **26**, 2616 (1961).

[5] H. Suginome, S. Kakimoto, J. Sonoda and S. Noguchi, *Proc. Japan Acad.*, **22**, 122 (1946); H. Suginome and S. Furusawa, This Bulletin, **32**, 354 (1959).

[*1] The name "lucaconine" should be revised to "delcosine."

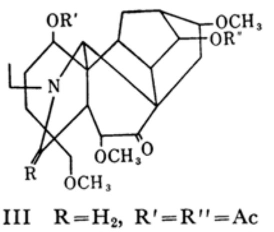
of their extensive research, Marion and his coworkers[6-9] have proposed a tentative structure I for delcosine with both the same carbon-nitrogen skeleton as lycoctonine (II)[10],[*2] and similar substituents at the same position as II. This structure, I, is supported by the results of study by other investigators[12] and by the observation of the NMR spectrum of I.[13]



I

On the other hand, it was previously reported by Furusawa of this laboratory that, on the treatment of I with acetyl chloride, one mole of water was lost and anhydro-diacetyldelcosine[*3] (anhydrodiacetyllucaconine) (III) ($C_{28}H_{41}O_8N$) was produced.[14] Compound III was also shown to absorb one mole of hydrogen.[14] Moreover, it was described that the treatment of oxolucaconine (IV) ($C_{24}H_{37}O_8N\cdot 1\frac{3}{4}\ H_2O$)[*4] with acetyl chloride, followed by hydrolysis gave anhydro-oxodelcosine (anhydrooxolucaconine) (VI) ($C_{24}H_{35}O_7H$).[14] Previously, compound III was independently prepared and partly investigated.[15] Investigations of the dehydration reactions of I and its derivatives, as well as of the novel hydrogenation reaction of compound III, have since been further continued. The present authors wish to describe here the results of these investigations.

Compound III showed carbonyl band at 5.77 and 5.81 μ due to ester carbonyl groups and a ketone carbonyl group newly formed by dehydration, but no hydroxyl band was shown in the infrared spectrum. Compound VI contained a hydroxyl band at 2.95 μ, a newly-formed ketone carbonyl band at 5.78 μ and a lactam carbonyl band at 6.16 μ in the infrared spectrum. The treatment with acetyl chloride of 1-dehydro-oxodelcosine (oxolucaconinone-II) (VII) ($C_{24}H_{35}O_8N$),[1,4a,6] a lactam with a six-membered ketone carbonyl group, followed by hydrolysis and further oxidation by a chromium trioxide-pyridine complex, gave a triketo-compound, anhydro-1, 10-didehydro-oxodelcosine (anhydrooxolucaconinedione) (VIII) ($C_{24}H_{31}O_7N$). Compound VIII had earleir been obtained from both compound III and compound IV through three steps involving the formation of compound VI.[14] This compound manifested carbonyl bands at 5.72 μ (five-membered cyclic ketone), 5.78 μ (ketone newly formed by dehydration), 5.83 μ (six-membered cyclic ketone), and 6.17 μ (six-membered lactam) in the infrared spectrum. No hydroxyl band was shown. The observation of the infrared spectra of these compounds indicates that in each compound, III, VI and VIII, obtained by treatment with acetyl chloride, a ketone carbonyl group was formed with the elimination of one mole of water between the two tertiary hydroxyl groups. The mechanism of the dehydration is considered to be analogous to that of the dehydration of oxolycoctonine or demethyleneoxodelpheline.[16] On the basis of the structure I, compounds III and VI are represented by structures III and VI respectively. The presence of the *N*-ethyl group in compound VI has already been shown.[14] Compound VI was obtained by the chromium trioxide-pyridine complex oxidation of compound III, followed by hydrolysis. This compound has also been obtained from compound III through two steps.[14]



III R=H_2, R'=R''=Ac
VI R=O, R'=R''=H

On hydrogenation over platinum in acetic acid, compound III absorbed one mole of hydrogen and yielded a dihydro compound, anhydro-dihydro-diacetyldelcosine (anhydrodihydrodiacetyllucaconine) (IX) ($X_{28}H_{43}O_8N$), mp 175°C. This compound revealed carbonyl bands at 5.77 and

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6) V. Skaric and L. Marion, *J. Am. Chem. Soc.*, **80**, 4434 (1958); V. Skaric and L. Marion, *Can. J. Chem.*, **38**, 2433 (1960).

7) R. Anet, D. W. Clayton and L. Marion, *ibid.*, **35**, 397 (1957).

8) R. Anet and L. Marion, *ibid.*, **36**, 766 (1958).

9) V. Skaric and L. Marion, *ibid.*, **39**, 1579 (1961).

10) M. Przybylska and L. Marion, *ibid.*, **34**, 185 (1956); O. E. Edwards, L. Marion and D. K. R. Stewart, *ibid.*, **34**, 1315 (1956).

