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A SUGGESTED STRUCTURE FOR DELSOLINE*

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Abstract—The alkaloid delsoline ($C_{25}H_{41}O_7N$) was oxidized by acid permanganate mostly to dehydro-oxodelsoline, and by neutral permanganate to anhydrohydroxydelsoline. Oxidation of the alkaloid with mercuric acetate produced anhydrohydroxy-N-de-ethyldelsoline which could be re-ethylated with ethyl iodide, thus showing the presence of an N-ethyl group in delsoline. Anhydrohydroxydelsoline was also obtained from O-acetyldelsoline perchlorate by oxidation to an anhydronium salt followed by hydrolysis with sodium hydroxide, and this method of preparation provides evidence of its carbinolamine structure. O-Acetyloxodelsoline, obtained from acetyldelsoline, is cleaved by lead tetra-acetate to a *seco*diketone that loses the elements of methanol on recrystallization. Hence the base contains two vicinal tertiary hydroxyls, one of which is β to a methoxyl group. Dehydro-oxodelsoline is also cleaved by lead tetra-acetate and the product undergoes an internal aldol rearrangement. These results are interpreted in the light of a structure that is tentatively suggested for delsoline.

Of the alkaloids present in *Delphinium consolida* L., delsoline was first reported by Markwood[1] and later by Cionga and Iliescu.[2] The perchlorate and hydrobromide were described by Marion and Edwards,[3] who assigned to the base the empirical formula $C_{25}H_{43}O_7N$. Delsoline has been investigated chemically, and the results now reported make it possible to advance a tentative structure for the alkaloid.

The analytical figures yielded by the base and several derivatives are in better agreement with $C_{25}H_{41}O_7N$ containing two hydrogens less than the previously assigned formula. Delsoline is a tertiary base containing four methoxyl groups and three active hydrogens that must arise from three free hydroxyls, and this accounts for all the oxygen in the molecule. One of the hydroxyls underwent acetylation quite easily and produced an amorphous derivative, which, however, formed a crystalline perchlorate. This hydroxyl, as will appear in the sequel, is secondary.

Oxidation of desoline (I) with potassium permanganate in acetone in the presence of acetic acid gave a complex mixture of neutral, basic and acidic substances. From it were isolated in small yield two bases (II) and (III), melting, respectively, at 185–187° and 218–220°, but the main fraction consisted of a neutral compound (IV), $C_{25}H_{37}O_8N$, m.p. 201°. No homogeneous product could be isolated from the acidic fraction. It must be emphasized that in all the following milder oxidation experiments no acidic material was isolated and, therefore, no primary alcoholic group appeared to be present. The neutral compound (IV) was obtained in better yield (62 per cent) when delsoline was oxidized with chromium trioxide–pyridine. Its infrared absorption spectrum contained two hydroxyl bands at 3500 and 3410 cm^{-1}, a carbonyl band at

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[1] L. N. Markwood, *J. Amer. Pharm. Ass.* **13**, 696 (1924).

[2] E. Cionga and C. Iliescu, *Ber. Dtsch. Chem. Ges.* **74**, 1031 (1941).

[3] L. Marion and O. E. Edwards, *J. Amer. Chem. Soc.* **69**, 2010 (1947).

1717 cm^{-1} indicative of a six-membered cyclic ketone and a band at 1640 cm^{-1} characteristic of a six-membered lactam carbonyl. The neutral compound (IV) is therefore a ketolactam and will be designated dehydro-oxodelsoline. It can be inferred that one of the hydroxyls in delsoline is secondary and located on a six-membered ring, while the remaining two are tertiary. Also that there is a methylene group next to the nitrogen.

That the band at 1640 cm^{-1} in the infrared spectrum of dehydro-oxodelsoline indicates a cyclic lactam and not an aliphatic amide (which is theoretically obtainable, since an N-ethyl group is present in the base, as shown below) was proved by the resistance of the compound to the action of sodium hydroxide, and to the action of hot 6 N sulphuric acid, which left about 80 per cent of the material unchanged.

The basic compound (III), m.p. 218–220°, already mentioned was obtained in much better yield when delsoline was oxidized with potassium permanganate in a solution buffered with magnesium sulphate. Its empirical formula, $C_{25}H_{39}O_7N$, differs from that of delsoline by two hydrogens. In the infrared region its spectrum contains no carbonyl nor double-bond absorption; it is similar to that of delsoline, but shows some change in the hydroxyl region, and two added sharp peaks at 998 and 897 cm^{-1}, which are probably indicative of a cyclic ether.[4] The transformation of delsoline into this new compound is accompanied by a drop of 2·2 units in pK_a (6·4 to 4·2), which suggests a change in the environment of the nitrogen. Since compound (III) does not contain more oxygen than delsoline, it cannot be a simple carbinolamine. If one of the hydroxyls in delsoline were located suitably close to react with the carbinolamine hydroxyl, an internal ether would result, and the product would contain one less hydroxyl than delsoline. Indeed, compound (III) contains one active hydrogen less than the original base. Further, compound (III) on reduction with sodium borohydride gave back delsoline, and as a simple cyclic ether would not be opened by this reagent, the compound must contain a carbinolamine ether, and will be designated anhydrohydroxydelsoline. A similar carbinolamine ether has been observed to form in the alkaloid delcosine.[4] It should be noted that anhydrohydroxydelsoline, just like anhydrohydroxydelcosine,[4] forms a perchlorate that is not an anhydronium salt. However, (III) was also obtained via another path that showed it clearly to be a carbinolamine ether. Oxidation of O-acetyldelsoline perchlorate with potassium permanganate in acetone, or with mercuric acetate in aqueous acetic acid, produced O-acetyldelsoline anhydronium perchlorate, and, when the aqueous solution of this salt was made basic with sodium hydroxide and heated for a short time on a steam-bath, anhydrohydroxydelsoline (III) was formed. The course of the reactions could be represented as in Fig. 1.

