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REACTIONS OF LYCOCTONINE ALKALOIDS CONTAINING A 7,8-METHYLENEDIOXY GROUP WITH Na IN LIQUID AMMONIA

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The reactions of 6-dehydroeldelidine and 6-dehydrodelcorine with sodium in liquid ammonia have been studied. Structures have been put forward for the compounds obtained. Features of the fragmentation of these compounds under electron impact are discussed.

One of the problems in the chemistry of the C-19 diterpene alkaloids is the elimination of oxygen functions and, in particular, the passage from the alkaloids of the lycoctonine type to alkaloids of the aconitine type. In this paper, we discuss the results obtained in the reactions of 6-dehydroeldelidine (I) and 6-dehydrodelcorine (II) with sodium in liquid ammonia.

In the first case, eldelidine (III) and two other products — (IV) and (V) — were obtained.

Product (IV), M+ 435, $C_{24}H_{37}NO_6$. The IR spectrum of (IV) contained the absorption band of a carbonyl group in a 5-membered ring (1740 cm^{-1}), and its NMR spectrum the signals of these methoxy groups but no signal of a methylenedioxy group. The position in the PMR spectrum of the H-14β signal at 4.09 ppm (1H, triplet, J = 4.5 Hz) showed that the hydroxy group at C-10 had been retained [1]. An intense peak of a $(M - 49)^+$ ion showed the presence of a hydroxy group at C-8 [2]. On the basis of what has been said above, this product had the structure (IV) and this was confirmed by the results of x-ray structural analysis (Scheme 1).

Product (V), M+ 419, $C_{24}H_{37}NO_5$, differed from the initial compound by a CO_2 group. Its mass spectrum was characteristic for C-19 diterpene alkaloids, and the maximum peak, $(M - OCH_3)^+$, showed the presence of a methoxy group at C-1 [2]. According to its PMR spectrum, the molecule of compound of (V) contained three methoxy groups (3.23, 3.26, and 3.27 ppm, singlets, 3H each), and there were no signals of olefinic protons or of a methylenedioxy group. The IR spectrum retained the absorption band of a carbonyl group in a five-membered ring (1745 cm^{-1}). On the basis of the facts given, for product (V) it is possible to suggest a structure differing from (IV) by the absence of one hydroxy group. The presence in the PMR spectrum of product (V) of a one-proton triplet at 3.94 ppm with J = 5 Hz due to a β-proton geminal to an α-methoxy group at C-14 is evidence in favor of the retention of the hydroxy group at C-10 [1]. Thus, the product under consideration may have structure (V) (see Scheme 1).

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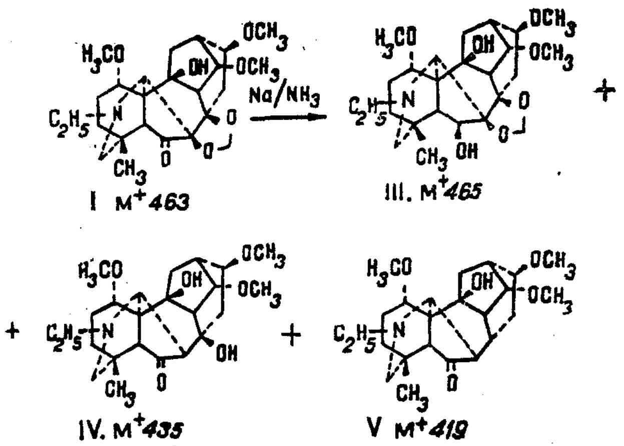
Scheme 1. Products of the reaction of 6-dehydroeldelidine (I) with sodium in liquid ammonia



The reaction of 6-dehydrodelcorine with sodium in liquid ammonia gave delcorine (VI) and products (VII), (VIII), and (IX).

