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The structures of two new natural compounds isolated from the essential oil of <u>Ledum palustre</u> L. have been established on the basis of their spectral characteristics as p-mentha-1,8(10)-diene 3,9-epoxide (lepaloks) and 3,10-epoxygermacr-4(14)-en-8-one (lepakson). The chemical structure of ledene as a sesquiterpene hydrocarbon has been determined by chemical correlation.

Among the minor component of <u>Ledum palustre</u> L. growing in Tomsk province [1] five compounds having spectral characteristics different from any in the literature have been isolated.

The structures of two new natural compounds have been established in the basis of their spectral characteristics. One of them is a monoterpene epoxide present in the essential oil in an average amount of 0.7%. According to its PMR spectrum it contains an exomethylene double bond (4.90 and 4.93 ppm, 1 H each, quartets, J = 2 Hz) and a trisubstituted double bond (5.50 ppm, 1 H, doublet of quartets, $J_1 = 2$ Hz, $J_2 = 1.5$ Hz). The corresponding signals in the ¹³C NMR spectrum were observed at 152.20 and 140.54 ppm (singlets), 119.86 ppm (doublet), and 103.26 ppm (triplet). In addition to these signals, the spectrum contained the signals of a methyl carbon (23.67 ppm, quartet), of two methylene carbons (24.62 and 28.02 ppm, triplets) and of one methine carbon (41.03 ppm, doublet). Signals of carbon atoms linked to oxygen atoms were observed at 69.87 ppm (triplet) and 76.26 ppm (doublet). The chemical shift (1.70 ppm) of the signal of the methyl group in the PMR spectrum is characteristic for a methyl at a trisubstituted double bond. The signals of the protons of a $-CH_2-O-$ group were observed in the weak-field region of the spectrum in the form of complex multiplets (4.38 and 4.26 ppm) with the geminal spin-spin coupling constant J = 13 Hz. The location of these protons in the allyl position to the exomethylene double bond was confirmed by the existence of spin-spin coupling (SSC) with the protons of this bond (with the constant J = 2 Hz, determined by the double-resonance method). In a similar way was shown the presence of fragment A, which can be realized in the structure of p-mentha-1,8(10)-diene 3,9-epoxide and which corresponds to the results of other spectral methods and also to the high content of compounds of the p-menthane series in the essential oil under investigation. The substance isolated (I) has been called "lepaloks."



On the basis of the form of the signal of the proton at C-4 (2.57 ppm) as a complex multiplet with J = 6.5 Hz, it could be assumed that this proton occupied the pseudoequatorial position, which is possible only with the cis linkage of the rings. The absolute configuration of this compound requires further investigation.

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TABLE 1. Parameters of the PMR Spectrum of 3,10-Epoxygermacr-4(14)en-8-one

Atom	δ, ppma,b	At.om	δ, ppm ^{a,b}
H-12 H-13 H-22 H-25 H-3 H-52 H-53 H-62	$ \begin{array}{c} 2,41 \\ 1,30 \\ 1,68 \\ 4,45 \\ 2,34 \\ 2,02 \\ 2,40 \end{array} $	H-63 H-7 H-9a H-93 H-11 3 ^H -12 (pro- <i>K</i>) 3 ^H -13 (pro- <i>S</i>) 2 ^H -14 3 ^H -15	1,622,052,731,991,490,770,804,731,16

 $a_{c} = 0.042 \text{ M in } C_{6}D_{6}.$

^bValues of the SSC constants (the signs of the constants were not determined) $J_{\text{Hi-Hj}}$ (i - j, Hz): $1\alpha - 1\beta = 12.7$, $2\alpha - 2\beta = 12.5$, $5\alpha - 5\beta = 15.0$, $6\alpha - 6\beta = 14.0$, $9\alpha - 9\beta = 11.7$, $1\alpha - 2\alpha = 8.0$, $1\beta - 2\alpha = 5.7$, $1\alpha - 2\beta = 8.5$, $1\beta - 2\beta = 8.9$, $2\alpha - 3 = 4.5$, $2\beta - 3 = 7.0$, $5\alpha - 6\alpha = 4.7$, $5\alpha - 6\beta = 7.7$, $5\beta - 6\alpha = 8.6$, $5\beta - 6\beta = 8.1$, 7 - 11 = 8.8, $6\alpha - 7 = 11.8$, $6\beta - 7 = 3.0$, 11 - 12, 13 = 6.6, $3 - 14 \approx 0.5$, $5\alpha - 5\beta - 14 \approx 0.5$.