The oxidation of O-acetyldelcosine with chromium trioxide–pyridine complex gave a neutral product, m.p. 148–150°, which in the infrared region showed a split lactam absorption band at 1630 and 1642 cm^{-1} and acetate bands at 1732 and 1250 cm.$^{-1}$ Unfortunately, it was not possible to obtain it sufficiently pure for analysis. After hydrolysis of the acetyl group and further oxidation with the same reagent, however, the product gave rise to dehydro–oxodelsoline (IV), thus showing that it must have consisted mostly of O-acetyloxodelsoline. The reactions described suggest that the hydroxyl involved in the internal ether formation is probably the same that is readily acetylated, and also the same that is oxidized to the ketonic group present in dehydro-oxodelsoline.

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[4] R. Anet, D. W. Clayton and L. Marion, *Canad. J. Chem.* 35, 397 (1957).

When either anhydrohydroxydelsoline or delsoline itself was oxidized with mercuric acetate in aqueous acetic acid, acetaldehyde was evolved and a compound, m.p. 185–187° was isolated in almost theoretical yield. This product was identical with compound (II) obtained in very small yield in the oxidation of the base with permanganate. It yielded analytical figures in agreement with the formula $C_{23}H_{35}O_7N$,

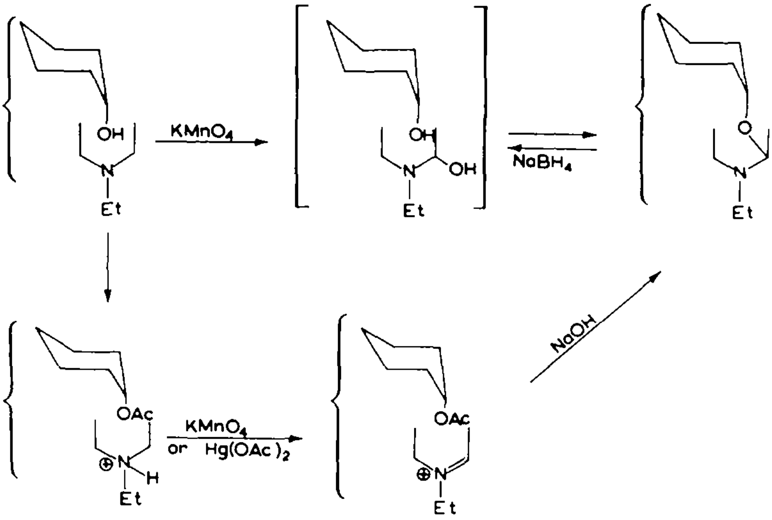

Fig. 1.

corresponding to N-de-ethylanhydrohydroxydelsoline. In fact, compound (II) on treatment with ethyl iodide in dimethylformamide was converted to anydrohydroxydelsoline (III). Consequently, delsoline in common with delcosine[4] and lycoctonine[5] is an N-ethyl base.

In order to establish the nature of the remaining two hydroxyls in the alkaloid, O-acetyloxodelsoline was oxidized with lead tetra-acetate. The crude reaction product, in benzene solution, was chromatographed on neutral alumina. Elution with benzene gave a small fraction that melted at 135–137°. On recrystallization from benzene-ether, the melting point jumped to 192–194°. Further elution of the chromatogram with chloroform gave a substance melting initially at 192–194°. The two products of same melting point were identical, and had an infrared spectrum showing no absorption in the OH region, but containing five characteristic sharp bands at 1740 and 1237 cm^{-1} (acetate) at 1765 cm^{-1} (*cyclo*pentane) at 1680 cm^{-1} (six membered $\alpha\beta$-unsaturated cyclic ketone)[6] and 1650 cm^{-1} (lactam carbonyl). That the cleavage product (V) (m.p. 192–194°) contained an $\alpha\beta$-unsaturated ketonic group was confirmed by the ultraviolet[7] spectrum: λ_{max} 222 mμ (log ε 3·98); λ_{max} 320 mμ (log ε 2·47); λ_{min} 272 mμ (log ε 1·88).

The analytical figures indicated the formula $C_{26}H_{35}O_8N$, showing that the reaction had involved not only the cleavage of a glycol, but also the elimination of the elements of methanol. The product (V) is therefore demethanol-O-acetyloxodelsoline *seco*-diketone. It can be concluded that delsoline contains two vicinal tertiary hydroxyls,

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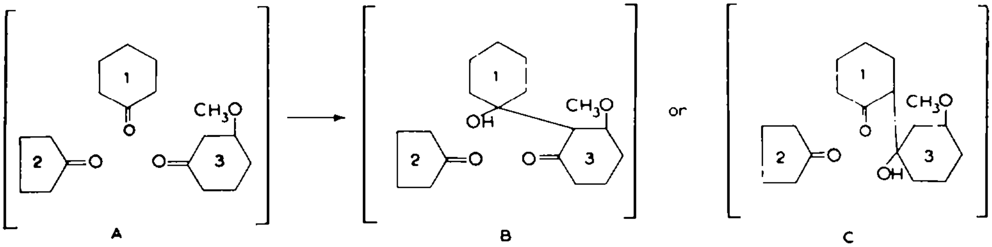
[5] O. E. Edwards and L. Marion, *Canad. J. Chem.* 32, 1146 (1954).