Product (VII), M+ 451, $C_{25}H_{41}NO_6$. Its IR spectrum lacked the absorption band of a carbonyl group. According to its PMR spectrum, compound (VII) contained four methoxy groups and an aminoethyl group and did not contain a methylenedioxy group or olefinic protons. These facts were confirmed by the PMR spectrum of the diacetate (X) of (VII) (M+ 535, $C_{29}H_{45}NO_9$) obtained by the acetylation of (VII) with acetyl chloride. The formation of the diacyl derivative showed the presence in (VII) of two hydroxy groups, while the presence in the PMR spectra of (VII) and (X) of only one one-proton signal in the 3.6-6 ppm region indicated that one of the hydroxy groups was tertiary and the other secondary. In the PMR spectrum of (VII), this signal was present at 4.26 ppm (1H, doublet, J = 6.5 Hz) and in the spectrum of (X) it was present at 5.18 ppm (1H, doublet, J = 6.5 Hz), which are characteristic for hydrogen at C-6 geminal to hydroxy and acetoxy groups, respectively [1]. In the mass spectrum of (X), the maximum peak was that of the ion $(M - OCH_3)^+$, and the second peak in intensity was that of the ion $(M - AcO - AcOH)^+$ with m/z 416. When the temperature of the direct introduction system was raised, there was a redistribution of the heights of the peaks of the $(M - AcO)^+$ and $(M - AcOH)^+$ ions in favor of the latter, which indicated the presence of an acetoxy group at C-8 [2]. Consequently, the initial compound before acylation corresponded to structure (VII) (Scheme 2).

Product (VIII), M+ 417. Its IR spectrum contained an absorption band of a carbonyl group in a five-membered ring (1740 cm^{-1}). In the PMR spectrum of (VIII) there were the signals of three methoxy groups, of an aminoethyl group, and of two olefinic protons – 5.34 ppm (1 H, doublet, J = 9 Hz) and 5.86 ppm (1 H, quartet, J_1 = 6 Hz and J_2 = 9 Hz) – and all the signals were broadened. The pattern of olefinic protons coincided practically completely with that of isopyroacetyltalatisamine [3] and of demethylenesecodemethanoldelcorine [4]. Thus, the reaction led to the elimination of a molecule of methanol at the expense of the methoxy group at C-16, the ease of elimination of which has been shown previously [5, 6].

When (VIII) was subjected to Adams reduction, the dihydro derivative (XI) was obtained

Scheme 2. Products of the reaction of 6-dehydrodelcorine with sodium in liquid ammonia

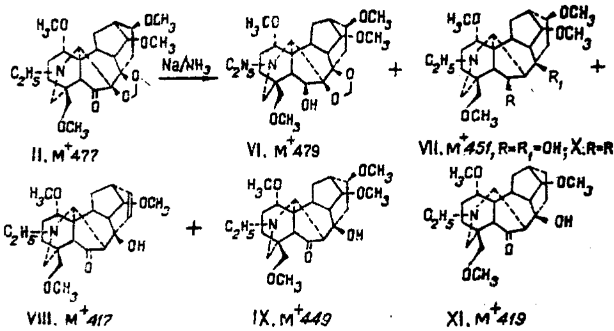


TABLE 1. Relative Intensities (%) of the Main Fragments in the

Compound	M^+	$(M-15)^+$	$(M-17)^+$	$(M-18)^+$	$(M-31)^+$	$(M-33)^+$	$(M-45)^+$	$(M-47)^+$	$(M-49)^+$	$(M-59)^+$	$(M-61)^+$
I	3	2	0,2	0,1	100	0,2	5	1	0,5	1	0,6
II	3	3	0,5	—	100	0,5	2	1	0,2	2	4
III	2	2	0,3	0,1	100	0,8	2	1	0,3	4	2
IV	2	2	1	0,8	100	2	3	4	15	1	1
V	3	3	1	2	100	3	3	6	1	2	1
VI	3	2	1	—	100	0,5	6	2	0,3	8	9
VII	2	4	1	4	100	15	3	11	32	1	6
VIII	3	2	1	1	100	2	2	16	80	2	3
IX	4	3	3	2	100	4	3	18	75	3	11
X	4	2	0,2	—	100	—	1	0,7	—	12	2
XI	3	2	3	1	100	3	5	12	80	3	10

