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THE STRUCTURE OF LAPPACONITINE. TYPE AND POSITION OF THE HYDROXYL GROUPS

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Lappaconitine (I) is isolated from various plants of the genus Aconitum (1,2,3). The authors have recently isolated it from Aconitum ranunculaefolium (4). It is an ester aconite alkaloid with the molecular formula $C_{32}H_{44}O_8N_2$. On alkaline hydrolysis it is decomposed into the alcamine lappaconine (II) with the molecular formula $C_{23}H_{37}O_6N$ and acetylanthranilic acid. The molecular formula of lappaconine is confirmed by its mass spectrum which has a peak at m/e 423. The functional analysis as well as its NMR spectra (5) reveal the presence of three methoxyl and three hydroxyl groups. The NMR spectrum of lappaconine contains peaks at 6.71, 6.68 and 6.58 τ (9H from $3CH_3O$) and that of completely acetylated lappaconine in addition to the above, contains three more peaks at 7.89, 7.96 and 8.05τ(9H from $3CH_3COO$). In the NMR spectra of both the lappaconine and triacetyllappaconine a triplet is observed with a center

at 8.94 τ (3H, J 7.5 cps) which in the NMR spectra of the delphinine like diterpene alkaloids is attributed to the methyl group of the N-ethyl group(6).

The IR spectrum(7) of alkamine II contains a slightly intense band at 1610 cm^{-1}, but it is not due to double bond, since no signals from aromatic or olefinic protons are observed in the NMR spectrum. Attempts at its catalytic hydration did not give positive results. The band at 3550 cm^{-1} in the region of absorption of the hydroxyl groups is also present in the ester alkaloid I, while the band at 3600 cm^{-1} appears only after hydrolysis. This hydroxyl group is acetylated with acetic anhydride and pyridine at room temperature. Monoacetyllappaconine is thus obtained, which has been characterized by its perchlorate, m.p. 146° (decomp.)(8). (Analysis. Calcd. for $C_{25}H_{39}O_7N.HClO_4$: C, 53.04; H, 7.12; N, 2.47; Cl, 6.26. Found: C, 52.58; H, 7.56; N, 2.49; Cl, 5.95). When this compound is treated with ammonia monoacetyllappaconine (III) is obtained, m.p. 150-2°. (Analysis. Calcd. for $C_{25}H_{39}O_7N$: C, 64.49; H, 8.44; N, 3.01. Found: C, 64.02; H, 8.44; N, 3,23). IR spectrum: 1730 cm^{-1} ($O.CO.CH_3$). 3550 cm^{-1} (OH). Lappaconitine is not acetylated under the above conditions. Diacetyllappaconitine(IV), m.p. 125-7° is obtained by treating lappaconitine with acetylchloride at room temperature for 8 days. (Analysis: Calcd. for $C_{36}H_{48}O_{10}N_2$: C, 64.65; H, 7.23; N, 4.19. Found: C, 63.99; H, 7.34; N, 4.28). IR spec-

trum: 1730 cm^{-1} ($O.CO.CH_3$), no OH group. Under the same conditions lappaconine gives triacetyllappaconine (V), m.p. 184-5°. (Analysis. Calcd. for $C_{29}H_{43}O_9N$: C, 63.37; H, 7.89. Found: C, 62.81; H, 7.78). IR spectrum: 1730 cm^{-1} ($O.CO.CH_3$), no OH group. All of the above mentioned acetyl derivatives give lappaconine upon alkaline hydrolysis.