[6] L. J. Bellamy, *The Infrared Spectra of Complex Molecules.* Methuen, London (1954).

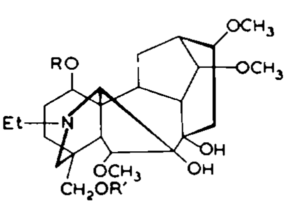
[7] A. Gillam and E. S. Stern, *Electronic Absorption Spectroscopy.* Edward Arnold, London (1954).

and that one of them is a substituent on a five-membered ring while the other is a substituent on a six-membered ring. Furthermore, since β-methoxyketones are known to eliminate methanol readily, it can be assumed that the tertiary hydroxyl that gives rise to the six-membered ketone is located β to a methoxyl, thus accounting for the easy elimination of methanol in the formation of (V). It seems probable that the compound melting at 135–137° first obtained from the chromatogram, might be O-acetyloxodelsoline*seco*diketone, which on recrystallization loses methanol and produces the higher-melting compound (V). This behavior parallels that of lycoctonam (oxolycoctonine) on similar oxidation.

Cleavage of the vicinal glycol system was also performed on dehydro-oxodelsoline (IV). The quantitative oxidation of (IV) with lead tetra-acetate showed a rapid uptake of 1 mole of reagent (30 min) and produced a substance (VI), $C_{25}H_{35}O_8N$, m.p. 243–245°. This product, also obtainable in much smaller yield from delsoline by oxidation with chromium trioxide in acetic acid, did not arise from a simple oxidation. Surprisingly its infrared absorption spectrum contained a hydroxyl band at 3440 cm^{-1} as well as two carbonyl bands at 1755 and 1738 cm^{-1} indicative of a five- and a six-membered cyclic ketone, and a lactam carbonyl band at 1653 cm^{-1} with a shoulder at 1640 cm^{-1}. The presence of one hydroxyl in the product (VI) was confirmed by an active-hydrogen determination (Zerewitinoff). One way to account for the presence of one hydroxyl in the product (VI) would be to assume that the expected triketone had undergone an internal aldol condensation such as has been observed with lycoctonine.[8] Such a reaction would lead to one or the other of the structures shown in the following formulae:



Since the product (VI) had not lost the elements of methanol, it appeared necessary to assume either that the carbonyl of the β-methoxyketone system was no longer present as in C, or that the α-carbon had become involved in the condensation (as in B), thus preventing the formation of a double bond. Furthermore, the only difference between O-acetyloxodelsoline and (IV), which on cleavage give rise to the two *seco*-diketones, is that the acetoxy group of the one is replaced by a carbonyl in the other.



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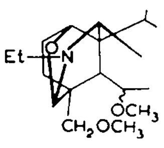

III

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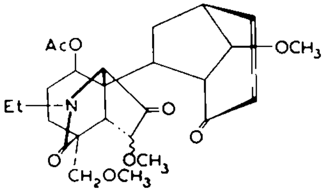
[8] O. E. Edwards and L. Marion, *Canad. J. Chem.* 32, 195 (1954).

In the formation of (VI) it must therefore be this original carbonyl (in ring 1, formula A) that undergoes condensation with the α-methylene of ring 3 as in formula B or its neighboring methylene with the carbonyl of ring 3 as in formula C.

Since there is no evidence of unsaturation in delsoline, its structure must be hexacyclic. If the oxygenated substituents be replaced by hydrogen, the formula becomes $C_{21}H_{33}N$, just as with lycoctonine,[9] delpheline[10] and delcosine.[4] Furthermore, the chemical behavior of delsoline offers many similarities with that of lycoctonine.[8] It may therefore be assumed that the structure of delsoline is closely related to that of lycoctonine. A partial elucidation of the structure of lycoctonine was achieved initially from the chemical investigation of the base,[5,8] and an X-ray crystallographic analysis[11] made it possible to advance a total structure (I, $R = CH_3$, $R' = H$), many features of which have since been confirmed chemically.[12] The chemistry of delsoline as established so far can be interpreted satisfactorily if it be assumed that the alkaloid possesses the same ring structure as lycoctonine, and that the substituents although partly different occupy the same positions. Structure (I, $R = H$, $R' = CH_3$) is therefore tentatively suggested for delsoline. It must be the secondary hydroxyl that becomes involved in the formation of the carbinolamine ether in anhydrohydroxydelsoline, as shown in formula (III), and this shows clearly that the orientation of this hydroxyl has to be towards the nitrogen, and so, opposite to that of the corresponding methoxyl in lycoctonine. This orientation may account for the low pK_a of delsoline (6·4) compared with that of lycoctonine (8·8). On the other hand, the orientation of the methoxyl group on the five-membered ring adjacent to the nitrogen ring is not yet known.

