The Aconite Alkaloids. XXXVI[1]. *Oxidation of Lucaconine and its Derivatives*[2b]

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Lucaconine (I) ($C_{24}H_{39}O_7N$) and monoacetyllucaconine (II) ($C_{26}H_{41}O_8N$) have been isolated from *Aconitum lucidusculum, Nakai*, and have been subjected to continuous research in this laboratory[4-7].

The present authors have further studied the degradation reactions of compound I and its derivatives; the oxidation reactions of these compounds, mainly with the chromium trioxide-pyridine complex, are reported on this paper (cf. Table I).

The oxidation of compound I with the chromium trioxide-pyridine complex yielded neutral products, oxolucaconine (III) ($C_{24}H_{37}O_8N \cdot 13/4H_2O$), oxolucaconinone-II(IV) ($C_{24}H_{35}O_8N$), m. p. 218°C, and oxolucaconinedione (V) ($C_{24}H_{33}O_8N$). Compound IV was a monoketo-lactam and showed absorption bands at 5.83 and 6.15 μ characteristic of a six-membered ring ketone and of a lactam carbonyl group in the infrared spectrum respectively. Its ultraviolet absorption spectrum showed a maximum (λ_{max} 298 mμ, log ε 1.90), indicating the presence of a ketone carbonyl group. Compounds III and V are a lactam and a diketo-lactam respectively; they had been previously obtained by Furusawa through other procedures[7]. Compound III manifested absorption bands in the infrared spectrum at 2.94 and 6.20 μ characteristic of hydroxyl and lactam carboxyl groups respectively. It was also obtained by chromium trioxide-pyridine complex oxidation of diacetyllucaconine (VI) ($C_{28}H_{43}O_9N$)[6], followed by hydrolysis. Compounds III and IV were further oxidized to compound V by the same reagent. The infrared spectrum of compound V manifested absorption bands at 5.72, 5.83 and 6.08 μ characteristic of a five-membered ring ketone, a six-membered ring ketone and a lactam carbonyl group respectively. The reduction of compound III with lithium aluminum hydride gave compound I again.

1) This is one part of a series entitled "The Aconite Alkaloids", by H. Suginome; for Part XXXV, cf. Ref. 2a.

2) a) T. Amiya, This Bulletin, **34**, 898 (1961); b) A preliminary note on part of the matter of this paper appeared in Ref. 4.

3) This paper comprizes part of a dissertation submitted by Takeo Shima, 1959, in partial fulfillment of the requirements for the Degree of Doctor of Science in Hokkaido University. Mr. Shima's present address: Teikoku Rayon Research Laboratory, Iwakuni, Yamaguchi.

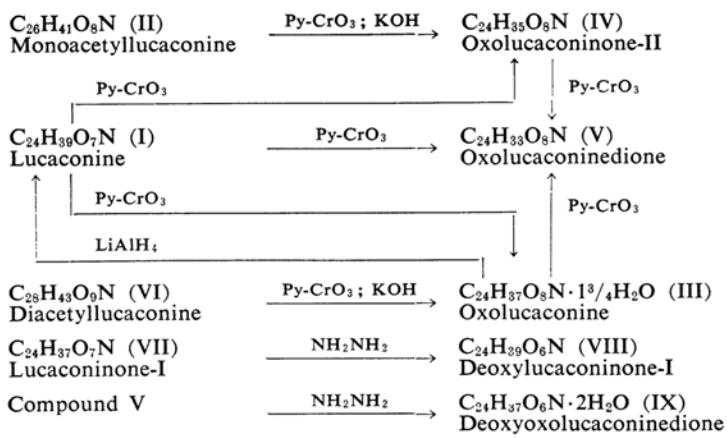
4) T. Amiya and T. Shima, This Bulletin, **31**, 1083 (1958).

5) H. Suginome, S. Kakimoto, J. Sonoda and S. Noguchi, *Proc. Japan Acad.*, **22**, 122 (1946).

6) H. Suginome and S. Furusawa, This Blletin, **32**, 354 (1959).

7) S. Furusawa, ibid., **32**, 399 (1959).