TABLE 2. Parameters of the ¹³C NMR Spectrum of 3,10-Epoxygermacr-4(14)en-one

ı	<u>δCⁱ, d.d.</u>			
	in CCI,-CDCI, (3:1) ²	C6D6D	∆∂Cİ	
1 23 4 5 6 7 8 9 10 11 12 13	$\begin{array}{c} 33,27\\29,02\\82,65\\148,10\\34,12\\27,00\\62,60\\213,26\\51,24\\82,37\\30,86\\21,21\\90,86\end{array}$	33,20 29,56 83,02 143,22 34,84 27,50 62,81 212,87 51,64 82,67 30,97 21,42 20,85	$\begin{array}{c} -0.07 \\ +0.54 \\ +0.37 \\ \div1.12 \\ +0.72 \\ +0.50 \\ +0.21 \\ -0.39 \\ +0.40 \\ \div0.30 \\ +0.11 \\ +0.21 \\ -0.01 \end{array}$	
14 15	113,26 31,09	113,11 31,06	-0.25 + 0.03	

 $a_c = 0.42 \text{ M}.$ $b_c = 0.61 \text{ M}.$

According to the results of IR, UV, PMR, and ¹³C NMR spectroscopy and mass spectrometry, the second compound, present in the essential oil in an amount of ~0.95%, was an intracyclic sesquiterpene ether. Its molecule included a ketone group (13C NMR - 213.26 ppm, singlet) and an exomethylene group (148.10 ppm, singlet, and 113.26 ppm, triplet). The PMR spectrum contained characteristic signals of the methyls of an isopropyl group (0.77 and 0.80 ppm, doublets, J = 7 Hz) and of a methyl group at a carbon atom linked to an oxygen function (1.16 ppm, singlet, 3 H). Analysis of the spectrum of this compound (Table 1), performed with the use of double resonance and homonuclear J-resolved 2D-NMR enabled structural fragments B, C, and D to be identified. The parameters of the 13 C NMR spectrum are given in Table 2. The assignment of the signals was made with the use of the values of the residual constants $J_{1^3C-^1H}$ in the spectrum with the off-resonance irradiation of protons [2] by comparison of the chemical shifts for different solvents (benzene-chloroform) calculated by additive schemes and found experimentally. The results obtained made it possible to ascribe to the compound under investigation, which has been called "lepakson," the structure of 3,10-epoxygermacr-4(14)-en-8-one or 3-methyl-7-methylene-10-isopropyl-3,6-epoxycyclodecanone (2). The relative configuration and the conformation of this compound in solution was determined by a comparison of the experimental values of the SSC constants and the calculated values for different configurational and conformational isomers. The values of the SSCCs were calculated from a refined geometry of the



Fig. 1. Spatial structure of the 3,10-epoxygermacr-4(14)-en-8one molecule (2). The arrows show the proton-proton interactions detected in the 2D-NOESY spectra.

molecule obtained by the method of molecular mechanics using the procedure described in [3]. In the calculations only those isomers were used the geometry of which satisfied the initial conditions following from experiments on the observation of the homonuclear Overhauser effect:

a) on irradiation of the hydrogen atoms of the C-15 methyl group the same increase in intensity of the signals of the two geminal H-9 protons was observed; and

b) on irradiation of the protons of the exomethylene group there was an increase in the intensity of the signals of one of the H-6 atoms (weak-field signal) and of the H-2 atom, which is present in the trans position relative to the H-3 atom in the tetrahydro-furan fragment.



The structure found in this way is shown in Fig. 1. This structure also satisfies the whole set of interactions detected on observation of the nuclear Overhauser effect in the two-dimensional variant (2D-NOESY).

A sesquiterpene hydrocarbon isolated in very small amount from the essential oil under investigation corresponded in its spectral properties to the structure of ledene (3). However, we have found no spectral characteristics of ledene in the literature. In view of a statement that ledene is obtained on the dehydration of ledol [4], we performed the dehydration of ledol under mild conditions. Analysis of the PMR spectrum of the dehydration product showed that of the three possible products (3), (4), and (5), the main one (~90%) was ledene, completely identical with the hydrocarbon that had been isolated from the essential oil. The same sign of the optical rotation unambiguously determined the absolute configuration of the compound, the stereochemistry of which is apparently the same as in ledol (6) [5].



