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Some Derivatives of Anhydrodiacetyldelcosine (Anhydrodiacetyllucaconine)[*1,2]

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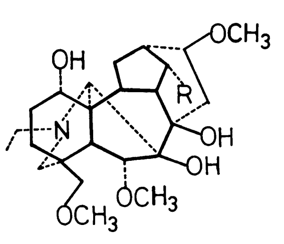
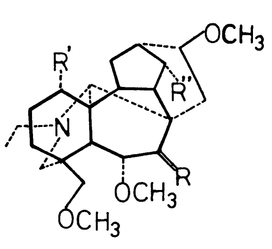
On the basis of the structure of delcosine (lucaconine), a diterpene alkaloid, the structures of anhydrodiacetyldelcosine and dihydroanhydrodiacetyldelcosine have previously been established. Some reactions of these compounds and their derivatives are described, and the reaction products are shown.

Delcosine (lucaconine) (**1**) ($C_{24}H_{39}O_7N$)[2] is an alkaloid isolated from species of Aconitum and Delphinium.[3] The structure of anhydrodiacetyldelcosine (anhydrodiacetyllucaconine) (**2**) ($C_{28}H_{41}O_8N$) has previously been proposed on the basis of the reactions as it undergoes[3] and the structure of delcosine.[4] The treatment of Compound **1** with acetyl chloride gave Compound **2** by the esterification of the two secondary hydroxyl groups, followed by the loss of one molecule of water between the two vicinal tertiary hydroxyl groups.

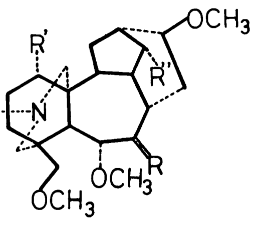


1 R=OH
7 R=H



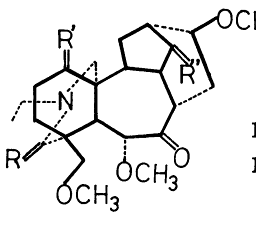
2 R=O R′=R″=OAc
4 R=OH, H R′=R″=OH

Compound **2** absorbs one molecule of hydrogen, giving dihydroanhydrodiacetyldelcosine (anhydrodihydrodiacetyllucaconine) (**3**) ($C_{28}H_{43}O_8N$). The structure and the mechanism of formation of **3** have previously been reported.[3,4]



3 R=O, R′=R″=OAc
5 R=O, R′=R″=OH
6 R=OAc, H, R′=R″=OAc
8 R=O, R′=OAc, R″=H

The present paper will deal mainly with some derivatives of Compounds **2** and **3**. The reduction of Compound **2** with lithium aluminium hydride yielded anhydrodelcosinol (anhydrolucaconinol) (**4**) ($C_{24}H_{39}O_6N$). Although the infrared spectrum of Compound **2** showed bands at 1733 and 1721cm^{-1} characteristic of an ester and carbonyl function respectively, Compound **4** showed no carbonyl band. This shows that the carbonyl group in Compound **2** was reduced in Compound **4**. The hydrolysis of Compound **3** gave dihydroanhydrodelcosine (anhydrodihydrolucaconine) (**5**) ($C_{24}H_{39}O_6N$), which showed a band due to a seven-membered cyclic ketone at 1689 cm^{-1} in the infrared spectrum. The reduction of Compound **5** by lithium aluminium hydride, followed by acetylation with acetic anhydride in pyridine, gave dihydroanhydrotriacetyldelcosinol (anhydrodihydrotriacetyllucaconinol) (**6**) ($C_{30}H_{47}O_9N$). This compound showed no carbonyl band near 1689 cm^{-1}, but did show bands due to ester functions in the infrared spectrum. These observations support the reduction of the carbonyl group in Compound **5**. The treatment of deoxy-14-dehydrodelcosine (deoxylucaconinone-I) (**7**) ($C_{24}H_{39}O_6N$)[5] with acetyl chloride, followed by hydrogenation over platinum in acetic acid, gave 1-monoacetyldihydroanhydrodeoxy-14-dehydrodelcosine (anhydrodihydromonoacetyldeoxylucaconine-I) (**8**) ($C_{26}H_{41}O_6N$). Compound **8** showed a seven-membered cyclic carbonyl band at 1686 cm^{-1} and a band due to an ester function at 1730 cm^{-1}. These observations suggest that Compound **8** resulted from **7** by an initial dehydration of **7** to give a cyclic ketone, which was subsequently hydrogenated, just as Compound **3** resulted from Compound **1** *via* **2** in analogous reactions.[3] The oxidation of Compound **3** with the chromium trioxide–pyridine complex, followed by hydrolysis, yielded dihydroanhydrooxodelcosine (**9**) ($C_{24}H_{37}O_7N$).



