The Aconite Alkaloids. XXVII. On Lucaconine*

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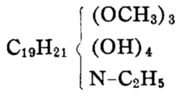
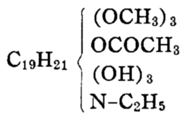
In the previous paper[1] the extended formulae of lucaconine (I), $C_{24}H_{39}O_7N$, and monoacetyllucaconine (II), $C_{26}H_{41}O_8N$, were given as follows:



$$C_{19}H_{21}\left\{\begin{array}{l}(OCH_3)_3\\(OH)_4\\N\text{-}C_2H_5\end{array}\right.$$

Lucaconine (I)



$$C_{19}H_{21}\left\{\begin{array}{l}(OCH_3)_3\\OCOCH_3\\(OH)_3\\N\text{-}C_2H_5\end{array}\right.$$

Monoacetyllucaconine (II)

The present paper describes further experiments, undertaken with the object of characterizing the hydroxyl groups of lucaconine. Acetylation of lucaconine (I)

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* This constitutes a part of a series entitled "The Aconite Alkaloids" by H. Suginome. Part XXVI, cf. foot note 1).

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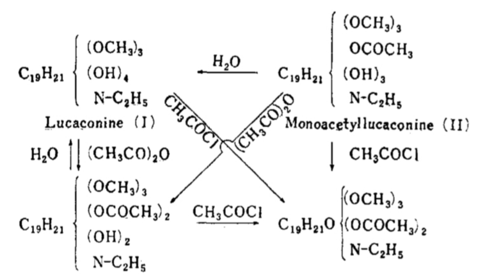
[1] H. Suginome and S. Furusawa, This Bulletin, **32**, 354.

with acetic anhydride gave diacetyllucaconine(III), $C_{28}H_{43}O_9N$[1], while, on treatment with acetyl chloride, lucaconine (I) yielded anhydrodiacetyllucaconine(IV), $C_{28}H_{41}O_8N$, m. p. 156°, $[\alpha]_D^{27}+20.0^\circ$. This anhydrodiacetyl-compound IV was obtained also from monoacetyllucaconine (II) and diacetyllucaconine (III) by the similar treatment. Anhydrodiacetyllucaconine (IV) decolorized bromine in acetic acid and absorbed one mole of hydrogen over platinum catalyst, showing the presence of a double bond. A small quantity of isodiacetyllucaconine, $C_{28}H_{43}O_9N$, m. p. 188° (decomp.), $[\alpha]_D$ 0°, was isolated as a by-product when lucaconine (I) was treated with a large quantity of acetyl chloride.



Lucaconine (I) Monoacetyllucaconine (II)

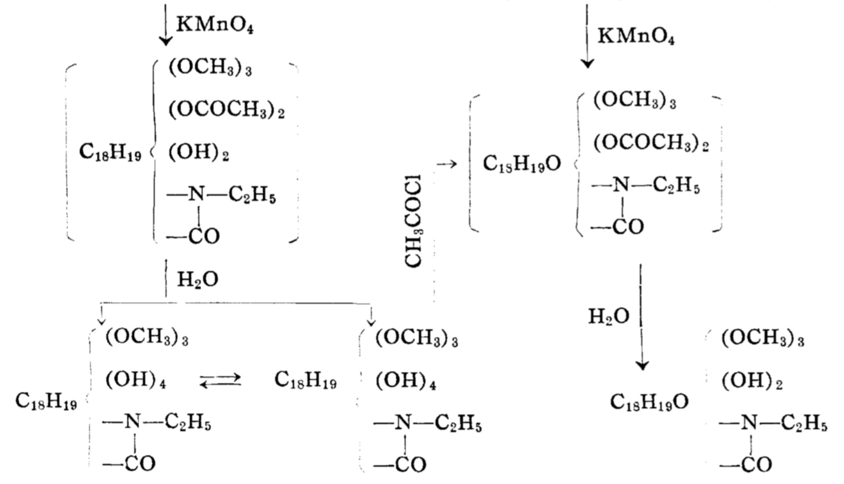
Diacetyllucaconine (III) Anhydrodiacetyllucaconine (IV)