From the still residue of the <u>L. palustre</u> essential oil we isolated in very small amount a sesquiterpene alcohol the spectral characteristics of which were close to those of β -elemenone (7) and corresponded to structure (8). β -Elemenone has been detected in the essential oils of <u>Rhododendron Adamsii</u> Rehd. [6], <u>L. palustre</u> L. [1, 7], and others. Since compounds (7) and (8) can be obtained in the trans-annular cyclization of germacrane [8], a possible hypothesis is that their stereochemistries are analogous. The structure of the alcohol (8) requires further refinement



Among the monoterpenes of the essential oil were found a hydroxyaldehyde the spectral characteristics of which corresponded to one of structures (9) and (10). However, it was impossible to decide which was correct in view of the small amount of the compound and its lability.

On the chromatogram given in [1], peak 55 corresponds to ledene, 63 to the monoterpene alcohol, and 26 to the monoterpene hydroxyaldehyde, the amounts of these compounds in the essential oil being, respectively, 1.4, 0.1, and 1.3%.

EXPERIMENTAL

The instruments and methods, and also the isolation of the compounds, have been described in [1].

<u>p-Mentha-1,8(10)-diene 3,9-Epoxide</u>, $C_{10}H_{14}O(1)$, $[\alpha]_D^{20}+33.9^{\circ}$ (c 1.1). Mass spectrum, m/z (%): 150 (M⁺, 25), 135 (100), 122 (36), 94 (27), 93 (23), 91 (25), 79 (58), 67 (21). IR spectrum $v_{max}^{CC1_4}$ (cm⁻¹): 897, 1045, 1062, 1384, 1453, 1678, 3080. The NMR spectrum is given in the discussion part.

 $\begin{array}{c} 3,10\text{-}Epoxygermacr-4(14)-en-8-one, C_{15}H_{24}O_2(2), [\alpha]_D^{20}-47.5^\circ \mbox{ (c 9.0)}. \mbox{ Mass spectrum,}\\ m/z (\%): 236 (M^+, 5), 218 (10), 193 (23), 178 (24), 149 (100). \mbox{ IR spectrum, } \nu_{max} CCl_4 (cm^{-1}): 912, 1055, 1377, 1470, 1698, 3080. \mbox{ The PMR and } ^{13}C \mbox{ NMR spectra were recorded on}\\ a \mbox{ Bruker AM 400 instrument } (^1\text{H} - 400.130 \mbox{ MHz; } ^{13}\text{C} - 100.627 \mbox{ MHz}) \mbox{ and are given in Tables 1}\\ and 2, \mbox{ respectively. The calculations by the method of molecular mechanics were carried}\\ out by the \mbox{ MM2 program [6].} \end{array}$

<u>Ledene</u>, $C_{15}H_{24}(3)$, $[\alpha]_D^{20}$ +23.38° (c 2.91). IR spectrum, $v_{max}^{CCl_4}$ (cm⁻¹): 1380, 1455. PMR (200 MHz, CDCl₃, ppm): 0.53, 1H, dt, $J_1 = 6$ Hz, $J_2 = 10$ Hz; 0.66, 1H, t, J = 10 Hz; 0.94, 3H, d, J = 7 Hz; 0.98, 1.05 and 1.56 each 3H, s. ¹³C PMR spectrum (50.32 MHz, CDCl₃, ppm): quartets - 15.56, 15.60, 28.31; triplets - 22.10, 31.69, 32.51, 36.55; doublets - 21.74, 25.30, 30.34, 37.18, 39.83; singlets - 18.50, 124.56, 139.83.

<u>Dehydration of Ledol.</u> A solution of 0.2 g of phosphorus oxychloride in 1 ml of pyridine was added to 0.15 g of ledol ($[\alpha]_D^{20}$ -7.1° (c 1.7)) in 1 ml of pyridine, and the mixture was left at 0°C for 7 h. The excess of phosphorus oxychloride was decomposed with ice, and after the addition of 10 ml of water to the reaction mixture it was extracted with diethyl ether. The ethereal extract was evaporated and chromatographed on silica gel (10 g). Petroleum ether eluted 0.1 g of a hydrocarbon fraction, $[\alpha]_D^{20}$ +59.26° (c 4.05).