[*2] The absolute configuration of (+)-des-(oxymethylene)-lycoctonine has recently been shown.[11] The skeleton of structure I in this paper is a mirror image of that of structure I shown in a previous paper.[4b]

11) M. Przybylska and L. Marion, *Can. J. Chem.*, **37**, 1843 (1959).

12) E. Ochiai, T. Okamoto and M. Kaneko, *Chem. Pharm. Bull.*, **6**, 730 (1958); *Ann. Rept. ITSUU Lab.*, **11**, 21 (1960); *ibid.*, **11**, 29 (1960).

13) A. Suzuki, T. Amiya and T. Matsumoto, This Bulletin, **34**, 455 (1961).

[*3] This compound is identical with the diacetyldelcosine (mp 159—161°C) obtained by Marion *et al.*;[15] it seems preferable to call it anhydro-diacetyldelcosine.

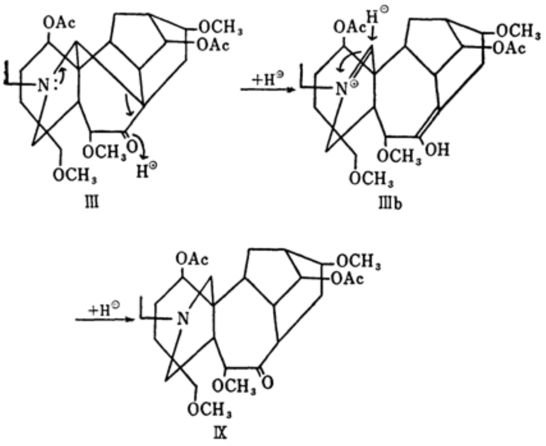
14) S. Furusawa, This Bulletin, **32**, 399 (1959).

[*4] Oxolucaconine (IV) is a hydrate of isooxolucaconine (oxodelcosine)[6] (V) ($C_{24}H_{37}O_8N$) and may easily be converted to compound V by the elimination of the crystal water.[14]

15) W. I. Taylor, W. E. Walles and L. Marion, *Can. J. Chem.*, **32**, 780 (1954).

16) E. S. Stern, "The Alkaloids, Chemistry and Physiology," Vol. VII, R. H. F. Manske, ed., Academic Press, New York (1960), p. 473.

5.93 μ due to ester carbonyl groups and a ketone carbonyl group, and no hydroxyl band in the infrared spectrum. In other words, compound III was found to absorb one mole of hydrogen, without any reduction of the carbonyl group. Compound VI was recovered unchanged after being subjected to the conditions producing the hydrogenation of compound III. On the basis of these experimental results, the formation of IX from III by hydrogenation may be expressed in the following way (III→IIIb→IX) (Scheme A):



Scheme A

The ultraviolet absorption spectrum of compound III in methanol manifested a maximum at 237 mμ (log ε 3.20) (Fig. 1). This seemed to be an abnormal phenomenon.[4b] A similar phenomenon had already been observed in the case of some delphinine and neoline derivatives.[17] Most recently, the results of detailed spectral studies of a new type of chromophore, in relation to the above interesting spectra, have been published.[18] According to this study, compound III is a β-amino ketone which is set up for a σ-coupled transition. The unexpected absorption maximum of this compound is abolished by amide formation (*cf.* the ultraviolet absorption spectra of compounds VI and VIII). The ultraviolet absorption spectrum of compound VI in methanol revealed a maximum at 301 mμ (log ε 2.01) (Fig. 1), while that of compound VIII contained a maximum at 305 mμ (log ε 2.10). These two spectra show absorption maxima ascribed to ketone carbonyl groups near 300 mμ as in the case of those of ketonic derivatives of the alkaloid,[1,6,9] these maxima are apparently to be distinguished from that of compound III.

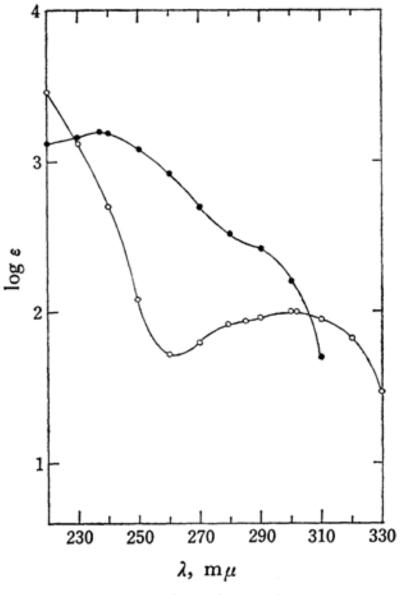


Fig. 1. The ultraviolet absorption spectra.
—●— Anhydro-diacetyldelcosine (III)
—○— Anhydro-oxodelcosine (VI)

Experimental

Anhydro-diacetyldelcosine (Anhydrodiacetyllucaconine) (III). The ultraviolet absorption spectrum of this compound in methanol showed λ_{max} 237 mμ log ε 3.20. The infrared absorption spectrum in Nujol showed the presence of ester carbonyl groups (5.77 μ) and a ketone carbonyl group (5.81 μ).