Oxidation of diacetyllucaconine (III) with potassium permanganate in acetone, followed by hydrolysis, gave two neutral products, oxolucaconine (V), $C_{24}H_{37}O_8N\cdot 1\,^3/_4\,H_2O$, m. p. 132°, $[\alpha]_D^{16.2}+24.2^\circ$, as a main product and isooxolucaconine (VI), $C_{24}H_{37}O_8N$, m. p. 242°, $[\alpha]_D^{22.6}+44.8^\circ$, as a by-product. The latter compound VI was also obtained by heating V at about 150° for 10 minutes under reduced pressure (1×10^{-5} mmHg) and VI was partly converted reversely into V on action of methanolic hydrogen chloride or alcoholic sodium hydroxide in a sealed tube. Treatment of oxolucaconine V with acetyl chloride, followed by hydrolysis, gave anhydrooxolucaconine (VII), m. p. 256°, $[\alpha]_D^{27}-25.0^\circ$. This compound VII was also obtained directly from anhydrodiacetyllucaconine(IV)by oxidation with potassium permanganate, followed by hydrolysis.

Acetylation of isooxolucaconine(VI) and of anhydrooxolucaconine (VII) by acetic anhydride gave no crystalline product, but the determination of acetyl groups of these amorphous products showed the production of diacetyl-compounds by these reactions.

On treatment with chromic acid in glacial acetic acid lucaconine (I) was converted into lucaconinone-I (VIII), $C_{24}H_{37}O_7N$, m. p. 210°, $[\alpha]_D^{27}+15.0^\circ$, which showed bands in the infrared spectrum at 2.99 and 5.72 μ, corresponding to hydroxyl and five-membered ring ketone group[2], and formed a monoxime melting at 223~224° (decomp.). Oxolucaconine(V)was converted by the same procedure into a diketo-compound, oxolucaconinedione(IX), $C_{24}H_{33}O_8N$, m. p. 209°, $[\alpha]_D^{26.7}+139^\circ$, which showed bands in the infrared spectrum at 2.90, 5.72, 5.83 and 6.08 μ, characteristic of hydroxyl, five-membered ring ketone, six-membered ring ketone and lactam carbonyl group, respectively[2], and further furnished

Diacetyllucaconine (III) Anhydrodiacetyllucaconine (IV)



Isooxolucaconine (VI) Oxolucaconine (V) Anhydrooxolucaconine (VII)

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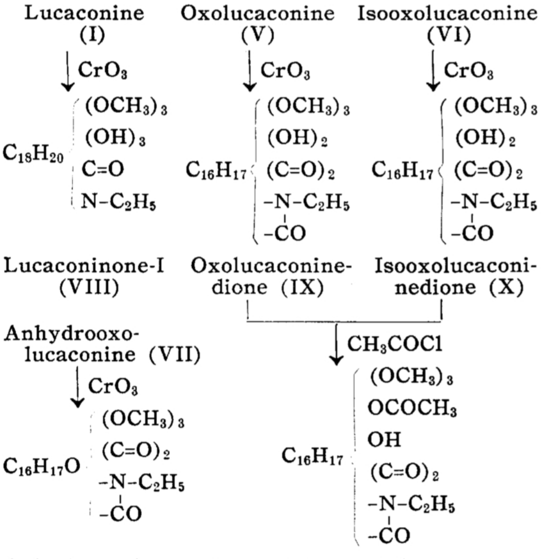
[2] H. Suginome, T. Amiya and T. Shima, unpublished work.

a monoxime melting at 246~248° (decomp.). In this case, a by-product, isooxolucaconinedione (X), $C_{24}H_{33}O_8N \cdot H_2O$, m. p. 136° (decomp.), $[\alpha]^{26}_{D}+33.7°$, which formed the same monoxime (m. p. 246~248°) as described above, was obtained***. Isooxolucaconine(VI) gave only isooxolucaconinedione(X) by similar procedure. Anhydrooxolucaconine(VII) was similarly oxidized into a diketo-compound, anhydrooxolucaconinedione (XI), $C_{24}H_{31}O_7N$, m. p. 272°, $[\alpha]^{26.5}_{D}-84.2°$, which showed bands in the infrared spectrum at 5.72 and 5.83 μ2), and gave a monoxime melting at 268° under decomposition.