<u>The sesquiterpene alcohol</u> $C_{15}H_{26}O(8)$. IR spectrum, $v_{max}CC1_4$ (cm⁻¹): 905, 1385, 1455, 1645, 3085, 3602. PMR spectrum (200 MHz, CDC1₃, ppm): 0.97, 3H, s; 1.70, 3H, s; 1.82, 3H, s; 4.30-5.00, 6H, m; 5.88, 1H, dd, $H_1 = 17$ Hz, $J_2 = 10$ Hz.

 $\frac{\text{The hydroxyaldehyde } C_{10}H_{14}O_{2}, \ [\alpha]_{D}^{20} - 39.4^{\circ} \ (c \ 8.62). \ \text{IR spectrum: } \nu_{\text{max}} CCl_{4} \ (cm^{-1}): \\ 900, \ 1380, \ 1442, \ 1645, \ 1675, \ 3085. \ \text{UV spectrum: } \lambda_{\text{max}} C_{2}H_{5}OH, \ \text{nm: } 250 \ (lg \ \epsilon = 3.9842). \\ \end{cases}$

Mass spectrum, m/z (%): 166 (M⁺, 36), 151(43), 150(94), 135(48), 122(42), 108(38), 107(100), 105(36), 93(39), 91(73), 82(41), 79(94), 77(40). PMR spectrum (200 MHz, CDCl₃, ppm): 1.66, 3H, s; 2.17, 3H, s; 3.58, 1H, broadened; 4.59, 1H, s; 4.68, 1H, s; 9.95, 1H, s. ¹³C NMR spectrum (50.32 MHz, CDCl₃, ppm): quartets - 14.39; 20.34; triplets - 28.42; 39.29; 109.17; doublet - 50.62; singlets - 139.52; 146.71; 163.70; 187.83.

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BECKMANN REARRANGEMENT OF THE E ISOMER OF CIS-4,6,6-TRIMETHYLBICYCLO[3.1.1]-HEPTAN-2-ONE OXIME

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The individual E isomer of 4,6,6-trimethylbicyclo[3.1.1]heptan-2-one oxime has been obtained, and its transformations under the conditions of acid catalysis have been studied. The action of sulfuric acid on a solution of the oxime in acetonitrile leads to the selective formation of 5,7,7-trimethyl-2-azabicyclo[4.1.1]octan-3-one, while the action of hydrochloric acid with heating gives 4-isopropyl-3-methylaniline.

The interest of research workers in the Beckmann rearrangement is due to the fact that the amides formed as a result of this reaction are used as intermediates for obtaining pharmacologically active azacyclic compounds [1, 2]. However, in the majority of cases the rearrangement of terpene bicyclic oximes forms a mixture of unsaturated nitriles [3, 4]. This circumstance is obviously connected with the high degree of strain of the carbon skeleton of the derivatives of a number of bicyclo[2.2.1]- and -[3.1.1]heptanes, leading to rupture of a carbon-carbon bond and to dehydration. Thus, under the conditions of the Beckmann rearrangement, oximes of ketones of the pinane series are mainly converted into mixtures of unsaturated nitriles, and only in some cases have the corresponding lactams been obtained, in low yield. Only from nopinone oxime by the action of benzenesulfonyl chloride in the presence of sodium hydroxide has 7,7-dimethyl-2-azabicyclo[4.1.1]octan-3one been obtained, with a yield of 43% [5]. When pinocamphone and isopinocamphone oximes were treated with p-toluenesulfonyl chloride in the presence of NaOH [6] or with polyphosphoric acid [2] the corresponding lactams were again obtained, but only in trace amounts. The action of sulfuric acid on verbanone oxime (I) formed nitriles exclusively [1], and only under the action of p-toluenesulfonyl chloride in pyridine on verbanone oxime, in the form of a mixture of the E and Z isomers in a ratio of 3:1 was a multicomponent mixture obtained from which it was possible to isolate a 2-azalactam [7].

The aim of the present work was to study the behavior of the oxime of verbanone (cis-4,6,6-trimethylbicyclo[3.1.1]heptan-2-one) (I)-under the conditions of the Beckmann rearrangement.

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