The cleavage of acetyldelsoline and of dehydro-oxodelsoline with lead tetra-acetate, and the loss of methanol in the *seco*diketone obtained from the former provide evidence for the presence of vicinal tertiary hydroxyls and of a methoxyl β to one of these hydroxyls, as required by the suggested structure. Demethanol-O-acetyloxodelsoline*seco*diketone would then be represented by formula (V).



V

Attempts to obtain an anhydro derivative from dehydro-oxodelsoline (IV) through a pinacolic rearrangement, as with lycoctonam (i.e., oxolycoctonine),[4] have not so far yielded definite results. The compound (IV) was not affected when heated with acetic acid (100 ml) containing sulphuric acid (0·1 ml) at 80° or 100°, while under similar conditions oxolycoctonine gave a pinacone in 95 per cent yield.[5] Heating under reflux with acetyl chloride also failed to produce the desired change. Under more drastic conditions (treatment for a few minutes at 100° with acetic anhydride containing 5 per cent of sulphuric acid) dehydro-oxodelsoline gave a very small quantity

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[9] O. E. Edwards and L. Marion, *Canad. J. Chem.* **30**, 627 (1952).
[10] R. C. Cookson and M. E. Trevett, *J. Chem. Soc.* 2689 (1956).
[11] M. Przybylska and L. Marion, *Canad. J. Chem.* **34**, 185 (1956).
[12] O. E. Edwards, L. Marion and D. K. R. Stewart, *Canad. J. Chem.* **34**, 1315 (1956).

of a high-melting compound (m.p. 315–320°), which had an infrared spectrum containing absorption bands indicative of a lactam carbonyl (1660 cm^{-1}) and two other carbonyl groups (1732 and 1755 cm^{-1}) that seemed to belong to two acetyl groups, since two intense bands at 1210 and 1240 cm^{-1} were also present in the spectrum. The product was not the diacetyl derivative of dehydro-oxodelsoline, since that compound was prepared and found to have different properties. Because of insufficient material no analytical figures were obtained, and any speculation as to the nature of this compound would be premature.

One attempt to correlate delsoline with lycoctonine required the inversion of the secondary hydroxyl group in the former. This was tried with dehydro-oxodelsoline by reduction with sodium borohydride, but the product of the reaction was amorphous. Since previous experience had shown that it was difficult to crystallize oxodelsoline or acetyldelsoline, the crude product of the reaction was acetylated and then oxidized with lead tetra-acetate. The *seco*diketone thus obtained crystallized well, and was identical with demethanol-acetyloxodelsoline*seco*diketone (V) prepared directly from O-acetyldelsoline, thus showing that the reduction with sodium borohydride was quite stereospecific in this case, and did not give an inversion.

Another route was explored by treating the methanesulphonyl derivative of delsoline with sodium methoxide. This reaction, however, instead of giving the expected inverted methoxyl group, hydrolyzed the mesyldelsoline and caused inversion of the hydroxyl, thus giving rise to epidelsoline. The tosylation of delsoline also produced some *epi*delsoline.

EXPERIMENTAL

The ultra-violet spectra were determined in 95% ethanol on a Beckman DU spectrometer. The infrared absorption spectra were determined on a Perkin–Elmer double-beam instrument (Model 21). In the text, the peaks are indicated by a wave number and the percentage absorption (in parentheses). Shoulders are denoted by an S after the wave number. Unless otherwise mentioned, the compounds were dispersed in Nujol mulls for the determination of the infrared spectra. All melting points were taken on a microscope hot stage and were not corrected.

Delsoline. The crude delsoline obtained from the seeds of *Delphinium consolida* L.* was heated on the steam-bath for 3 hr in a nitrogen atmosphere, with 0·5 N sodium hydroxide (water : methanol = 1 : 1) in order to hydrolyse any acetyldelsoline that could be present. The methanol was evaporated under reduced pressure and the mixture of delsoline and delcosine extracted with chloroform. The chloroform solution (dried over sodium sulphate) was evaporated to dryness under diminished pressure, and the residue was dissolved in benzene and chromatographed on Woelm alumina (activity IV, Brockmann scale). The benzene-eluted fraction was purified by repeated crystallization from 95% ethanol. The pure delsoline thus obtained melted at 213–216° (Found: C, 64·37; H, 9·01; O, 24·00; N, 2·98; OCH_3, 26·32; N—C_2H_5, 5.41; active H (Zerewitinoff), 0.73. Calc. for $C_{25}H_{41}O_7N$: C, 64·21; H, 8·84; O, 23·95; N, 3·00; 4OCH_3, 26·56; N—C_2H_5, 6·21; 3 active H, 0·65 per cent. pK_a, 6·4 (value of pH at half titration in 50% methanol). Infrared absorption: 3442(48), 3300(36).