Upon treatment with acetyl chloride, both oxolucaconinedione (IX) and isooxolucaconinedione (X) gave the same monoacetyloxolucaconinedione (XII), $C_{26}H_{35}O_9N$, m. p. 269° (decomp.), $[\alpha]^{26.7}_{D}+113°$. On hydrolysis with methanolic sodium hydroxide, this compound XII afforded nearly an equal amounts of IX and X.

Selenium was liberated on heating lucaconinone-I (VIII) and oxolucaconinedione(IX) with selenium dioxide in glacial acetic acid. On the contrary, lucaconine(I) and oxolucaconine(V) did not give selenium under similar conditions. That may probably be due to the presence of a methylene group adjacent to a keto group in VIII and IX.



On the basis of these facts, it may be reasonably concluded that, of four hydroxyl groups of lucaconine, two can be acetylated or oxidized to oxo groups, one being attached to a five-membered ring and the other to a six-membered ring, but the remaining two hydroxyl groups can be neither acetylated nor oxidized under usual conditions. Furthermore, it is to be noted that the latter two hydroxyl groups split off one mole of water on treatment with acetyl chloride. These observations will be discussed in a later paper.

In conclusion mention will be made of the action of nitric acid on lucaconine. Upon treatment with concentrated nitric acid, lucaconine(I) was converted into nitronitrosolucaconinic acid (XIII), $C_{16}H_{19}O_9N_3$, m. p. 214° (decomp.), $[\alpha]^{27}_{D}-117°$. This compound contained two methoxyl groups but no *N*-ethyl group and was soluble in alkali with a pale yellowish green color.

Experimental

Anhydrodiacetyllucaconine (IV).—*a) From Lucaconine.*—A mixture of 2.0 g. of lucaconine and 10 cc. of acetyl chloride was allowed to stand in a sealed tube for ten days. After removal of the excess of acetyl chloride, the residue was treated with ice-water and made alkaline with aqueous ammonia to give a white precipitate. This material was recrystallized from ethanol to obtain anhydrodiacetyllucaconine in colorless plates, m. p. 156°, $[\alpha]^{27}_{D}+20.0°$ (94% ethanol). Yield 1.5 g.

Anal. Found: C, 64.63; H, 7.83; N, 2.90; OCH_3, 19.73; $COCH_3$, 18.14. Calcd. for $C_{28}H_{41}O_8N$: C, 64.72; H, 7.95; N, 2.70; OCH_3, 17.90; 2-$COCH_3$, 16.56%. 6.459 mg. of the substance absorbed 2.84 cc. of hydrogen (1.04 mol.).

When a mixture of 1.0 g. of lucaconine and 10 cc. of acetyl chloride was refluxed for 40 min., and treated in the usual manner, it yielded 0.4 g. of anhydrodiacetyllucaconine and a small quantity (ca. 0.01 g.) of a crystalline substance, isodiacetyllucaconine, m. p. 188° (decomp.), $[\alpha]_D$ 0°.

Anal. Found: C, 62.69; H, 8.37; N, 2.80; OCH_3, 16.84; $COCH_3$, 16.81. Calcd. for $C_{28}H_{43}O_9N$: C, 62.55; H, 8.05; N, 2.61; 3-OCH_3, 17.31; 2-$COCH_3$, 16.02%.

b) From Monoacetyllucaconine(II).—A mixture of 0.5 g. of monoacetyllucaconine and 4.5 cc. of acetyl chloride was refluxed for 40 min. The reaction mixture was treated in the usual manner to give 0.38 g. of anhydrodiacetyllucaconine.

c) From Diacetyllucaconine (III).—A mixture of 0.25 g. of diacetyllucaconine and 5 cc. of acetyl chloride was allowed to stand at room temperature for a week. After treatment as described above, 0.2 g. of anhydrodiacetyllucaconine was obtained.