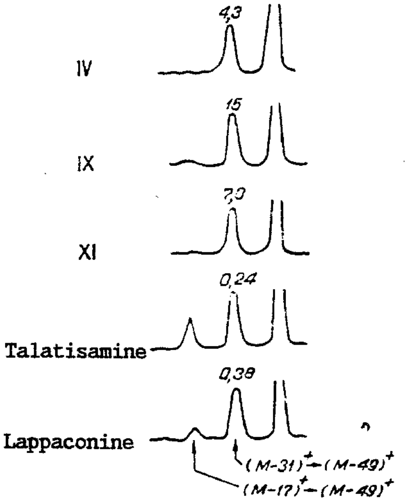


Fig. 1. MD spectra of the $(M-49)^+$ ions of a number of compounds. The values of A are given above the maxima of the metastable peaks of the $(M-31)^+ \rightarrow (M-49)^+$ transition.

with M^+ 419, the IR spectrum of which showed the retention of the carbonyl group in a five-membered ring (1740 cm^{-1}), while the signals of the olefinic protons in the PMR spectrum had disappeared. In the mass spectra of (VIII) and (XI) the peaks of the $(M-OCH_3)^+$ ions had the maximum intensity, which showed the presence of a methoxy group at C-1 in each case.

In the spectrum of each of the compounds the peak of the $(M-49)^+$ ion was second in intensity at 80% of the maximum peak. The great increase in the intensity of the peak of the $(M-49)^+$ peak showed the presence of a hydroxy group at C-8 [2]. The appearance in the PMR spectrum of a one-proton triplet at 3.59 ppm with J = 5 Hz was connected with the presence of a methoxy group at C-14. On the basis of the facts given above, the compound with M^+ 417 had structure (VIII) (see Scheme 2).

Product (IX), with M^+ 449, gave an IR spectrum containing the absorption band of a cyclopentanone (1740 cm^{-1}). The mass spectrum of (IX) was close to that of (XI), the peak of the

Mass Spectra of Compounds (I-XI)

$(M-63)^+$	$(M-65)^+$	$(M-73)^+$	$(M-75)^+$	$(M-77)^+$	$(M-79)^+$	$(M-81)^+$	$(M-89)^+$	Other ions, m/z (I, %)
1	0,1	3	0,5	0,4	0,4	0,7	1	372 [$(M-91)^+$, 1]; 368 (1); 340 (1)
1	—	5	1	0.6	—	—	2	419 [$(M-58)^+$, 2]; 360 (2); 251 (2); 234 (3)
0,8	0,2	0,2	0,5	1	0,8	0,2	0,8	374 (0,8); 358 (1); 344 (1)
2	1	0,3	0,8	1	1	2	0,3	344 (1); 342 (1); 340 (2); 206 (13)
2	0,7	0,6	1	1	0,8	0.4	—	279 (3)
1	—	2	3	1	0,6	—	4	388 (1); 374 (1); 360 (1); 358 (1)
10	9	—	2	15	10	10	—	368 (4); 360 (4); 358 (4); 342 (4); 238 (4)
2	1	0,7	2	3	2	0,8	1	326 (1); 324 (1)
9	4	1	4	5	11	5	2	358 (4); 356 (4); 354 (3); 236 (2)
—	—	22	10	0.4	—	—	58	492 [$(M-43)^+$, 4]; 475 [$(M-60)^+$, 7]; 416 [$(M-119)^+$, 98]
5	2	2	5	6	3	1	3	328 (3); 316 (3)

$(M-31)^+$ ion being the maximum and that of the $(M-49)^+$ amounting to 75% of $I_{(M-31)^+}$. According to its PMR spectrum, (IX) contained four methoxy groups, one of which was present at C-14 (3H, triplet at 3.53 ppm, J = 4.5 Hz). On the basis of these facts, the product formed had the structure (IX) (see Scheme 2).

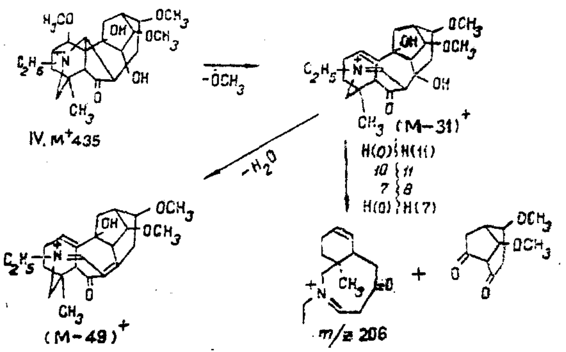
Thus, the reaction of the 6-dehydro derivatives of diterpene alkaloids containing a 7,8-methylenedioxy group with sodium in liquid ammonia gives as the main products the 7-deoxy compounds and may serve as a method for converting alkaloids of the lycoctonine type into alkaloids of the aconitine type. At the present time only one method for such passage has been described in the literature [7].