Monoacetyldelsoline. Delsoline (500 mg) was dissolved in dry pyridine (8 ml) and freshly distilled acetic anhydride (8 ml) was added to the solution, which was kept at

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* About 5 g from 18 kg of seeds.

room temperature (25°) for 6 hr. The reaction mixture was concentrated under reduced pressure to a thick oil, which was dissolved in methanol and the solution was evaporated to dryness. The residue was dissolved in chloroform, shaken with ice-cooled 5% aqueous sodium carbonate, washed with water, dried and evaporated to dryness. The residue was dissolved in ether–pentane (1 : 1), and the solution was kept in the refrigerator for several hours and filtered to remove a small quantity of crystalline delsoline that had been deposited. The mother-liquor was evaporated to dryness, the residue was dissolved in methanol and the solution was neutralized with perchloric acid. Monacetyldelsoline perchlorate was precipitated and, after repeated crystallization from hot methanol, melted at 212–214° (Found: C, 53·16; H, 7·29. Calc. for $C_{25}H_{40}O_7N(COCH_3).HClO_4$: C, 53·15; H, 7·27 per cent). The infrared absorption spectrum of the salt contained peaks at 3430(66), 3380(60) indicative of hydroxyl groups, at 3140(64) due to an $\overset{+}{\equiv NH}$ grouping and at 1762(89), 1220(72) cm^{-1} attributable to the O-acetyl group.

Methanesulphonyldelsoline. Delsoline (300 mg) was dissolved in thoroughly dried pyridine (3 ml) and methanesulphonyl chloride was added to the solution. The mixture was left for 48 hr in the refrigerator and subsequently evaporated under reduced pressure at room temperature. The residue was dissolved in chloroform and a little ice was added to the solution, which after a few minutes was shaken with 5% aqueous sodium carbonate, dried over sodium sulphate and evaporated. The residue was washed with ether–pentane (1 : 1) and dissolved in boiling ether. The ether solution was filtered to remove an insoluble residue and concentrated until crystals began to separate. The crystalline product consisted of short thick needles (40 mg), m.p. 124°, which could not be recrystallized without some decomposition and could not be further purified (Found: C, 58·38; H, 8·52. Calc. for $C_{25}H_{40}O_7N(CH_3{-}SO_2{-})$: C, 57·22; H, 7·94 per cent). Although the analytical figures were not very satisfactory, they seemed to indicate that the product consisted mostly of the desired substance. The infrared absorption spectrum contained the following sharp bands: 3480(60), 1165(83), 917(77), 895(72) and 875(73).

Reaction of mesyldelsoline with sodium methoxide (epidelsoline). Mesyldelsoline (250 mg) was added to a solution of sodium (90 mg) in absolute methanol (3 ml) and left at room temperature for 3 days The methanol was evaporated under reduced pressure, the residue was dissolved in water and the solution was extracted with chloroform. The material obtained from the chloroform was dissolved in benzene and chromatographed on Woelm alumina (activity III). The benzene-eluted material consisted of two substances, which were separated by fractional crystallization from ether. One was sparingly soluble and proved to be delsoline (probably present in the starting material), while the more soluble fraction melted at 148–154° and had an infrared absorption spectrum showing little, but very significant, difference from that of delsoline (Found: OCH_3, 26·42. Calc. for $C_{25}H_{41}O_7N$: $4OCH_3$ 26·56 per cent).

Attempted tosylation of delsoline. Toluene-*p*-sulphonyl chloride (135 mg) was dissolved in dried pyridine (2 ml) and added to a strongly cooled solution of delsoline (300 mg) in the same solvent (3 ml). The mixture was allowed to stand in the refrigerator for 60 hr. A little ice was then added and after another hour the reaction mixture was treated with aqueous sodium carbonate and extracted with chloroform. The extract was evaporated to dryness under reduced pressure and the residue was digested with ether. An insoluble fraction was filtered out, which consisted of unchanged delsoline (170 mg). The ether-soluble material was chromatographed on Woelm neutral alumina (activity II–III). A first fraction, eluted with benzene–chloroform, consisted of delsoline, while a second fraction, eluted with chloroform containing 5% of methanol, and crystallized from ether, melted at 143–150°. The latter had an infrared absorption spectrum superimposable on that of epidelsoline.

Oxidation of delsoline with potassium permanganate [dehydro-oxodelsoline]. Delsoline (500 mg) was dissolved in acetone (25 ml) containing glacial acetic acid (1·5 ml) and water (1·5 ml) and oxidized by the gradual addition of finely powdered potassium permanganate. When the color of the permanganate persisted for 2 hr, the manganese dioxide was filtered off and washed twice with acetone and once with aqueous sodium carbonate. The washings and filtrate were combined, evaporated to dryness and the residue subjected to the usual separation into acid, basic and neutral fractions.

The basic fraction when chromatographed on alkaline alumina (activity V) was separated into two compounds, eluted, one with hexane–benzene, the other with benzene. When crystallized from acetone, the first compound (III) (10 mg) separated as thick needles, m.p. 218–220°. The second compound (II) crystallized from ether as fine needles, m.p. 185–187°. These two products, which have been obtained in better yields under different conditions of oxidation, are described below.

The neutral fraction when dissolved in benzene and chromatographed on alumina (activity IV) yielded 90 mg of a crystalline product, which after recrystallization from benzene–ether melted at 200–201° (Found: C, 62·46; H, 7·65; N, 3·00. Calc. for $C_{25}H_{37}O_8N$: C, 62·61; H, 7·78; N, 2·92 per cent), $[\alpha]_D^{24}$ +117·6 (*c*, 1·36 in ethanol). This product, dehydro-oxodelsoline, in solution in chloroform, showed the following bands in the infrared: 3500(44), 3410(50) due to hydroxyl groups, 1717(88) (six-membered cyclic ketone), 1640 cm^{-1} (99) (six-membered lactam carbonyl). In a Nujol mull, the bands were at 3460(68), 1717(77) and 1635(91) cm^{-1}. Further elution of the chromatogram with chloroform and methanol did not yield any crystallizable material.