9 R=O, R′=R″=α-OH,H
10 R=R′=R″=O
11 R=H$_2$, R′=α-OH,H, R″=O

Compound **9** is a monoketo lactam and showed absorption bands at 1689 and 1621 cm^{-1} characteristic of a seven-membered ring ketone and of a lactam respectively. Its ultraviolet absorption spectrum showed a maximum (λ_{max} 307 nm, log ε 1.94) due to a carbonyl group. The oxidation of Compound **5** with the chromium trioxide–pyridine complex gave a neutral product, dihydroanhydro-1,14-didehydrooxodelcosine (**10**) ($C_{24}H_{33}O_7N$), and a base, dihydroanhydro-14-dehydrodelcosine (**11**) ($C_{24}H_{37}O_6N$). Compound **10** is a triketo lactam and showed absorption bands at 1754, 1712, 1681, and 1647 cm^{-1} characteristic of a five-membered ring ketone, a six-membered ring ketone, a seven-membered ring ketone, and a lactam respectively. Its ultraviolet absorption spectrum showed a maximum (λ_{max} 300 nm, log ε 2.11) due to carbonyl groups. Compound **11** is a diketo base.

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It showed bands at 1751 and 1686 cm^{-1} in the infrared absorption spectrum due to the presence of a five-membered ring ketone and a seven-membered ring ketone respectively.

Experimental

*Anhydrodelcosinol (Anhydrolucaconinol) (**4**).* Anhydrodiacetyldelcosine(**2**) (0.5 g) was dissolved in dioxane (10 ml). Lithium aluminium hydride (0.2 g) dissolved in 10 ml ether was then added, and the temperature was raised until the ether evaporated. The mixture was thereafter refluxed for 30 min. Upon cooling, the excess reagent was destroyed by the addition of water, and the aluminium hydroxide formed was removed; the solution was then evaporated *in vacuo.* After the addition of 1 ml of aqueous 10% sodium hydroxide, the residue was extracted with chloroform. The evaporation of the chloroform left a residue (30 mg). The aluminium hydroxide was dissolved in 20 ml of a 10% sodium hydroxide solution and extracted with chloroform five times. A residue (200 mg) was obtained upon the removal of the chloroform. These residues were combined and neutralized with about 5% perchloric acid, and the mixture was allowed to stand to crystallize anhydrodelcosinol perchlorate. The recrystallization of the salt from water gave crystals (150 mg); mp 230 °C. This salt (150 mg) was dissolved in 1 ml of 10% aqueous sodium hydroxide and extracted with chloroform. The removal of the chloroform gave a residue was crystallized from ether. Recrystallization from ethanol gave crystals; mp 185—190 °C. Yield, 0.1 g. The ultraviolet absorption spectrum of this compound in methanol showed an end-absorption and no maximum. The infrared absorption spectrum (in Nujol) showed a hydroxyl absorption (3472 cm^{-1}), but did not show any bands attributable to the presence of an ester or carbonyl group near 1700 cm^{-1}.

Found: C, 66.22; H, 8.47; OCH_3, 20.31%. Calcd for $C_{24}H_{39}O_6N$: C, 65.87; H, 8.98; OCH_3, 21.27%.

