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MASS SPECTRA OF 18,19-EPOXYCARDENOLIDES

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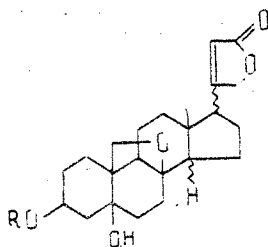
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The mass spectra of six 18,19-epoxycardenolides (ECs) with various substituents in the 3 β position — OH, OAc, rhamnosyloxy have been studied. In all the spectra the contribution of the fragments characteristic for cardenolides formed by the cleavage of the bonds of rings C and D were lowered. The strongest peaks were those of ions with m/z 259, 272, and 285 arising on the splitting out of the elements of rings A and B. It was established by the metastable defocusing (MD) method that in the case of the 3 β -ols these fragments are formed from M^+ and in the case of acetyl derivatives, in addition, they may arise from the $(M - \text{AcOH})^+$ ions. The spectra of the epoxycardenolides were compared with the structure of 3 β ,5 β ,14 β ,19-tetrahydroxycardenolide (strophanthidol) and its 3 β -monoacetate and 3 β ,19-diacetate. The MD spectra and elementary compositions of the ions showed that other mass-spectrometric conditions strophanthidol monoacetate decomposes partially in the form of the 8,19-epoxycardenolide.

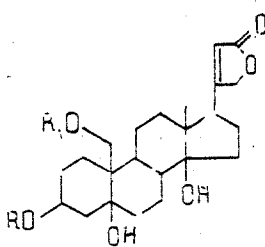
The task of the fragmentary mass spectrometry of organic compounds is, in addition to establishing the general directions of the fragmentation of certain groups of substances, the analysis of spectra revealing unusual properties with relatively small structural changes. Having studied over a number of years the mass spectra of the aglycones of cardenolides and their derivatives [1-3], we have established that the intensities of the peaks of the molecular and key fragmentary ions depend not only on the number and positions of the oxygen-containing functional groups but also on the nature of the substituent at C-10 of the steroid nucleus. The role of this factor is due to the fact that the first act of the fragmentation of cardenolides, as of other steroid systems, is the cleavage of one of the C-C bonds adjacent to a quaternary carbon atom, most frequently the C-1-C-10 bond. In all the spectra studied previously, the changes on passing from substance to substance have borne a mainly quantitative nature.

We have achieved the possibility of observing qualitative changes, and these sharp ones, on analyzing the spectra of the 8,19-epoxycardenolides: 3 β ,5-dihydroxy-5,10-epoxy-5 β ,14 α ,17 β -card-20(22)-enolide (I), its 14 β ,17 α - isomer (II), their 3 β -acetates (III) and (IV), the 3 β -rhamnoside of the 14 β ,17 α -epoxycardenolide (V), and its triacetate (VI). These substances were obtained as by-products in the synthesis of the rhamnosides of strophanthidol by the orthoester method [4].

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I-VI



VII-IX

I R = H 14 α 17 β

II R = H 14 β 17 α

VII R = R₁ = H VIII R = Ac R₁ = H

III R = Ac 14 α 17 β

IV R = Ac 14 β 17 α

IX R = R = Ac

V R = Rh 14 β 17 α

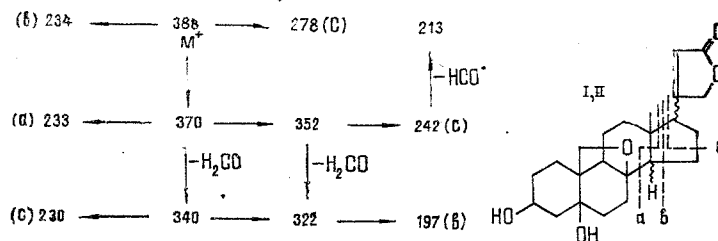
VI R = AcRh, 14 β 17 α

As can be seen from the mass spectra of compounds (I)-(VI), which are given in Fig. 1, the type of C/D linkage and the configuration of the substituent at C17 have little effect on the intensities of the peaks of the main fragments. Let us then compare the spectra of (I) and (II) and of (III) and (IV) with the spectra of strophanthidol (VII) and its mono- and diacetates (VIII and IX, respectively) (see Fig. 2).