The acidic fraction was very small. On treatment with diazomethane and distillation in a high vacuum, it yielded two small oily fractions, which could not be purified further.

Oxidation of delsoline with chromium trioxide. Dehydro-oxodelsoline can be obtained in much better yield when chromium trioxide is used as an oxidant. Chromium trioxide (1·2 g) was added portionwise to dry ice-cooled pyridine (12 ml) and under vigorous stirring finely powdered delsoline (1·0 g) was added to the resulting suspension. After a few minutes a black precipitate was formed, and the reaction mixture was shaken gently for 15 hr. The pyridine was evaporated under reduced pressure, and ice and 0·5 N sulphuric acid were added to the residue. Sulphur dioxide was bubbled through the solution, which was subsequently extracted with chloroform. The extract was washed with water, 4% aqueous sodium hydroxide, again with water and then evaporated to dryness. There was left a neutral residue (800 mg), which after crystallization from benzene–ether (620 mg) melted at 200–201°, either alone or in admixture with dehydro-oxodelsoline.

Dehydro-oxodelsoline is not affected by heating at 100° with either 6 N sodium hydroxide for 2 hr or 6 N sulphuric acid for 30 min. It was also recovered unchanged after heating for 1 hr at 100° with acetic acid containing 0·1% of sulphuric acid.

Treatment of dehydro-oxodelsoline with acetic anhydride containing 5% of sulphuric acid, however, yielded a very small quantity of a product, m.p. 315–320°, which could not be purified further. It had an infrared absorption spectrum that did not show clearly the presence of a hydroxyl band. It did not appear to be the expected pinacolic rearrangement product, nor was it diacetyldehydro-oxodelsoline, as shown by the preparation of that compound.

Diacetyldehydro-oxodelsoline. Dehydro-oxodelsoline (200 mg) was dissolved in acetyl chloride (10 ml) and the solution was heated under reflux for 4 hr in a nitrogen atmosphere. The acetyl chloride was evaporated under reduced pressure, ice was added to the residue, and the resulting aqueous solution was made basic with sodium carbonate and extracted with chloroform. The product (176 mg) recovered from the extract was redissolved in benzene and chromatographed on Woelm neutral alumina (activity IV). Elution with chloroform gave a substance that crystallized well from acetone–ether, m.p. 210–213° (Found: C, 62·62; H, 7·49. Calc. for $C_{29}H_{41}O_{10}N$: C, 61·79; H, 7·33 per cent). The infrared spectrum showed no absorption in the hydroxyl region, but contained bands at 1752(69), 1735(77), 1255(94) and 1240(82) cm^{-1} due to the acetyl groups, at 1720(64) cm^{-1} due to the six-membered cyclic ketone and at 1645(89) cm^{-1} attributable to the lactam carbonyl.

When this compound was hydrolyzed with 0·1 N sodium hydroxide in water and methanol, it gave back dehydro-oxodelsoline, thus confirming that it was an *OO*-diacetyl derivative.

Oxidation of delsoline with potassium permanganate under neutral conditions [anhydrohydroxydelsoline (III)*].* Delsoline (500 mg) was dissolved in acetone (25 ml) and water (5 ml), and magnesium sulphate (3 g) was added to the solution. Under vigorous stirring, finely powdered potassium permanganate (230 mg) was added portionwise. The manganese dioxide was filtered off and washed twice with acetone–water (5 : 1). The combined filtrate and washings were evaporated under reduced pressure, the residue was dissolved in water and the solution was extracted with chloroform. The chloroform solution was evaporated to dryness and the residue, after two crystallizations from acetone, consisted of colorless hexagonal prisms (230 mg), m.p. 217–220°, either alone or in admixture with one of the minor products, compound (III), of the oxidation of delsoline with acid potassium permanganate mentioned above (Found: C, 64·33; H, 8·26; active H, 0·384. Calc. for $C_{25}H_{39}O_7N$: C, 64·49; H, 8·44; 2 active H, 0·429 per cent), $[\alpha]_D^{24}$ +57·0 (*c*, 1·27 in ethanol), pK_a 4·2 (value of pH at half titration in 50% methanol with 0·05 N hydrochloric acid). The infrared absorption spectrum contained the following characteristic bands: 3500(27), 3440(47), 3380(37), 997(85) and 895(62) cm^{-1}.

Anhydrohydroxydelsoline perchlorate. A solution of anhydrohydroxydelsoline (50 mg) in methanol (2 ml) was made just acid with 70% perchloric acid diluted with methanol. The dropwise addition of ether with stirring caused the salt to separate as hexagonal plates. After recrystallization from methanol–ether it melted at 227° (dec.). The infrared spectrum contained bands at 3460(60); 3400S(53) cm^{-1} in the hydroxyl region, and 3160(42) cm^{-1} indicative of the group $=\overset{+}{N}H$, but no absorption in the 1550–1800 cm^{-1}, so that the perchlorate is not an anhydronium salt.