*Dihydroanhydrodelcosine (Anhydrodihydrolucaconine) (**5**).* Dihydroanhydrodiacetyldelcosine (**3**) (1.5 g) was hydrolyzed under a stream of nitrogen for 1 h by boiling it in methanolic potassium hydroxide. Upon the removal of the methanol, a residue was obtained. Water was added to the residue, and it was extracted with chloroform three times. The residue obtained after the evaporation of the chloroform was crystallized from ethanol. Recrystallization from ethanol afforded crystals; mp 205—210 °C; $[\alpha]_D$ +43.4° (chloroform); pK_a 7.0. The ultraviolet absorption spectrum of this compound in methanol showed an end-absorption and no maximum. The infrared absorption spectrum (in Nujol) showed the presence of hydroxyl groups (3484, 3425, 3356 cm^{-1}) and a carbonyl group (1689 cm^{-1}).

Found: C, 65.98; H, 9.11%. Calcd for $C_{24}H_{39}O_6N$: C, 65.87; H, 8.98%.

*Dihydroanhydrotriacetyldelcosinol (Anhydrodihydrotriacetyllucaccninol) (**6**).* A solution of dihydroanhydrodelcosine (**5**) (0.3 g) and lithium aluminium hydride (0.2 g) in tetrahydrofuran was refluxed for 1.5 h. The reaction mixture was allowed to stand overnight, after which the excess reagent was decomposed by the addition of water; after the removal of the aluminium hydroxide formed, the solution was extracted with chloroform. The removal of the chloroform afforded a residue (0.2 g) which was subsequently dissolved in a mixture of acetic anhydride (1 ml) and pyridine (1 ml). The solution was allowed to stand in a sealed tube at room temperature for 3 days. The reaction mixture was poured into 100 ml of water to precipitate the product. Recrystallization from ethanol gave crystals; mp 130—133 °C. Yield, 40 mg. The infrared absorption spectrum (in Nujol) showed the presence of ester groups (1739 and 1727 cm^{-1}).

Found: C, 64.19; H, 8.62; OCH_3, 19.66; $COCH_3$, 20.18%. Calcd for $C_{30}H_{47}O_9N$: C, 63.69; H, 8.38; OCH_3, 16.46;[6] $COCH_3$, 22.83%.

*1-Monoacetyldihydroanhydrodeoxy-14-dehydrodelcosine (Anhydrodihydromonoacetyldeoxylucaconine-I) (**8**).* A mixture of 50 mg of deoxy-14-dehydrodelcosine (**7**) and 1 ml of acetyl chloride was allowed to stand in a sealed tube at room temperature for a week. After the removal of the excess acetyl chloride, the residue was treated with water (3 ml) and then with aqueous ammonia to give a precipitate (40 mg). This precipitate was dissolved in 5 ml of glacical acetic acid and hydrogenated with 20 mg of platinum oxide for 1h. After the subsequent removal of the platinum, the solution was evaporated to dryness *in vacuo.* The treatment of the residue with water and then with aqueous ammonia gave a precipitate. Recrystallization from ethanol gave crystals; mp 84—90 °C. Yield, 20 mg. The infrared absorption spectrum (in Nujol) showed the presence of a carbonyl group (1686 cm^{-1}) and an ester function (1730 cm^{-1}).

Found: C, 67.41; H, 9.26; OCH_3, 21.58; $COCH_3$, 10.63%. Calcd for $C_{26}H_{41}O_6N$: C, 67.36; H, 8.91; OCH_3, 20.08; $COCH_3$, 9.28%.

*Dihydroanhydrooxodelcosine (**9**).* A mixture of dihydroanhydrodiacetyldelcosine (**3**) (0.5 g) and chromium trioxide (0.5 g) in pyridine (10 ml) that had been allowed to stand overnight at room temperature was evaporated to dryness *in vacuo.* Water (20 ml) was then added to the residue, and the mixture was reduced with sulfur dioxide to remove the excess reagent. The acid solution thus obtained was extracted with chloroform. The evaporation of the chloroform extract gave a residue (0.3 g) which was then hydrolyzed with boiling ethanolic potassium hydroxide for 1 h. After cooling, the solution was evaporated and the residue was extracted with chloroform following the addition of water (10 ml). After the evaporation of the solvent, the residue was crystallized from acetone. The product was recrystallized twice from ethanol to give crystals; 0.2 g; mp 290 °C. The ultraviolet absorption spectrum of this compound in methanol showed λ_{min} 280 nm, log ε 1.71 and λ_{max} 307 nm, log ε 1.94. The infrared absorption spectrum (in Nujol) showed the presence of hydroxyl groups (3497, 3448 cm^{-1}), a carbonyl group (1890 cm^{-1}), and a lactam group (1621 cm^{-1}).