TABLE I



Lucaconinone-I (VII) ($C_{24}H_{37}O_7N$), a monoketo-base, was prepared from compound I by Furusawa[7]. It showed a band at 5.72 μ in the infrared spectrum due to the presence of a five-membered ring ketone carbonyl group. The ultraviolet absorption spectrum exhibited a maximum (λ_{max} 292 mμ, log ε 1.53). Compound VII was reduced to deoxylucaconinone-I (VIII) ($C_{24}H_{39}O_6N$), m. p. 165°C, by the Wolff-Kishner method. Its infrared spectrum showed no absorption characteristic of a ketone carbonyl group. The ultraviolet spectra of compounds III, VI and VIII showed only end absorptions.

Next, compound II, a naturally occurring base, was oxidized by the chromium trioxide-pyridine complex and subsequently hydrolyzed, giving compound IV. This result shows that an acetylated hydroxyl group in compound II is a secondary one attached to a carbon atom in a five-membered ring.

In view both of the experimental results previously obtained[7] and of those described in this investigation, the partial formula of compounds I and II may be extended as follows:

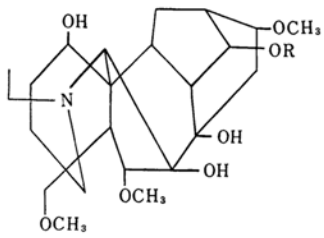
$C_{14}H_{17}$ { $(OCH_3)_3$, $(\rightarrow COH)_2$, $\rangle CHOR$ (five-membered ring), $\rangle CHOH$ (six-membered ring), $-N-C_2H_5$, $-\overset{|}{C}H_2$

I, R=H II, R=Ac

On the other hand, it has been suggested by Stern[8] that lucaconine seems to be identical with delcosine[9]. Since then, several reports concerning delcosine have been published by Marion and his co-workers[10-13]. In those reports a structure of delcosine has been proposed after a revision and the further possibility of identifying delcosine with lucaconine has been considered. Comparison of the physical properties of lucaconine and its derivatives and those of delcosine and its derivatives also leads to the supposition that lucaconine is identical with delcosine. Recently, lucaconine has been found to be identical in melting point and infrared spectrum with Takao base-I[14,15], showing no depression in mixed melting point; therefore, lucaconine must be identical with delcosine, which has already been shown to be identical with Takao base-I[14]. Accordingly, the name "lucaconine", must be revised to "delcosine", and derivatives of compound I should be named as those of delcosine.

According to the structure of delcosine (compound I) proposed by Skaric and Marion[13], compound II, a naturally occurring base, ought to have the structure shown in Scheme A. While oxidation and subsequent hydrolysis of monoacetyldelcosine have given dehydrooxodelcosine[13], compound II has yielded compound IV[4] on the same treatment. As compound IV seems to be identical with dehydrooxodelcosine, compound II is probably identical with monoacetyldelcosine, as has been pointed out by Canadian workers[13].

8) E. S. Stern, "The Alkaloids, Chemistry and Physiology", Vol. 4, Ed. by R. H. F. Manske and H. L. Holmes, Academic Press, Inc., New York (1954), p. 328.
9) L. Marion and O. E. Edwards, *J. Am. Chem. Soc.*, **69**, 2010 (1947).
10) W. I. Taylor, W. E. Walles and L. Marion, *Can. J. Chem.*, **32**, 780 (1954).
11) R. Anet, D. W. Clayton and L. Marion, ibid., **35**, 397 (1957).
12) R. Anet and L. Marion, ibid., **36**, 766 (1958).
13) V. Skaric and L. Marion, *J. Am. Chem. Soc.*, **80**, 4434 (1958); V. Skaric and L. Marion, *Can. J. Chem.*, **38**, 2433 (1960).
14) E. Ochiai, T. Okamoto and M. Kaneko, *Chem. Pharm. Bull.*, **6**, 730 (1958); *Ann. Rept., ITSUU Lab.*, **11**, 21 (1960); ibid., **11**, 29 (1960).
15) The authors are grateful to Professors Ochiai and Okamoto and to Dr. Kaneko, Faculty of Pharmaceutical Science, the University of Tokyo, for kindly supplying sample.