Anhydro-oxodelcosine (Anhydrooxolucaconine) (VI) from III. A mixture of III (0.5 g), chromium trioxide (0.5 g), and pyridine (10 m*l*) was allowed to stand at room temperature overnight. It was then evaporated to dryness *in vacuo*. After the addition of water (40 ml), the residue was reduced with sulfur dioxide. The excess reagent having been reduced, the acid solution thus obtained was extracted with chloroform three times. After the removal of the solvent, a residue (0.4 g) was obtained. This residue was then hydrolyzed with boiling methanolic potassium hydroxide under a stream of nitrogen for 1 hr. After cooling, the solution was evaporated, and the residue was neutralized with 1 N hydrochloric acid and extracted with chloroform. After the removal of the chloroform, the residue was crystallized from acetone. Recrystallization from ethanol gave crystals, mp 260°C. Mixture with anhydrooxolucaconine, prepared according to the direction of Furusawa,[14] did not alter the melting point. The ultraviolet absorption spectrum of this compound in methanol showed λ_{min} 260 mμ, log ε 1.72, and λ_{max} 301 mμ, log ε 2.01. The infrared absorption spectrum in Nujol showed the presence of hydroxyl groups (2.95 μ) a ketone carbonyl group (5.78 μ), and a lactam carbonyl group (6.16 μ).

Anhydro-1, 10-didehydro-oxodelcosine (Anhydrooxolucaconinedione) (VIII) from 1-Dehydro-oxodelcosine (Oxolucaconinone-II) (VII). A mixture of 0.5 g of VII and 3 m*l* of acetyl chloride was allowed to stand in a sealed tube for two weeks. After the removal of the excess acetyl chloride, the residue was

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[17] K. Wiesner, H. W. Brewer, D. L. Simons, D. R. Babin, F. Bickelhaupt, J. Kallos and T. Bogri, *Tetrahedron Letters*, **1960**, No. 3, 17.

[18] R. C. Cookson, J. Henstock and J. Hudeck, *J. Am. Chem. Soc.*, **88**, 1060 (1966).

dissolved in chloroform. The solution was washed with 1 N hydrochloric acid and then with a 1 N sodium hydroxide solution. After the removal of the solvent, an amorphous residue (0.4 g) was obtained. This residue was hydrolyzed with boiling methanolic potassium hydroxide under a stream of nitrogen for one hour. After the removal of the solvent, the residue was neutralized with 1 N hydrochloric acid and extracted with chloroform. The chloroform extract was then evaporated to give an amorphous residue (0.3 g). A mixture of this residue (0.3 g), chromium trioxide (0.3 g), and pyridine (6 m*l*) was allowed to stand at room temperature overnight. The reaction mixture was treated in the same way as in the above described oxidation. The chloroform extract from the acid solution gave an amorphous residue on evaporation. This residue was crystallized from ethanol. Two recrystallizations from ethanol gave crystals, mp 270°C. Mixture with anhydrooxolucaconinedione, prepared according to the directions of Furusawa,[14] did not alter the melting point. The ultraviolet absorption spectrum of this compound in methanol showed λ_{min} 260 mμ log ε 1.58 and λ_{max} 305 mμ, log ε 2.10. The infrared absorption spectrum in Nujol showed the presence of ketone carbonyl groups (5.72, 5.78, and 5.83 μ) and a lactam carbonyl group (6.17 μ).

Anhydro-dihydro-diacetyldelcosine (Anhydrodihydrodiacetyllucaconine) (IX). Anhydrodiacetyldelcosine (III) (0.54 g) was dissolved in 15 m*l* of glacial acetic acid and hydrogenated with 0.1 g of platinum oxide. The absorption of hydrogen stopped within 10 min. After the removal of the platinum, the solution was evaporated to dryness *in vacuo*. On the treatment of the residue with water and then with aqueous ammonia, a precipitate was obtained. On two crystallizations from ethanol, crystals, mp 175°C, $[\alpha]_D+12.7°$ (chloroform), were obtained. Yield, 0.35 g (pK_a 5.4). The ultraviolet absorption spectrum of this compound in methanol showed an end-absorption and no maximum. The infrared absorption spectrum in Nujol had no peak attributable to a hydroxyl group, but did show the presence of ester carbonyl groups (5.77 μ) and a ketone carbonyl group (5.93μ).

Found: C, 64.42; H, 8.03; OCH_3, 17.54%. Calcd for $C_{29}H_{43}O_8N$: C, 64.47; H, 8.31; OCH_3, 17.85%.

Attempted Hydrogenation of Anhydro-oxodelcosine (Anhydrooxolucaconine) (VI). Anhydro-oxodelcosine (VI) (0.08 g) was dissolved in 5 m*l* of glacial acetic acid and hydrogenated with 0.05 g of platinum oxide for three hours. After the removal of the platinum, the solution was evaporated to dryness *in vacuo*. When the residue was treated with acetone, crystals (70 mg), mp 260°C, were obtained. Mixture with the starting material did not alter the melting point. The two samples also showed superimposable infrared spectra.

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