Found: C, 63.23; H, 8.22; N, 2.97; OCH_3, 18.99; (N)-C_2H_5, 4.70%. Calcd for $C_{24}H_{37}O_7N$: C, 63.83; H, 8.26; N, 3.10; OCH_3, 20.62; (N)-C_2H_5, 6.44%.

*Dihydroanhydro-1,14-didehydrooxodelcosine (**10**).* A mixture of dihydroanhydrodelcosine (**5**) (0.5 g) and chromium trioxide (1 g) in pyridine (20 ml) that had been allowed to stand overnight at room temperature was evaporated to dryness *in vacuo.* After the addition of water (20 ml), the residue was treated with sulfur dioxide to reduce the excess reagent. The resulting acid solution was extracted with chloroform. A residue (0.3 g) was obtained upon the evaporation of the chloroform. The further oxidation of the residue with the same reagent (0.3 g of chromium trioxide and 6 ml of pyridine), followed by the subsequent treatment mentioned above, gave 0.2 g of a residue. It was dissolved in chloroform (2 ml) and placed in an alumina column (2 g). The column was eluted with chloroform, and then with chloroform containing 1% methanol. From the chloroform eluate, a residue (0.1 g) was obtained. It was crystallized from ethanol. Repeated recrystallizations from ethanol gave a product which melted at 204—207 °C. The ultraviolet absorption spectrum of this compound in methanol showed $\lambda_{\min}$ 260 nm, log ε 1.75 and $\lambda_{\max}$ 300 nm, log ε 2.11. The infrared absorption spectrum (in Nujol) showed the presence of carbonyl groups (1754, 1712, 1681 cm^{-1}) and a lactam group (1647 cm^{-1}).

Found: C, 64.79; H, 7.91; N, 3.15; OCH_3, 20.15%. Calcd for $C_{24}H_{33}O_7N$: C, 64.41; H, 7.43; N, 3.13; OCH_3, 20.80%.

*Dihydroanhydro-14-dehydrodelcosine (**11**).* The acid solution obtained after the chloroform extraction of Compound **10** in the oxidation of Compound **5** was made alkaline by aqueous ammonia. The chromic hydroxide formed was removed by filtration, and the filtrate was extracted with chloroform. The evaporation of the chloroform gave a residue which was dissolved in chloroform (4 ml) and placed in an alumina column (1.5 g). The column was eluted with chloroform (15 ml), and then with chloroform containing 1% of methanol (30 ml). From the chloroform-methanol eluate a residue was obtained. It was crystallized from acetone. Further recrystallization from ethanol gave crystals which melted at 155 °C. The ultraviolet absorption spectrum of this compound in methanol showed an end-absorption and no maximum. The infrared absorption spectrum (in Nujol) showed the presence of a hydroxyl group (3448 cm^{-1}) and carbonyl groups (1751 and 1686 cm^{-1}).

Found: C, 66.30; H, 8.39; N, 3.08; OCH_3, 20.62%. Calcd for $C_{24}H_{37}O_6N$: C, 66.18; H, 8.56; N, 3.22; OCH_3, 21.38%.

References

1) A preliminary note on part of the contents of this paper appeared in T. Amiya and T. Shima, *Bull. Chem. Soc. Jpn.*, **31**, 1083 (1958).

2) Lucaconine was identical with delcosine.

3) T. Amiya and T. Shima, *Bull. Chem. Soc. Jpn.*, **40** 1597 (1967).

4) S. W. Pelletier and L. H. Keith. "The Alkaloids, Chemistry and Physiology," Vol. XIII, ed by R. H. F. Manske, Academic Press New York (1970), p. 32; S. W. Pelletier and S. W. Page. "MTP Int. Rev. Sci., Org. Chem., Ser. One "Vol. 9, ed by K. Wiesner. Butterworths, London (1973), p. 322.

5) T. Amiya and T. Shima, *Bull. Chem. Soc. Jpn.*, **35**, 740 (1962).

6) The theoretical value in Ref. 1 is revised to this value.