In the spectra of (VIII) and (IX), the height of the M^+ peak is very small, and the intensities of the peaks of the ions formed by the successive elimination of H_2O (AcOH) and CH_2O molecules from it have risen. The spectrum of strophanthidol is characterized by a large combined contribution of the key ions of series a [1, 5], with m/z 253, 235, 217, 199, and 187. A similar feature is characteristic of the diacetate (IX), with the difference that the latter decomposes more selectively, forming the ions of series a with m/z 159, 217, and 199 (100%). In the spectrum of the monoacetate (VIII) the ions of the same series, having the same mass numbers, undergo competition from the fragment of series c with m/z 231, 212, and 211.

As is known, the ion with m/z 334 in the spectrum of strophanthidol (VII) is the product of the retrodiene decomposition of ring A taking place after the elimination of H_2O at the expense of the 3β -OH group [1, 7]. The contribution of this process falls in the spectra of the strophanthidol acetates: in the case of the monoacetate, the ion with this mass number consists of the $(M - AcOH - C_4H_6)^+$ fragments to the extent of only half, the remainder being contributed by $(M - AcOH - 3 H_2O)^+$; in the spectrum of the diacetate the peak of the $(M - AcOH - C_4H_6)^+$ ion with m/z 376 has a very low intensity.

In the spectra of the epoxy compound (I-IV) the stability of the molecular ions is raised, and of the products of the ejection of substituents only the peaks of the $[M - H_2O(AcOH)]^+$ ions with m/z 370 are distinguished by their intensity.



Scheme 1

The processes of formation of the key fragments of the cardenolide series a, b, c, are suppressed to a considerable degree. The mass numbers of the peaks of the ions in the series observed in the spectra of the epoxy compounds (I) and (II) are given in scheme I. It can be seen from the scheme and the spectra that fragments of types b and c are the most common. The composition of the m/z 197 ion ($C_{15}H_{17}$) apparently shows that it belongs to series a. However, its precursors, determined with the aid of the method of metastable defocusing (MD), are ions with m/z 215 and 322 $(M - H_2O - CH_2O)^+$, which gives grounds for assigning the $C_{15}H_{17}$