An analysis of the mass spectra of the products of the interaction of 6-dehydrodelcorine and 6-dehydroeldelidine with Na in liquid ammonia showed, together with the retention of the predominating process of the splitting out of OCH_3 from C-1, the presence of a number of features permitting compounds with different sets of structural elements at C-6–C-8 to be distinguished. As mentioned above, the relative intensities of the peaks of the $(M-49)^+$ ions in the 8-hydroxy-6-ketones (IV, VIII, IX, and XI) were very high, several times exceeding the intensities of the $(M-47)^+$ and, particularly, the $(M-45)^+$ ions (Table 1). Conversely, in the spectrum of compound (V), containing no oxygen substituent at C-8, it amounted to 1% and was less than the heights of the peaks of the $(M-45)^+$ and $(M-47)^+$ peaks. On passing from the 6-keto derivative (IX) to the 6-hydroxy derivative (VII), the intensity of the peak of the $(M-49)^+$ ion decreased more than twofold. On the other hand, this magnitude depends little on the degree of saturation of the C-15–C-16 bond and the presence of substituents at C-16 (compare (VIII), (IX), and (XI)) (see Table 1). As follows from Table 1, the disappearance of the methylenedioxy group led only to a decrease in the ratio of the heights of the peaks of the $(M-59)^+$ and $(M-61)^+$ ions characteristic for compounds with a 7,8-methylenedioxy group to the heights of the peaks of the $(M-63)^+$ and $(M-65)^+$ ions.

The MD spectra of the $(M-49)^+$ ions of the 8-hydroxy-6-ketones under consideration (Fig. 1) differed greatly from the analogous spectra of bases, the molecules of which do not contain a keto function at C-8 (talatisamine, lappaconine, etc. [8]). The peaks of the $(M-32)^+ \rightarrow (M-49)^+$ transition occupied the leading position and many times exceeded the metastable peaks of the $(M-17)^+ \rightarrow (M-49)^+$ process. As a rule, the values of A for the $(M-31)^+ \rightarrow (M-49)^+$ transition of the 6-keto derivatives is an order of magnitude higher than for bases of the talatisamine type.

So far as concerns the differences between analogous products of the reactions with dehydrodelcorine and dehydroeldelidine, they appear most clearly in a comparison of the spectra of

Scheme 3



compounds (IV) and (IX): the intensity of the peak of the (M − 49)+ ion for the first compound is smaller, and simultaneously we observe in this spectrum the occurrence of an unusual process of breakdown at the bonds of ring B. As a result, the ion with m/z 206, composition $C_{13}H_{20}NO$, of medium intensity arises. According to the MD spectrum, it is formed mainly from the (M − 31)+ ion. The occurrence of this process is favored by the presence of a hydroxy group at C-10 (Scheme 3).

This fragmentation pathway is not characteristic of compound (V), the molecule of which contains no hydroxy group at C-8, and in the spectra of delcorine derivatives it is shown only by the presence of weak peaks of ions with m/z 236 (IX) and 238 (VII).

EXPERIMENTAL

The homogeneity of the substances was checked chromatographically in a thin layer of alumina (for chromatography) in the hexane—ether (1:1), hexane—ether (1:10), ether, chloroform, ether—methanol (100:1), and ether—methanol (50:1) systems. IR spectra were taken on a UR-20 instrument (tablets with KBr), and PMR spectra on BS-567A, JEOL, and JNM C-60 HL spectrometers (δ scale, $CDCl_3$, HMDS).