Oxolucaconine (V).—To a solution of 3.2 g. of diacetyllucaconine in 100 cc. of acetone, 3.5 g. of powdered potassium permanganat was gradually added under stirring and chilling. Manganese

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*** There is a possibility that isooxolucaconinedione (X) is a hydrate of oxolucaconinedione(IX), but it is preferable to call it an "iso-" compound because of difference in optical activities.

dioxide was filtered off and the filtrate was evaporated to dryness. The residue was treated with boiling ethanolic potassium hydroxide for 30 min. After cooling, the solution was made slightly acidic with hydrochloric acid and was evaporated up. The residue was then extracted with absolute ethanol and the ethanolic extract was evaporated to give ca. 1.8 g. of colorless crystals which were recrystallized from ethanol. Oxolucaconine was obtained in colorless crystals, m. p. 132°, $[\alpha]_D^{16.2}+24.2°$ (94% ethanol). This material was insoluble in water, diluted hydrochloric acid and diluted aqueous ammonia, and it seemed to be neutral.

Anal. Found: C, 57.54; H, 7.96; N, 2.72; H_2O, 6.06; (N)-C_2H_5, 4.32. Calcd. for $C_{24}H_{37}O_8N \cdot 1^3/_4 H_2O$: C, 57.75; H, 8.18; N, 2.81; H_2O, 6.32; (N)-C_2H_5, 5.82%.

From the mother liquor of the above recrystallization, a small quantity of a crystalline substance, m. p. 242°, identical with isooxolucaconine mentioned next, was obtained.

Isooxolucaconine (VI). — When 0.2 g. of oxolucaconine was heated at 150° for 5 min. under reduced pressure (1×10^{-5} mmHg), it decomposed under foaming, became glassy and crystallized on cooling. On recrystallization from ethanol, isooxolucaconine was obtained in colorless needles, melting at 242°, $[\alpha]_D^{22.6}+44.8°$ (94% ethanol).

Anal. Found: C, 61.17; H, 8.16; OCH_3, 20.73. Calcd. for $C_{24}H_{37}O_8N$: C, 61.65; H, 7.98; 3-OCH_3, 19.93%.

Upon heating with methyl iodide in a sealed tube, isooxolucaconine could not be methylated but yielded oxolucaconine. The same substance was also produced when isooxolucaconine was heated in a sealed tube with ethanolic potassium hydroxide or with methanolic hydrogen chloride.

Acetylation of Isooxolucaconine (VI).—A solution of isooxolucaconine in a mixture of pyridine and acetic anhydride (1:1) was allowed to stand at room temperature overnight. After removal of the solvents, an amorphous product was treated with aqueous ammonia and extracted with ether. An amorphous residue, obtained on evaporating the ethereal extracts, was purified by repeated precipitation from dilute ethanol.

Anal. Found: $COCH_3$, 16.85. Calcd. for $C_{24}H_{35}O_8N(COCH_3)_2$: 2-$COCH_3$, 15.60%.

Anhydrooxolucaconine (VII). — *a) From Anhydrodiacetyllucaconine (IV).*—To a solution of 0.6 g. of anhydrodiacetyllucaconine in 20 cc. of acetone, 0.4 g. of powdered potassium permanganate was added. After being kept for 24 hr. manganese dioxide was filtered off and the filtrate was evaporated to give 0.5 g. of an amorphous residue. This product was treated with ethanolic potassium hydroxide and then crystallized from ethanol. On repeated recrystallization from ethanol, anhydrooxolucaconine, m. p. 256°, $[\alpha]_D^{27}-25.0°$ (94% ethanol) was obtained. It was soluble in methanol and slightly so in acetone, ether and water.