Reduction of anhydrohydroxydelsoline. Anhydrohydroxydelsoline (75 mg) was dissolved in 50% aqueous methanol (3 ml) and sodium borohydride (20 mg) was added to the solution. The solution was kept at room temperature overnight, subsequently heated on the steam-bath for 1 hr and evaporated under reduced pressure to remove the methanol. The aqueous residue was extracted with chloroform, and the white powder recovered from the extract was crystallized from 95% ethanol. The crystalline product melted at 213–216°, either alone or in admixture with delsoline. A comparison of the infrared spectra confirmed the identity.

Oxidation of anhydrohydroxydelsoline with mercuric acetate [*anhydrohydroxy*-N-*de-ethyldelsoline* (II)]. To anhydrohydroxydelsoline (50 mg) dissolved in 6% aqueous acetic acid (2 ml), mercuric acetate (250 mg) was added. The solution was heated on the steam-bath for 30 min, during which acetaldehyde was evolved and was detected with Tollens's reagent. The precipitated mercurous acetate was filtered off and the filtrate was extracted with chloroform. The extract was washed with aqueous sodium bicarbonate, dried and evaporated to dryness. The residue was dissolved in ether and the solution, after filtration, evaporated to the point of incipient crystallization. Anhydrohydroxy-N-de-ethyldelsoline was thus obtained as long thin needles (37 mg), m.p. 185–187°, either alone or in admixture with compound (II) mentioned above (Found: C, 63·28; H, 8·16. Calc. for $C_{23}H_{33}O_7N$: C, 63·14; H, 8·06 per cent). Infrared absorption spectrum: 3430S(41), 3385(65), 3295(34) cm^{-1}.

Ethylation of anhydrohydroxy-N-*de-ethyldelsoline*. Anhydrohydroxy-N-de-ethyldelsoline (50 mg) was heated for 5 hr on the steam-bath with ethyl iodide (600 mg), dimethylformamide (300 mg) and sodium carbonate (20 mg). The product, crystallized from acetone–ether, melted at 217–219°, either alone or in admixture with anhydrohydroxydelsoline. The identity was confirmed by comparison of the infrared spectra.

Oxidation of delsoline with mercuric acetate. Delsoline (300 mg) was dissolved in 6% aqueous acetic acid (12 ml), mercuric acetate (1500 mg) was added and the solution was heated on the steam-bath for 60 min. The precipitated mercurous acetate was filtered off and washed with 6% aqueous acetic acid, and the combined filtrate and washings were extracted with chloroform. The extract was washed with aqueous sodium bicarbonate and with water, dried and evaporated to dryness. There was left a residue, which after crystallization from ether (yield 120 mg) melted at 184–186°, alone or in admixture with anhydrohydroxy-N-de-ethyldelsoline (II) described above.

Oxidation of acetyldelsoline perchlorate with potassium permanganate. To a solution of acetyldelsoline perchlorate (305 mg) in acetone (25 ml) and water (5 ml), finely powdered potassium permanganate (57 mg) was added. The permanganate was reduced rapidly, and the manganese dioxide was filtered off and washed with acetone–water. The filtrate was evaporated to dryness under reduced pressure. The solid residue left was washed several times with boiling ether. The combined ether solutions yielded a quantity of acetyldelsoline. The residue (116 mg), which was insoluble in ether, consisted of acetyldelsoline anhydronium perchlorate and potassium perchlorate. It was dissolved in hot absolute ethanol in which potassium perchlorate was less soluble than the anhydronium salt. After many separations and crystallizations from absolute ethanol, the anhydronium salt was obtained as thin needles, m.p. 253–255° (dec.). The analysis showed that the sample still contained a little potassium perchlorate. The infrared spectrum of acetyldelsoline anhydronium perchlorate contained the following absorption bands: 3440(68), 3360(58) (hydroxyl); 1760(71), 1748(87), 1230(91) (acetate); 1690(33) cm^{-1} due to $-\mathrm{C}=\overset{+}{\mathrm{N}}\langle$.

Oxidation of acetyldelsoline perchlorate with mercuric acetate. Acetyldelsoline perchlorate (305 mg) was dissolved in 6% aqueous acetic acid (12 ml) and acetone (6 ml). Mercuric acetate (1·0 g) was added and the solution was heated for a short time on a steam-bath. The precipitated mercurous acetate was filtered off and the remaining mercury salt was removed with hydrogen sulphide. The filtered solution was evaporated to dryness under reduced pressure and the residue (acetyldelsoline anhydronium perchlorate) was crystallized from ethanol as before.

Reaction of acetyldelsoline anhydronium perchlorate with sodium hydroxide. Acetyldelsoline anhydronium perchlorate (20 mg) was dissolved in water (4 ml), 6 N sodium hydroxide (0·5 ml) was added and the solution was heated for 15 min on the steam-bath. The cooled solution was extracted with chloroform and the extract was evaporated to dryness. There was left a residue which crystallized from acetone (yield 12 mg), m.p. 216–219° either alone or in admixture with anhydrohydroxydelsoline. The identity was confirmed by the infrared absorption spectra which were superimposable.