Dehydrooxolappaconitine (VI), m.p. 146-150°, can be successfully isolated upon the oxydation of lappaconitine with potassium permanganate in acetone solution. (Analysis. Calcd. for $C_{32}H_{40}O_9N_2 \cdot 2H_2O$: C,60.75; H, 7.00; N, 4.43; H_2O, 5.75. Found: C, 61.18; H, 6.71; N, 4.84; H_2O, 5.73). IR spectrum: wide band with a max. at 1690 cm^{-1}(O-acetylanthranoyl,δ-lactam and a cyclic ketone) and 3540 cm^{-1}(OH).Amorphous dehydrooxolappaconine (VII), m.p. 78-85°, is obtained upon alkaline hydrolysis.(Analisis. Calcd. for $C_{23}H_{33}O_7N$: C, 63.43; H, 7.64; N, 3.23. Found: C, 62.92; H, 7.90; N, 2.90). This product does not change after 4 hrs' heating in 10% hydrochloric acid at 100°. IR spectrum of VII shows a band at 1645 cm^{-1}. Since it does not change under the conditions of acid hydrolysis it is assumed that this band belongs to δ-lactam. The absorption max. at 1745 cm^{-1} belongs to a five-membered cyclic ketone. It should be noted that only the 3540 cm^{-1} band appears in the hydroxyl region of the IR spectrum of VII. The 3600 cm^{-1} band in the IR spectrum of II is revealed here only as an inflex with a cen-

ter at 3595 cm^{-1}.

Dehydrooxolappaconitine (VI) is obtained yet in another way. When lappaconitine is oxidized first with mercuric acetate hydroxylappaconitine (VIII) is obtained, m.p. 169-174°. (Analysis. Calcd. for $C_{32}H_{44}O_9N_2$: C, 63.98; H, 7.38; N, 4.66. Found: C, 64.34; H, 7.57; N, 4.70). The IR spectrum of this compound contains,as compared with that of II, more intense bands at 1090 cm^{-1} and 1280 cm^{-1}. VIII contains a new hydroxyl group adjacent to the nitrogen atom and upon oxidation with potassium permanganate in acetone medium VIII is converted to VI.

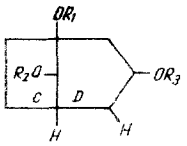
Amorphus didehydrooxolappaconine (IX), m.p. 58-64° is isolated as the main product when lappaconine is oxidized with potassium permanganate in acetone solution. (Analysis. Calcd. for $C_{23}H_{31}O_7N.2H_2O$: C, 58.83; H, 7.51; H_2O, 7.67. Found C, 59.28; H, 8.08; H_2O, 7.54). The IR spectrum of IX contains in addition of the δ-lactam max. at 1660 cm^{-1} a wide band with max. at 1720 cm^{-1}. The latter should be attributed to the summing up of the bands of a six-membered and a five-membered cyclic ketones. In the region of hydroxyl absorption there is only one max. at 3530 cm^{-1}.

All the chemical and spectral date presented so far would permitt to make the following assumptions about the type of hydroxyl groups of lappaconitine (I): the hydroxyl group esterified with acetylanthranilic acid is secondary and it is attached to a six-membered

ring. In didehydrooxolappaconine (IX) it is converted to six-membered cyclic ketone (ν_{max} 1720 cm^{-1}). One of the remaining two hydroxyl groups is secondary and it is attached to a five-membered ring, since a cyclopentanone band (ν_{max} 1745 cm^{-1}) is observed in the IR spectrum of dehydrooxolappaconine (VII). The third hydroxyl group is tertiary, because it is not oxidized by potassium permanganate.

The problem of the structure of the skeleton of lappaconine (II) has not yet been subject of our studies. The behaviour of the hydroxyl groups however is close enough to that of the hydroxyl groups in the alkaloids delphinine and aconitine to justify the assumption that lappaconine contains in its structure the rings C and D of delphonine (X) and aconine (XI). For this reason the compounds described as well as some of their chemical conversions are represented by formulae which express the partial structures of these compounds.

By oxidation of IX with lead tetraacetate one mole of IX takes up 1.14 moles of oxydant. The seco ketoacid of lappaconine (XII) is isolated from the reaction mixture and it can be directly methylated with diazomethane. The methyl ester of the seco ketoacid of lappaconine (XIII) has a m.p. of 93-6°. (Analysis. Calcd. for $C_{24}H_{33}O_8N$: C, 62.19; H, 7.18; N, 3.02. Found: C, 62.64; H, 7.48; N, 3.33). The IR spectrum of the seco ketoacid (XII) is similar to



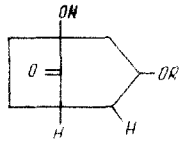
I. R_1= R_2= H;
R_3= $CO.C_6H_4.NH.OC.CH_3$