Anal. Found: C, 64.32; H, 7.91; N, 3.27; OCH_3, 20.69; (N)-C_2H_5, 4.72. Calcd. for $C_{24}H_{35}O_7N$: C, 64.17; H, 7.85; N, 3.12; 3-OCH_3, 20.72; (N)-C_2H_5, 6.46%.

b) From Oxolucaconine (V).—A mixture of 2.0 g. of oxolucaconine and 20 cc. of acetyl chloride was refluxed for 30 min. After removal of the excess of acetyl chloride, the residue was treated with alkali to give 1.0 g. of a crystalline substance. On recrystallization from ethanol, anhydrooxolucaconine, m. p. 257°, was obtained.

Acetylation of Anhydrooxolucaconine (VII).—A mixture of 0.05 g. of anhydrooxolucaconine, 0.5 cc. of pyridine and 0.2 cc. of acetyl chloride was allowed to stand at room temperature overnight. After removal of the solvent, the residue was treated with aqueous ammonia to give a white precipitate. This precipitate was dissolved in ethanol and was reprecipitated by addition of water. After repetition of this treatment, the precipitate was dried and analyzed.

Anal. Found: $COCH_3$, 17.64. Calcd. for $C_{24}H_{33}O_7N(COCH_3)_2$: 2-$COCH_3$, 16.15%.

Lucaconinone-I (VIII).—To a solution of 2.0 g. of lucaconine in 25 cc. of glacial acetic acid, a solution of 0.7 g. (2 mol.) of chromic trioxide in 15 cc. of acetic acid was dropped in under stirring and coolling. After standing overnight and after the removal of the solvent, a glassy substance was obtained. This material was dissolved in water; the solution was made alkaline and was extracted with chloroform. On evaporation of the chloroform solution, 0.64 g. of a crystalline residue was yielded, which was recrystallized from 99% ethanol to give crystals melting at 200~201°. Yield 0.4 g. This substance was converted into perchlorate, melting at 236° after being recrystallized from ethanol. It was transformed into the free base by the usual method. The base, lucaconinone-I, thus obtained melted at 210°, $[\alpha]_D^{27}+15.0°$ (94% ethanol).

Anal. Found: C, 63.82; H, 8.31; N, 3.18. Calcd. for $C_{24}H_{37}O_7N$: C, 63.83; H, 8.26; N, 3.11%.

Perchlorate. — m. p. 236° (decomp.) (from ethanol).

Anal. Found: Cl, 6.92. Calcd. for $C_{24}H_{37}O_7N \cdot HClO_4$: Cl, 6.79%.

Oxime. — m. p. 223~224° (decomp.) (from ethanol).

Anal. Found: N, 6.12. Calcd. for $C_{24}H_{38}O_7N_2$: N, 6.01%.

Oxolucaconinedione (IX).—To a solution of 0.8 g. of oxolucaconine in 10 cc. of glacial acetic acid, a solution of 0.28 g. (2.2 mol.) of chromic anhydride in 10 cc. of the same solvent was added slowly under stirring and cooling. After the mixture was set aside overnight, it was treated in the usual manner to give 0.3 g. of a crystalline product which was recrystallized from ethanol. Oxolucaconinedione was obtained as colorless needles melting at 209°, $[\alpha]_D^{26.7}+139°$ (94% ethanol).

Anal. Found: C, 62.10; H, 7.40; N, 3.11. Calcd. for $C_{24}H_{33}O_8N$: C, 62.13; H, 7.18; N, 3.02%.

Oxime. — m. p. 246~248° (decomp.) (from ethanol).

Anal. Found: N, 5.91. Calcd. for $C_{24}H_{34}O_8N_2$: N, 5.86%.

The mother liquor from which the above mentioned crystals were separated was extracted with chloroform and the chloroform extracts were evaporated to dryness. The residue was crystallized from ethanol to give 0.1 g. of a colorless crystalline substance, m. p. 136~137° (decomp.), which was identified with isooxolucaconinedione mentioned below.