I, R=H II, R=Ac

Scheme A

The Wolff-Kishner reduction of compound V, a diketo-lactam, gave a lactam (IX) ($C_{24}H_{37}O_6N \cdot 2H_2O$), m. p. 80~85°C. It showed no absorption band characteristic of ketone carbonyl in the infrared spectrum. The ultraviolet spectrum of compound IX showed only end absorption. From a consideration of the molecular formula as well as of the spectra of compound IX, it has reasonably been assumed that in this reduction two carbonyl groups of compound V were converted into methylene groups. Oxidation of compound IX, a di-tertiary glycol containing no more than two hydroxyl groups, with periodic acid gave an amorphous material X, the infrared spectrum of which showed bands at 5.70 and 5.92 μ. These bands at 5.70 and 5.92 μ suggest the probable presence of a five-membered and of an α, β-unsaturated six-membered ring ketone carbonyl group respectively, derived from the cleavage of a 1, 2-glycol constituent. This experimental consequence confirms the findings of the Canadian group[11-13], in which compound I has been shown to be a di-tertiary 1, 2-glycol; it also coincides with the result of the oxidation of anhydrohydroxydelcosine with periodic acid[12]. Accordingly, it may be concluded that compound I is not a di-tertiary 1,3-glycol[14].

Thus, the experiments mentioned above, together with the NMR spectrum of compound I[16], strongly support the structure of compound I (Scheme A) suggested by Skaric and Marion[13].

Experimental

Oxidation of Lucaconine (I) with the Chromium Trioxide-Pyridine Complex. — *A) Oxolucaconine (III) and Oxolucaconinone-II (IV).* — A mixture of lucaconine (1 g.) and chromium trioxide (1 g.) in pyridine (20 ml.) that had been allowed to stand at room temperature overnight was evaporated to dryness in vacuo. After the addition of water (100 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 removal of the solvent, the chloroform extract gave a residue which was redissolved in chloroform (13 ml.) and chromatographed on alumina (5 g.). The chromatogram was eluted with chloroform alone (100 ml.), and then with chloroform containing 1% of methanol (100 ml.). From the chloroform portion the residue was obtained. It was crystallized from acetone. On recrystallization from ethanol, it melted at 132°C; yield, 0.05 g. Mixture with oxolucaconine prepared according to the directions of Furusawa[7] did not affect the melting point. The ultraviolet absorption spectrum of this compound in methanol showed end absorption and no maximum. The infrared absorption spectrum in Nujol, identical with that of isooxolucaconine[7], showed the presence of hydroxyl groups (2.94 μ) and of a lactam carbonyl group (6.20 μ).

From the portion of the chloroform containing 1% of methanol of elute, oxolucaconinone-II (0.1 g.) was obtained on evaporation. It crystallized from acetone. On two recrystallizations from ethanol, it melted at 218°C; yield, 0.1 g. The ultraviolet absorption spectrum of this compound in methanol showed λ_{max} 298 mμ, log ε 1.90. The infrared absorption spectrum in Nujol showed the presence of hydroxyl groups (2.87 and 2.98 μ), a ketone carbonyl group (5.83 μ) and a lactam carbonyl group (6.15 μ).

Found: C, 62.31; H, 7.64; OCH_3, 18.22. Calcd. for $C_{24}H_{35}O_8N$: C, 61.92; H, 7.58; $3OCH_3$, 19.99%.

The aqueous liquor described above was made alkaline with sodium carbonate and extracted with chloroform. After removal of the chloroform, a basic substance (0.3 g.) was left. It was crystallized from acetone and further recrystallized from ethanol twice. It melted at 199~200°C either alone or mixed with naturally occurring lucaconine.