Oxidation of acetyldelsoline. Acetyldelsoline perchlorate (610 mg) was suspended in ice-cooled water (10 ml) and chloroform. The suspension was stirred vigorously while cooled externally and N sodium hydroxide (12 ml) was added. After a few minutes the chloroform solution was separated and the aqueous layer was extracted several times with chloroform. The combined chloroform solution was dried and evaporated to dryness under diminished pressure. The residue, dissolved in pyridine (3 ml), was added to a suspension of chromium trioxide (400 mg) in pyridine (9 ml). After it had been kept gently shaking overnight, the reaction mixture was worked up in the same way as described for the oxidation of delsoline. The chloroform extract was washed with water, with ice-cooled sodium carbonate solution, again with water and then dried over sodium sulphate. The residue obtained after the evaporation of the chloroform extract was dissolved in a little benzene, and pentane was added. After 2 days in the cold a few crystals had been deposited, m.p. 148–150°. The residue left after evaporation of the mother-liquor was a colorless glass. The infrared spectra of the crystals and of the glass did not show any important difference. The main absorption bands were: 3460(55), 3420(54) due to hydroxyls, 1732(92), 1250(95) due to an acetate group and 1640(90), 1630(90) cm^{-1} indicative of a lactam carbonyl.

*Oxidation of acetyloxodelsoline [demethanol-acetyloxodelsoline*secodiketone (V)]. Acetyldelsoline (200 mg) was dissolved in 20 ml of an acetic acid solution of lead tetra-acetate (2 g in 75 ml) and left to stand for 90 min. A saturated solution of sodium metasulphite was added until no reaction was obtained on a starch–iodide paper. A small quantity of Cellite was added and the solution was centrifuged. The clear acid centrifugate was evaporated to dryness under reduced pressure, the residue was dissolved in chloroform and the solution was washed with aqueous sodium bicarbonate. Evaporation of the dried chloroform solution left an oil, which was dissolved in benzene and chromatographed on Woelm neutral alumina (activity IV). The material eluted with benzene was obtained as a glassy substance that crystallized when ether and pentane were added as fine needles, m.p. 135–137°. On recrystallization from benzene–ether the melting point jumped to 192–194°, presumably showing a change in the nature of the compound. Further elution of the chromatogram with chloroform yielded a second fraction that crystallized on contact with ether, m.p. 187–193°, and after recrystallization from benzene–ether, at 192–194°. It was identical with the above-mentioned compound (Found: C, 63·48; H, 6·98. Calc. for $C_{26}H_{35}O_8N$: C, 63·79; H, 7·21 per cent). Ultraviolet absorption spectrum: λ_{max} 222 mμ, (log ϵ 3·98), λ_{min} 277 mμ (log ϵ 1·88), λ_{max} 319 mμ (log ϵ 2·47). The infrared spectrum contained bands at 1765(73), five-membered cyclic ketone; 1740(88), 1237(93) (acetate), 1680(75), $\alpha\beta$-unsaturated six-membered ketone, 1650(93) cm^{-1} (lactam).

Hydrolysis and oxidation of acetyloxodelsoline. Acetyloxodelsoline (100 mg) was heated on a steam-bath with N sodium hydroxide for 30 min. The cooled solution was extracted with chloroform and the extract on evaporation yielded oxodelsoline as a colorless glass. The glass was dissolved in dry pyridine (1 ml) and added to a suspension of chromium trioxide (100 mg) in pyridine (1 ml). After 15 hr the reaction mixture was worked up as described before. The residue obtained after evaporation of the chloroform extract was crystallized from benzene–ether, m.p. 199–201°, either alone or in admixture with dehydro-oxodelsoline.

Reduction of dehydro-oxodelsoline with sodium borohydride. To a solution of dehydro-oxodelsoline (230 mg) in 1 : 1 aqueous methanol (8 ml), sodium borohydride (230 mg) was added and the solution was allowed to stand overnight. Methanol was distilled off under reduced pressure, water was added and the solution was extracted with chloroform. Evaporation of the extract left a clear glassy material (180 mg), which could not be crystallized.

The glassy material (180 mg) thus obtained was treated with acetic anhydride (3 ml) and pyridine (3 ml) at room temperature for 6 hr. The colorless amorphous product (isolated as previously described) was dissolved in 10 ml of an acetic acid solution of lead tetra-acetate (2 g in 75 ml of acetic acid). After 90 min the reaction mixture was worked up as already described for the similar oxidation of acetyloxodelsoline, and the same demethanol-acetyloxodelsoline*seco*diketone, m.p. 192–194°, was obtained. Hence the reduction with sodium borohydride must have heen stereospecific.

Oxidation of dehydro-oxodelsoline with lead tetra-acetate. The keto-lactam (79 mg) was dissolved in acetic acid (15 ml) containing lead tetra-acetate (2 g per 75 ml of acid) and left to stand for 1 hr. Titration at the end of 1 hr determined that 1·16 moles had been taken up. A saturated solution of sodium metabisulphite was added until no reaction was obtained with starch–iodide paper. Some Cellite was added and the solution was centrifuged. The clear acid solution was then evaporated to dryness under reduced pressure, the residue was dissolved in aqueous sodium bicarbonate and the solution was extracted with chloroform. The oil recovered from the chloroform extract was chromatographed on Woelm neutral alumina (activity IV) and eluted with chloroform. A fraction (60 mg) was thus obtained which crystallized from methanol–ether (yield 75 per cent), m.p. 243–245° (Found: C, 62·49; H, 6·95. Calc. for $C_{25}H_{35}O_8N$: C, 62·57; H, 7·37 per cent). Infrared absorption: 3440(61), 1755(85), 1738(82), 1653(90), 1640S(66) cm^{-1}.

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