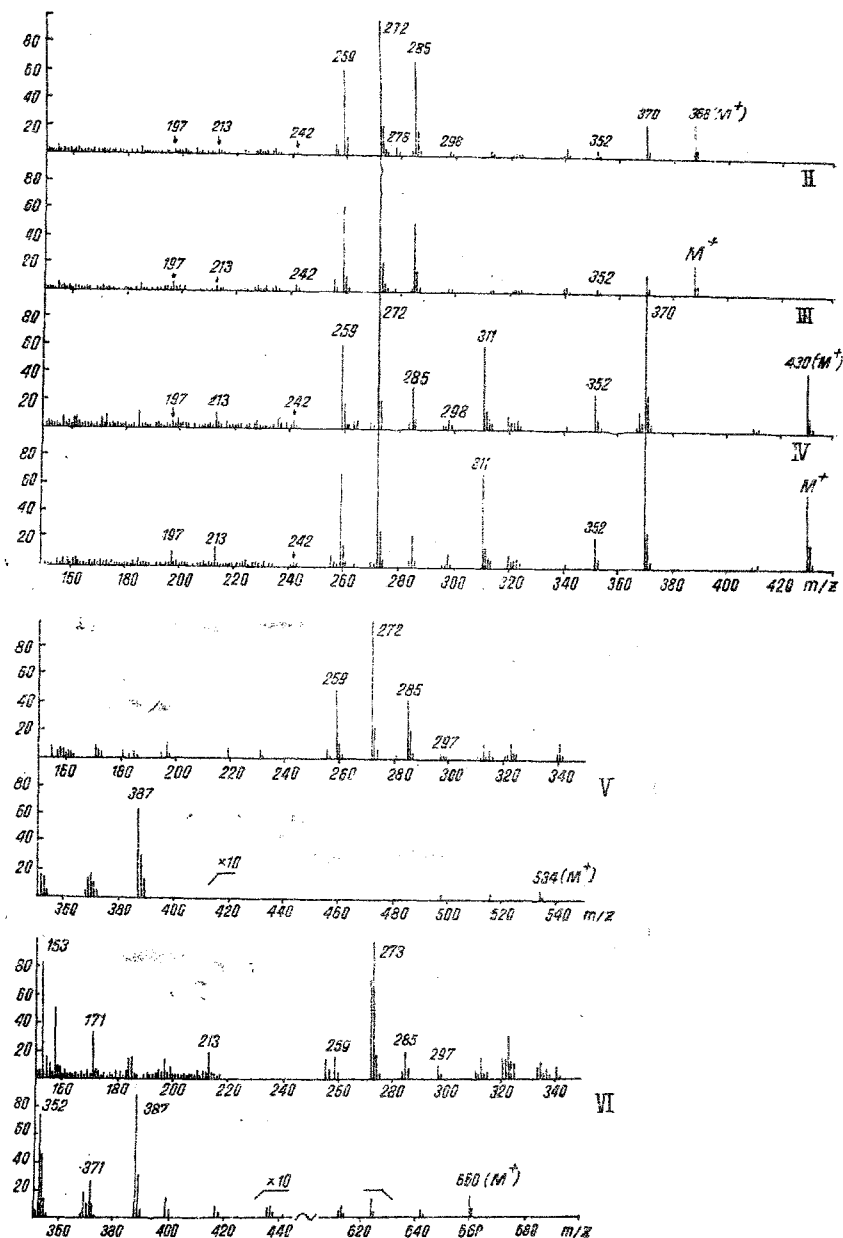


Fig. 1. Mass spectra of compound (I)-(VI).

ions to series c (the loss of the C-19 atom is compensated by the inclusion of the C-14 atom). It is interesting that the peaks of this fragment are substantially higher in the spectra of the compounds of the 14 β ,17 α series (II and IV). Quantitative differences between isomers of the same order are observed for the $(M - 110)^+$ ions of series c (m/z 278 for (I and II) and 320 for (III and (IV)), but in this case the compounds of the 14 α ,17 β series (I and III) are distinguished by higher intensities.

No retrodiene decomposition of ring A, which would lead to the formation of an ion with m/z 316, takes place in compounds (I-VI).

The most important property of the spectra of the epoxy compounds (I-VI) is the presence of intense peaks of ions with m/z 259, 272, and 285 and less intense ones with m/z 298, and the peaks of ions with m/z 311 which are characteristic for the acetates (III) and (IV) and are not common in the other spectra (see Fig. 1).

All the ions mentioned have the formula $C_nH_{n+3}O_3$ ($n = 16-20$). Analysis of metastable transitions and the results of exchange deuteration indicate that these fragments are formed by the elimination of rings A and B, which is uncharacteristic for ordinary cardenolides. Scheme 2 gives the most probable structures of the ions mentioned.