B) Oxolucaconinedione (V) and Oxolucaconinone-II (IV). — A mixture of lucaconine (1 g.) and chromium trioxide (2 g.) in pyridine (40 ml.) was allowed to stand at room temperature for two days. It was treated by the same procedure as the above A), and the obtained acid solution was extracted with chloroform three times. The chloroform extract was evaporated. The residue was chromatographed on alumina (5 g.) as in the case of the above A). Evaporation of the chloroform portion (100 ml.) of elute and the subsequent addition of acetone gave a crystalline material, m. p. 203°C. Two recrystallizations from ethanol yielded crystals melting at 209°C, reported[13] m. p. 211~212°C. Mixture with oxolucaconinedione, prepared according to the direction of Furusawa[7], did not alter the melting point. The infrared absorption spectrum of this compound in Nujol showed the presence of hydroxyl groups (2.90 μ), ketone carbonyl groups (5.72 and 5.83 μ), and a lactam carbonyl group (6.08 μ)[7]. It was reported[13] as $\lambda_{max}^{chloroform}$ 3446, 1757, 1720 and 1653 cm^{-1}.

Oxime.—It melted at 248°C and did not depress the melting point of the sample of the oxime prepared by Furusawa[7].

The portion of the chloroform containing 1% of

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

methanol (100 ml.) of elute gave a residue crystallized from acetone. On recrystallization from ethanol it melted at 218°C and did not depress the melting point of the oxolucaconinone-II described above.

In this oxidation reaction from the aqueous liquor, the basic substance was not obtained.

Diacetyllucaconine (VI).—The ultraviolet absorption spectrum of this compound in methanol showed end absorption and no maximum.

Oxolucaconine (III) from Diacetyllucaconine (VI)[13].—A mixture of diacetyllucaconine (0.3 g.), chromium trioxide (0.3 g.) and pyridine (6 ml.) was allowed to stand at room temperature overnight. The chloroform extract, obtained from the acid solution prepared by the same treatment as described above, was evaporated to give a residue (0.3 g.). It was then hydrolyzed with boiling ethanolic potassium hydroxide for 1 hr. After cooling, the solution was evaporated, and the residue neutralized with 1 N hydrochloric acid and extracted with chloroform. After removal of the chloroform, the residue (0.2 g.) was crystallized from acetone. Two recrystallizations from ethanol gave crystals, m. p. 132°C, which did not depress the melting point of the authentic sample (oxolucaconine) described above.

Oxolucaconinedione (V) from Oxolucaconine (III).—A mixture of oxolucaconine (0.3 g.), chromium trioxide (0.3 g.) and pyridine (6 ml.) was allowed to stand at room temperature overnight. The reaction mixture was treated in the above-described manner, and the chloroform extract from the acid solution was evaporated to give a residue, which crystallized from acetone. Two recrystallizations from ethanol yielded 0.2 g. of crystals, m. p. 209°C. It did not alter the melting point of the authentic sample (oxolucaconinedione).

Oxolucaconinedione (V) from Oxolucaconinone-II (IV).—A mixture of oxolucaconinone-II (0.5 g.), chromium trioxide (0.5 g.) and pyridine (10 ml.) was treated in just the above-mentioned manner to give 0.4 g. of oxolucaconinedione, m. p. 209°C. Mixture with the authentic sample did not alter the melting point.

Reduction of Oxolucaconine (III) with Lithium Aluminium Hydride. — Oxolucaconine (0.2 g.) was dissolved in dioxane (5 ml.). An ether solution (3 ml.) of lithium aluminium hydride (0.1 g.) was added and the temperature gradually raised until the ether evaporated. Then the solution was further refluxed for an hour. The excess reagent was destroyed by the use of water, and, after removal of the formed aluminium hydroxide, the solution was evaporated in vacuo. After the addition of water (1 ml.), the residue was extracted with chloroform. Removal of the chloroform left a residue, which was crystallized from acetone. Two recrystallizations from ethanol yielded crystals, m. p. 200°C, which did not depress the melting point of lucaconine.

Lucaconinone-I (VII). — The ultraviolet absorption spectrum of this compound in methanol showed λ_{max} 292 mμ, log ε 1.53. The infrared absorption spectrum in Nujol showed the presence of hydroxyl groups (2.99 μ) and a ketone carbonyl group (5.72 μ)[7]. It was reported as λ_{max}^{Nujol} 1751 cm^{-1} [14] and λ_{max}^{Nujol} 1755 cm^{-1} [11].