Isooxolucaconinedione (X).—Isooxolucaconine was oxidized with chromic anhydride in glacial acetic acid by the method described above to give isooxolucaconinedione, colorless crystals melting at 136~137° (decomp.), $[\alpha]^{26}_{D}+33.7°$ (94% ethanol).

Anal. Found: C, 59.77; H, 7.43; N, 3.17; H_2O, 3.62. Calcd. for $C_{24}H_{33}O_8N \cdot H_2O$: C, 59.82; H, 7.34; N, 2.91; H_2O, 3.75%.

The oxime prepared from isooxolucaconinedione melted at 246~248° (decomp.) and showed no depression of the melting point on admixture with the above-mentioned oxolucaconinedione oxime.

When isooxolucaconinedione was heated in an oil bath at 160~170° for 10 min. under reduced pressure (1×10^{-5} mmHg), it melted under foaming and crystallized on cooling. Recrystallization from ethanol gave a crystalline substance, m. p. 136° (decomp.), which showed no depression of the melting point on admixture with the starting material.

Anhydrooxolucaconinedione (XI). — With 0.08 g. of chromic anhydride in acetic acid, 0.25 g. of anhydrooxolucaconine was oxidized as described above to give 0.2 g. of anhydrooxolucaconinedione, which was recrystallized from ethanol, m. p. 272°, $[\alpha]^{26.5}_{D}-84.2°$. It was sluble in methanol, ethanol and acetone and sparingly soluble in ether and benzene.

Anal. Found: C, 64.30; H, 7.50; N, 3.27. Calcd. for $C_{24}H_{31}O_7N$: C, 64.70; H, 7.01; N, 3.14%.

Oxime.—m. p. 268° (decomp.).

Anal. Found: N, 6.52. Calcd. for $C_{24}H_{32}O_7N_2$: N, 6.08%.

Monoacetyloxolucaconinedione (XII). — A mixture of 0.26 g. of oxolucaconinedione and 3 cc. of acetyl chloride was heated under reflux for 30 min. After removal of the solvent, the residue was treated with aqueous ammonia to give white precipitate which was crystallized from ethanol. Monoacetyloxolucaconinedione melted at 269° (decomp.), $[\alpha]^{26.7}_{D}+113°$ (ethanol). It was soluble in methanol and ethanol and sparingly soluble in acetone, benzene and water.

Anal. Found: C, 62.62; H, 7.56; $COCH_3$, 8.79. Calcd. for $C_{24}H_{32}O_8N(COCH_3)$: C, 61.80; H, 6.98; $COCH_3$, 8.51%.

This substance was also obtained from isooxolucaconinedione by the same procedure as described above.

Hydrolysis of Monoacetyloxolucaconinedione (XII).—A solution of 0.1 g. of monoacetyloxolucaconinedione in 2 cc. of N-methanolic sodium hydroxide was heated for 20 min. After removal of the solvent, the residue was treated with water and the precipitate was fractionally recrystallized from ethanol. Isooxolucaconinedione melting at 132° (decomp.) and oxolucaconinedione melting at 207° were yielded in nearly equal amounts.

Nitronitrosolucaconinic Acid (XIII). — A mixture of 3.0 g. of lucaconine and 20 cc. of nitric acid (*d*: 1.43) was heated on a water bath at 80° for 1 hr. with stirring. After cooling, 30 cc. of water was added and yellow precipitate was collected, which was repeatedly precipitated from diluted ethanol and finally crystallized from diluted acetone. Nitronitrosolucaconinic acid was obtained in pale yellow plates, melting at 214°, $[\alpha]^{27}_{D}-117°$. It was easily soluble in acetone and sparingly so in water, methanol, ethanol, ether and chloroform.

Anal. Found: C, 48.60; H, 4.81; N, 10.83; OCH_3, 15.32; COO-, 24.64; (N)-C_2H_5, neg. Calcd. for $C_{12}H_{13}O_3N_3(OCH_3)$-$(COO)_2$: C, 48.47; H, 4.78; N, 10.57; 2-OCH_3, 15.62; 2-COO-, 22.66%.

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