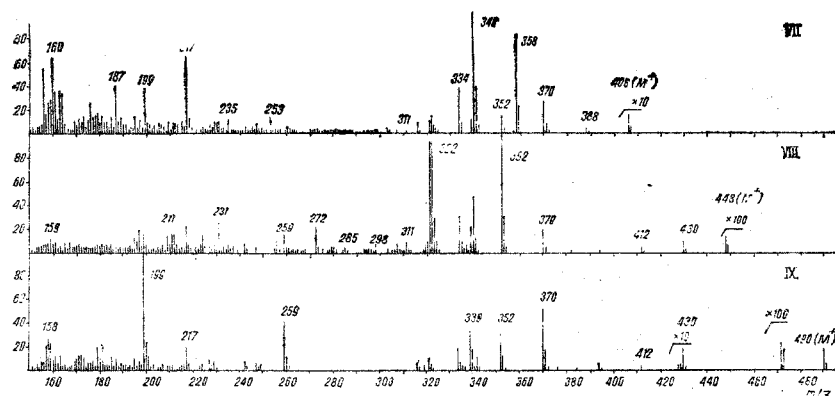
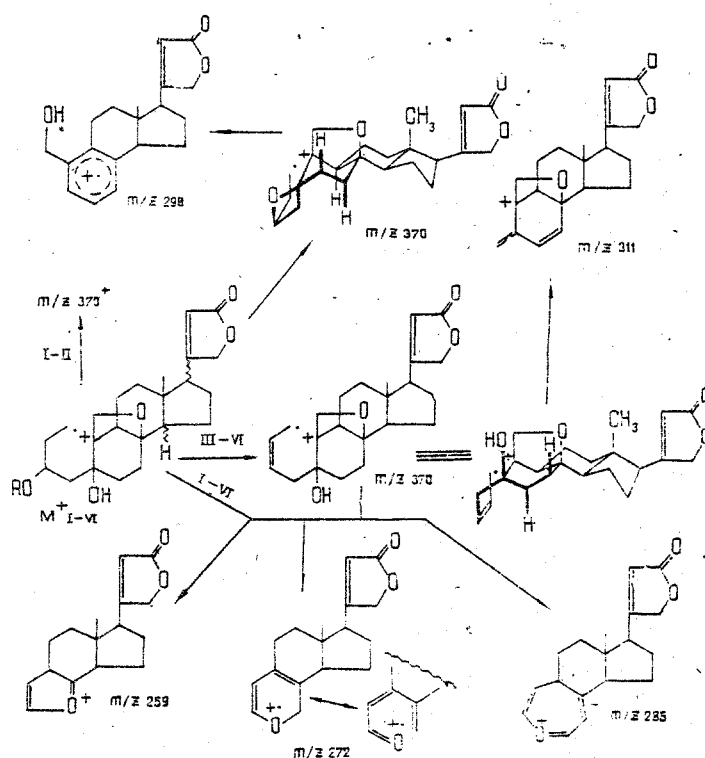


Fig. 2. Mass spectra of compounds (VII)-(IX).

Scheme 2



The MD method (Fig. 3) showed that the processes of the formation of the ions with m/z 259, 272, and 285 depend on the nature of the substituent in the 3 β position: when $R = OH$ (I and II), the only precursors of these ions are the molecular ions, but for the acetates (III) and (IV) they also arise in the breakdown of the $(M - ROH)^+$ ions with m/z 370, and for the 3 β -rhamnoside (V), in addition to the ions with m/z 370, a fragment with m/z 388 that is the product of the splitting out of the rhamnose residue from M^+ with migration of hydrogen to the charged fragment, has been established as a maternal ion. In the case of compounds (I) and (II) the ion with m/z 370 $(M - H_2O)^+$ did not form fragments with m/z 259, 272, and 285. This is obviously due to the nonspecific process of the loss of a molecule of water at the expense of the 3 β -OH group, which prevents decomposition in this direction. At the same time, the molecular ions of the acetates (III) and (IV) and of the rhamnoside (V) form $(M - ROH)^+$ ions mainly by a mechanism of 1,2-elimination [6] (see Scheme 2). Ions of this structure may be precursors of the fragments with m/z 259, 272, and 285. Furthermore, the existence of a specific method for the elimination of $R-OH$ in the acetates also explains the increase in the intensity of the peaks of ions with m/z 311 (see Fig. 1). This is illustrated in the scheme with the aid of a transitional state of the ion with m/z which is capable of losing H_2O and C_3H_5 synchronously. For confirmation we may add that, judging from the MD spec-