Deoxylucaconinone-I (VIII) from Lucaconinone-I (VII).—A solution of lucaconinone-I (40 mg.) in triethylene glycol (1 ml.) and 85% hydrazine hydrate (0.5 ml.) was refluxed for 1 hr. at 130°C. Then potassium hydroxide (80 mg.) was added and the temperature gradually raised to 200°C during an hour, while water and excess hydrazine hydrate were distilled off. After it had been refluxed for an additional 5 hr. at 195~200°C, the solution was cooled, diluted with water, and extracted with chloroform three times. After removal of the chloroform, a residue was obtained. Recrystallization from ethanol gave crystals (30 mg.), m. p. 165°C, $[\alpha]_D$ +64.65° ($CHCl_3$) reported[14] m. p. 170~171°C, $[\alpha]_D$ +51° ($CHCl_3$). The ultraviolet absorption spectrum of this compound showed end absorption and no maximum. The infrared absorption spectrum showed the presence of hydroxyl groups (2.99 μ).

Found: C, 66.16; H, 8.96; OCH_3, 19.25. Calcd. for $C_{24}H_{39}O_6N$: C, 65.87; H, 8.98; $3OCH_3$ 21.27%.

The analysis of this compound has also been reported[14].

Oxolucaconinone-II (VI) from Monoacetyllucaconine (II). — A mixture of monoacetyllucaconine (2 g.), chromium trioxide (2 g.) and pyridine (40 ml.) 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 (2 g.) on evaporation which was hydrolyzed with boiling ethanolic potassium hydroxide for an hour. After cooling, the solution was evaporated. The residue was neutralized with 1 N hydrochloric acid and extracted with chloroform. After removal of the chloroform, the residue was crystallized from acetone. Two recrystallizations from ethanol gave 1.6 g. of crystals, m. p. 218°C, which did not depress the melting point of the authentic sample described above.

Deoxyoxolucaconinedione (IX). — A solution of oxolucaconinedione (730 mg.) in triethylene glycol (10 ml.) and anhydrous hydrazine (3.5 ml.) was refluxed for 3 hr. at 140°C, potassium hydroxide (1 g.) was added, and the temperature was gradually raised to 200°C over the course of an hour without the condenser. After it had been refluxed for an additional 5 hr. at about 200°C, the solution was cooled, diluted with water, and extracted with chloroform five times. The chloroform extract was washed with 1 N hydrochloric acid and evaporated. The residue was redissolved in 5 ml. of chloroform and then chromatographed on alumina (5 g.). The chromatogram was eluted with chloroform (100 ml.). The elute was evaporated. The residue was crystallized from petroleum ether and diethyl ether. Two recrystallizations from aqueous ethanol gave 350 mg. of needle, m. p. 80~85°C. The ultraviolet absorption spectrum of this compound in methanol showed end absorption and no maximum. The infrared absorption spectrum in Nujol showed the presence of hydroxyl groups (2.96 and 2.99 μ) and a lactam carbonyl group (6.19 μ).

Found: C, 60.76; H, 8.71; N, 2.86; OCH_3,

20.15; H_2O, 7.55. Calcd. for $C_{24}H_{37}O_6N \cdot 2H_2O$: C, 61.12; H, 8.76; N, 2.97; $3OCH_3$, 19.74; H_2O, 7.64%.

Cleavage of the Lactam (IX) with Periodic Acid. — To the lactam (IX) (230 mg.) in ethanol (20 ml.), 0.1 N periodic acid (30 ml.) was added, and the mixture was allowed to stand at room temperature for 5 days. After the addition of water (100 ml.), the solution was extracted with chloroform. Evaporation of the chloroform gave a residue. The residue was redissolved in a small quantity of chloroform and chromatographed on alumina (3 g.). The chromatogram was eluted with chloroform (50 ml.). The elute was evaporated to leave 0.15 g. of an amorphous residue. The infrared absorption spectrum in Nujol showed the presence of hydroxyl groups (2.96 μ), a five-membered cyclic ketone (5.70 μ), an α,β-unsaturated six-membered cyclic ketone (5.92 μ) and a lactam carbonyl group (6.11 μ).

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