II. R_1= R_2= R_3= H

III. R_1= R_2= H; R_3= $CO.CH_3$

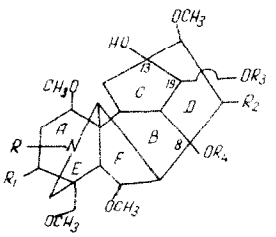
IV. R_1= R_2= $CO.CH_3$;
R_3= $CO.C_6H_4.NH.OC.CH_3$

V. R_1= R_2= R_3= $CO.CH_3$



VI. R = $CO.C_6H_4.NH.OC.CH_3$

VII. R = H

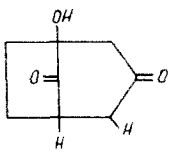


X. R = CH_3; R_1= R_2= R_3= R_4= H

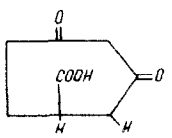
X-a. R = CH_3; R_1= R_2= H;
R_3= $CO.C_6H_5$; R_4= $CO.CH_3$

XI. R = C_2H_5; R_1= R_2= OH;
R_3= R_4= H

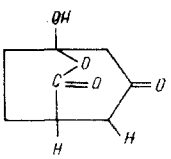
XI-a. R = C_2H_5; R_1= R_2= OH;
R_3= $CO.C_6H_5$; R_4= $CO.CH_3$



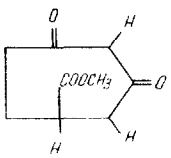
IX



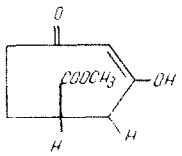
XII



XII[a]



XIII



XIII[a]

that of the seco ketoacid obtained by the oxidation of α-oxodelphonone with chromic acid or α-oxodelphonine with periodic acid and subsequent oxidation with potassium permanganate (9). Wiesner et al. assume that this acid is in equillibrium with the corresponding pseudoacid which is dominant in chloroform solution. In fact the IR spectrum of XII reveals bands of δ-lactone at 1740 cm^{-1} and bands of hydroxyl groups at 3530 cm^{-1}(XII-a). In addition absorption maxima are observed of a six-membered cyclic ketone at 1715 cm^{-1} and of δ-lactam at 1640 cm^{-1}, contained by the original IX. This behaviour of the seco ketoacid XII give rise to the assumption that the tertiary hydroxyl group(10) and the hydroxyl group attached to the five-membered ring are adjacent and are situated as in delphonine and aconine, viz., at C_{13} and C_{19}. The tertiary hydroxyl group of lappaconine (II) cannot be situated at C_8, since attempts to pyrolize triacetyllappaconine (V) (30 min. at 195°, 5 mm Hg) resulted in unchanged V as the main product.This assumption is corroborated by the NMR spectrum of triacetyllappaconine (V), which in contrast to that of lappaconine (II) contains one unresolved multiplet at about 5.12 τ (1H). Similar proton signal is attributed to the interaction of single hydrogen atoms attached to two adjacent carbon atoms, one of which carries an aromatic ester group. Such configuration in the molecules of delphinine (X-a) and aconitine (XI-a) corresponds to the position of

the secondary hydroxyl group attached to the five-membered ring at C_{19} (11). This adjacent position of the two hydroxyl groups might explain the lower absorption band (at 3550 cm^{-1}) of these hydroxyl groups and the more difficult acetilation of the secondary group attached to the five-membered ring.

The IR spectrum of the ester XIII makes it possible to draw conclusions about the position of the secondary hydroxyl group attached to the six-membered ring. The spectrum exhibits intense bands at 1610, 1653, 1710 (with inflexes at 1740 cm^{-1}) and 3520 cm^{-1}. The bands at 1610, 1710 and 3520 cm^{-1} may be due to the enol form of a 1,3-diketone (XIII-a). These conclusions are supported by the UV spectrum (λ_{max} 249 mμ, ε = 5000) which is of the type of UV spectra shown by 1,3-diketones such as benzoylacetone. Such a disposition of hydroxyl group on the six-membered ring can explain the inflex at 3595 cm^{-1} in VII in terms of the effect on the hydroxyl group of the carbonyl at C_{19} (12).

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