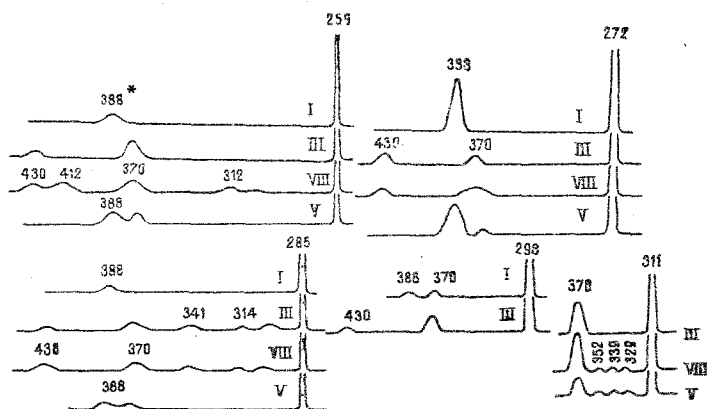


Fig. 3. MD spectra of the daughter ions with the general formula $C_nH_n + 30$, formed in the fragmentation of compound (I), (III), (V), and (VIII) (* - mass numbers of the maternal ions).

tra, the ions with m/z 311 of the acetates (III) and (IV) are formed only from the ions with m/z 370 (Fig. 3).

We must dwell particularly on the process of generation of the ion with m/z 298, the composition of which shows that it is formed as the result of elimination of the C-1-C-4 chain with the additional loss of a molecule of water. This process cannot be realized in one stage. The MD spectra both of the alcohols (I) and (II) and also of the acetates (III) and (IV) show two transitions $M^+ \rightarrow 298^+$ and $370^+ \rightarrow 298^+$. The first indicates the possibility of the synchronous elimination from M^+ of the particles $R-OH$ and C_4H_8O . It must be emphasized that in the MD spectra of the ion with m/z 298 from the acetates (III) and (IV) the transitions $(M - H_2O)^+ \rightarrow 298^+$ and $316^+ \rightarrow 298^+$ are not observed. Consequently, the ions with m/z 298 are formed directly from the $(M - ROH)^+$ ions regardless of the nature of R. Now, in order to imagine the mechanism of the formation of the ion with m/z 298, we have assumed that some part of the $(M - ROH)^+$ ions with m/z 370 in the case of the acetates (III) and (IV) had the epoxy form (scheme 2) arising as the result of the elimination of $R-O$ with the spatially close $5B-OH$ hydrogen. The contribution of this form to the total height of the peaks of the $(M - ROH)^+$ ions with m/z 370 in the spectra of the acetates (III) and (IV) is small, judging from the absence of appreciable differences between the intensities of the polyisotopic M^+ and $(M - ROH)^+$ peaks in the deuterium exchange products of these compounds.

Let us consider the features of the spectra of substances including a carbohydrate unit (V and VI). As also for the epoxy compounds (I-IV) the intensities of the M^+ peaks in them have risen in comparison with the cardenolide analogs. In view of the stability of the neutral fragments Rh^+ and $AcRh^+$, and RhO^+ and $AcRhO^+$ that is characteristic of glycosides in the spectra under consideration, the contribution of even-electronic fragments with m/z 387 rises and, together with the m/z 370 ion, the peak of a m/z 371 ion is present. This fact does not prevent the appearance of ions with m/z 259, 282, and 285 but it decreases the intensity of the peak of the m/z 311 ion, and in place of the m/z 298 ion the peak of an ion with m/z 297 appears.

No products of the decomposition of the rhamnosyl cation appear in the spectrum of the glycoside (V). Thus, an usual [9], the acetylated form gives the peak of an ion with m/z 273 (100%) and the peaks of the products of its subsequent decomposition with m/z 213, 171, 153, and 111.