MKh 1310 mass spectrometer with double focusing, SVP 5 device for the direct introduction of the sample, temperature of the ionization chamber 90-120°C, temperature of the heating bulb 80-160°C, ionizing voltage 50 V, collector current 40 μA. Defocusing: E, H = const., automatic scanning of the accelerating voltage from 2.5 to 4.5 kV at the rate of 0.1 kV/sec; chart speeds 5 and 10 mm/sec. The initial bases — 6-dehydroeldelidine (I) and 6-dehydrodelcorine — were obtained by the procedure of [4].

Reaction of 6-Dehydroeldelidine with Sodium in Liquid Ammonia. With constant stirring, 0.15 g of dehydroeldelidine (I) in 50 ml of ether was added dropwise to a solution of 1.5 g of sodium in 150 ml of liquid ammonia. The mixture was stirred for 6 h and was left overnight. The excess of sodium was decomposed with ethanol. The solvent was evaporated off, and the residue was dissolved in 50 ml of water and extracted with chloroform. The reaction product after the evaporation of the chloroform extract was chromatographed on a column of deactivated alumina. The column was washed successively with hexane, ether, and methanol. Elution with ether yielded 20 mg (V), mp 152-155°C (ether), and 15 mg of 6-dehydroeldelidine (I), while ether—methanol (20:1) gave 60 mg of (IV), mp 163-166°C (ether), and 30 mg of eldelidine (III).

Reaction of 6-Dehydrodelcorine with Na/NH_3. The reaction was performed with 150 mg of (II) by the procedure described above. The reaction products were separated on a column of deactivated alumina, which was washed successively with hexane and with ether. On elution with hexane—ether (1:2), 10 mg of dehydrodelcorine (II) was isolated, while hexane—ether (1:3) gave 25 mg of the amorphous product (VIII) and 15 mg of the amorphous product (IX), and ether gave 15 mg of delcorine (VI) and 45 mg of product (VII) with mp 151-152°C (ether).

Hydrogenation of Product (VIII). A solution of 25 mg of product (VIII) in 5 ml of ethanol was hydrogenated over a platinum catalyst at room temperature for 10 h. The catalyst was separated off and the solution was evaporated to give 23 mg of the amorphous product (XI).

Acetylation of Product (VII). A solution of 40 mg of (VII) in 4 ml of acetyl chloride was left in a sealed tube at 45-50°C for 138 h. The excess of acetyl chloride was evaporated off and, with cooling, the residue was dissolved in water and the solution was made alkaline with sodium carbonate and was extracted with chloroform. The reaction product was chromatographed on a column of deactivated alumina. Elution of the column with ether gave 26 mg of the homogeneous amorphous diacetate (X). IR spectrum: 1720 cm^{-1} (ester carbonyl).

SUMMARY

Structures have been put forward for the products of the reaction of dehydroeldelidine and dehydrodelcorine with sodium in liquid ammonia. Features of the fragmentation of these compounds under electron impact are discussed.

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MASS-SPECTROMETRIC METHOD OF ANALYZING MIXTURES OF DITERPENE BASES FROM PLANTS OF THE GENUS Aconitum

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The qualitative composition of the mixture of diterpene alkaloids from the roots of Aconitum septentrionale from various growth sites has been studied. Twenty-one bases have been detected. The mass-spectrometric method of multipeak monitoring has been used for the rapid checking of the amounts of the main component and seven subsidiary components.

We have previously made a qualitative analysis of the saponified mixture of alkaloids from the epigeal part of Aconitum leucostomum gathered in the fruit-bearing period and a quantitative determination of the main components of this mixture by the ion-current integration (ICI) method [1].

In connection with the search for sources of lappaconitine — the base for the production of the antiarrhythmic drug allapinin — we have undertaken the analysis of the qualitative and quantitative compositions of Aconitum septentrionale growing in many regions of the USSR.

To solve this problem we propose to use the method of multipeak monitoring (MM) which consists in the repeated rapid recording of part of the spectrum containing all the characteristic ions up to the moment of the complete evaporation of a calibrated sample introduced through the direct introduction system. As compared with the ICI method, this is far more laborious, but with its aid it is possible to follow simultaneously the composition of the sample and its changes under the temperature conditions and to perform the quantitative determination of the components. A disadvantage of the MM method is that it is carried out in a low-resolution regime, where the peaks of the characteristic ions may be increased at the expense of the peaks of isobaric impurity ions.

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