Definite prerequisites have existed for representing the formation of the epoxide ridge in compounds with hydroxyl-containing substituents at C-19 and C-14 under the conditions of mass spectrometry [2]. One of the aims of comparing the structure of the epoxy compounds (I-IV) with the spectra of strophanthidol and its acetates (VII-IX) was the search among the latter for signs of the occurrence of such processes. It follows from what has been said above that, obviously, the "test" for the formation of an epoxide bond must be the presence in the spectrum of the $C_nH_n + 3 + O_3$ series of ions. In the spectrum of strophanthidol, the peaks of the ions of this series have a very low intensity, although in elementary composition they agree with the corresponding fragments of the spectra of (I-VI).

On passing the 3 β -monoacetate (VIII) we observed a rise in the intensity of the peaks of the ions with m/z 259, 272, 285, and 311, the compositions of which satisfy the formula mentioned above. This may indicate a partial transition of the monoacetate (VIII) into epoxy compounds of the type of (III) and (IV) under the conditions of mass spectrometry. A chromatogram of the residue of a sample of compound (VIII) after the recording of the mass spectrum showed, in addition to the main spot of the initial compound, weak spots coinciding in their R_f values with the epoxy compounds (III) and (IV), which does not exclude the possibility of a thermal transition. The MD spectra of the daughter ions with m/z 272 and 285 in the case of the acetates (III), (IV), and (VIII) agree, which also confirms the formation of an epoxy group. So far as concerns the MD spectra of the ions with m/z 259 and 311 from the acetate (VIII), simultaneously with the transitions characteristic of the acetates (III) and (IV) they have indications of the occurrence of other processes, as well, such as $412^+ \rightarrow 259^+$, $318^+ \rightarrow 259^+$, and $339^+ \rightarrow 311^+$. These facts are in harmony with the assumption that in addition to fragments with the compositions $C_{16}H_{19}O_3$ and $C_{20}H_{23}O_3$ these daughter ions contain fragments with different combinations of atoms. Thus, 20% of the ions with m/z 259 have the composition $C_{17}H_{23}O_2$ and may be, for example, ions of cardenolide type a, which have lost two molecules of water but have retained the acetoxy group. A tenth of the ions with m/z 311 corresponds to the composition $C_{21}H_{27}O_2$. Such ions can arise as the result of the successive elimination from an ion with m/z 370 of a hydroxymethylene radical, which gives a fragment with m/z 339, and then of carbon monoxide. Another feature of the MD spectrum of the ion with m/z 311 from strophanthidol acetate consists in the detection of two additional transitions: $352^+ \rightarrow 311^+$ and $329^+ \rightarrow 311^+$. These transitions show an alternative sequence of elimination from the ion with m/z 370 of H_2O and C_3H_5 fragments which are not recorded in the MD spectra of the acetates of the epoxy compounds (III) and (IV). Apparently, this difference is due to a difference in the reserve of energy of the ions with m/z 370. Analogous transitions are found in the MD spectrum of the rhamnoside (V) (Fig. 3).

On passing to strophanthidol diacetate, the indications of the formation of an epoxide bond between the C-8 and C-19 atoms disappear, which is possibly due to other methods of fragmentation of the substituent at C-10 and in particular, to the ejection of the $\cdot CH_2OCOCH_3$ radical from the $(M - H_2O - AcOH)^+$ ion. This leads to the substantial redistribution of the peak intensities in the spectrum of (V) as compared with that of the monoacetate (VIII) that was mentioned above. One of the consequences of the type of fragmentation just mentioned is a decrease in the intensity of the peak with m/z 160 and a rise in the heights of the peaks of the ions with m/z 159 ($C_{12}H_{15}$) and 158 ($C_{12}H_{14}$), which, by analogy with the m/z 160 ion of strophanthidol, are formed on the cleavage of the C-8-C-14 and C-12-C-13 bonds [1].

EXPERIMENTAL

A MKh 1310 mass spectrometer with a SVP 5 system for the direct introduction of the sample was used. The temperature of the evaporator bulb and of the ionization chamber was 125-175°C, the ionizing voltage was 50 V and the collector current 60 μA . The elementary compositions of the ions were measured in relation to the reference peaks of perfluorokerosene. The resolving power was 10,000 or, in the measurement of the doublet with m/z 334 or the monoacetate (VIII), 20,000. The relative error in the determination of accurate masses did not exceed $5 \cdot 10^{-6}$. The metastable defocusing spectra were obtained by the automatic scanning of the accelerating voltage in the interval from 2.5 to 5.0 kV with a constant strength of the energy analyzer and strength of the magnetic field corresponding to the mass of the daughter ion.

Exchange deuteration was carried out with the aid of CD_3OD .

CONCLUSION

The main direction of the fragmentation of 8,19-epoxycardenolides with various substituents in the 3 β position is the cleavage of the bonds of rings A and B with the formation of ions having the general formula $C_nH_{n+3}O_3$ ($n = 16-20$). It has been shown that under the conditions of mass spectrometry strophanthidol 3 β -monoacetate decomposes in part in the form of the 8,19-epoxycardenolide.

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STRUCTURE OF SIBIRINE

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UDC 547.944/945

The new optically based sibirine with $[\alpha]_D -22.5^\circ$ (c 0.81; chloroform), M^+ 183, has been isolated from the epigeal part of the *Nitraria sibirica* by column chromatography. On the basis of the results of chemical transformations (acetylation, oxidation), analysis of spectral characteristics (UV, IR, mass, PMR, ORD), and also a comparison of the alkaloid with the N-methyl derivatives of nitramine and isonitramine, the structure of sibirine has been established as methyl-2-azaspiro-[5.5]undecan-7-ol.

Continuing an investigation of the total alkaloids of the epigeal part of *Nitraria sibirica* Pall. (family *Zygophyllaceae*) collected in the environs of the village of Rybach'e, KirgSSR, in May 1976 [1], we have isolated a new optically active liquid base with the composition $C_{11}H_{21}NO$, $[\alpha]_D -22.5^\circ$ (c 0.81; chloroform), which we have called sibirine (I), and have obtained a number of derivatives.

In the UV, compound (I) is transparent. The IR spectrum contains an absorption band of active hydrogen at 3320 cm^{-1} . The acetylation of (I) with acetic anhydride led to the O-acetyl derivative of sibirine (II). In the IR spectrum of (II) the absorption band of active hydrogen had disappeared and a strong absorption band of an ester carbonyl group had appeared.

The mass spectrum of (I) contains the peaks of ions with m/z 183 M^+ (100%), 182, 169, 168, 166, 155, 140, 122, 112, 110, 98, 96, 84, 57. Such fragmentation is characteristic for nitramine [2] and isonitramine [1], but it differs from them by 14 m/z .

Since the PMR spectrum of (I) contains a signal from N-methyl protons (2.19 ppm), we assumed that base (I) was the N-methyl derivative of nitramine or of isonitramine. To confirm this, we obtained N-methylnitramine (III) and N-methylisonitramine (IV). The spectral characteristics of compound (IV) (IR, PMR) were identical with those of sibirine. The IR spectra of the O-acetyl derivatives of (I) and (IV) are also identical.

In the PMR spectrum of (I) at 3.54 ppm there is a well-defined one-proton multiplet with a half-width of the line of 18 Hz, which is apparently due to the proton at C_7 geminal to the hydroxy group. The half-width of the signals shows the axial orientation of this proton and, consequently, as in isonitramine [1], the equatorial nature of the hydroxy group.

The ORD curves of (I) and (IV) are similar in nature but opposite in sign. The signs of the optical rotations of these bases are also opposite.

Thus, it follows from the facts given above that sibirine is the antipode of N-methyl-isonitramine and has the structure of 2-methyl-2-azaspiro[5.5]undecan-7-ol (I).

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