

Saponification of Artapshin Diacetate. A solution of 0.05 g of artapshin diacetate in 10 ml of 5% aqueous KOH was heated on the water bath for 2 h and was left at room temperature for 16 h. Part of the water was evaporated off and the remaining solution was acidified with dilute sulfuric acid and extracted with ethyl acetate. The extract was dried over Na_2SO_4 , filtered, and evaporated. The residue was recrystallized from a mixture of chloroform and hexane. mp 118-120°C.

SUMMARY

A new sesquiterpene lactone with composition $\text{C}_{15}\text{H}_{22}\text{O}_4$, which has been called artapshin, has been isolated from *Artemisia fragrans* gathered on the Apsheron peninsula. A structure has been proposed for artapshin.

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OXIDATIVE TRANSFORMATIONS OF CEMBRANE DITERPENOIDS.

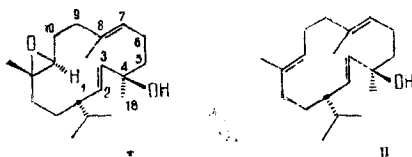
VI. EPOXIDATION OF ISOCEMBROL

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The stereochemistry of the epoxidation of the diterpene alcohol isocembrol has been studied. The main direction of attack of peracids is the C_{11} double bond of isocembrol, with the predominant formation of the 11S,12S-epoxide. The ratio of the monoepoxyisocembrols does not change appreciably with a variation in the temperature of the reaction or in the peracid used. 11S,12S-Epoxyisocembrol has been isolated as a natural product from the oleoresin of the Siberian stone pine.

In communication [1] we reported the formation of 11S,12S-epoxyisocembrol (I) as the main product of the epoxidation of isocembrol (II) by peracetic acid. The structure and stereochemistry of this compound were shown by its conversion into the known 11S,12S-epoxycembrene on dehydration with phosphorus oxychloride in pyridine. The spectral characteristics of compound (I) coincided with those for trocheliophorol — a component of soft corals of *Sarcophyton* sp. [2], which enabled the stereochemistry of the latter to be obtained, this being latter confirmed by Carmely [3].



In the present paper we give the results of a more detailed investigation of the epoxidation of isocembrol. As compared with the epoxidation of cembrene [4], this reaction leads to a more complex mixture of monoepoxides. The ease of identification of the epoxide (I) is due to its greater accessibility, since it is readily separated by chromatography from the other products — monoepoxides which, in TLC on Silufol, give two overlapping spots with R_f 0.72 and 0.62 (the R_f value of the epoxide (I) was taken as 1.00). The substances corre-

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TABLE 1. Values of the Chemical Shifts and Spin-Spin Coupling Constants (shown in parentheses) in the PMR Spectra of Compounds (I) and (III-VI)*

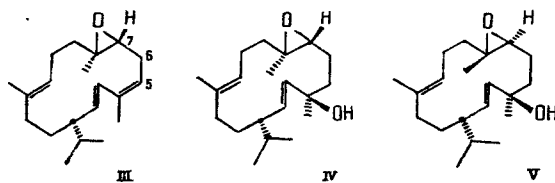
Sub-stance	H ₂	H ₃	Me ₄	Me ₅	Me ₁₂	H ₇	H ₁₁	-CH (CH ₃) ₂
I	5.15 dd (15.7; 8.4)	5.54 d (15.7)	1.26 s	1.67 s	1.11 s	5.2 m	2.65 dd (7.0; 3.5)	0.85 d (6.7) 0.80 d (6.7)
III	5.4 ₁ dd (15.3; 8.0)	6.27 d (15.3)	1.81 s	1.19 s	1.52 s	2.94 dd (7.5; 5.1)	4.78 m	0.88 d (6.5) 0.85 d (6.5)
IV	5.21 dd (16.0; 8.0)	5.61 d (16.0)	1.18 s or 1.30 s	1.30 s or 1.18	1.49 s	2.76 tm (~6.5)	4.94 m	0.86 d (6.6) 0.83 d (6.6)
V	5.26 dd (16.0; 8.5)	5.49 d (16.0)	1.31 s or 1.21 s	1.21 s or 1.31	1.49 s	2.54 dd (6.5; 4.0)	5.06 tm (~6)	0.86 d (7.0) 0.81 d (7.0)
VI	5.44 dd (16.0; 6.0)	5.59 d (16.0)	1.22 s	1.62 s	1.14 s	5.21 tm (~6.5)	2.53 dd (9.~3.5)	0.81 d (7.0) 0.77 d (7.0)

*Arbitrary symbols: d - doublet; s - singlet; m - multiplet; dd - doublet of doublets; tm - triplet of multiplets (broadened singlets). The values of the spin-spin coupling constants are given in hertz.

sponding to these two spots were obtained by chromatographing their mixture on a column of silica gel.

The substance giving on TLC a homogeneous spot with R_f 0.62 was, according to the results of GLC in a glass capillary column, a mixture of two components with one of them predominating. The rechromatography of this substance on silica gel with the composition of the fractions being monitored by GLC, showed that a mixture of the two components was first eluted and then the pure compound that was the main component of the initial mixture. The PMR spectrum of this product (Table 1) was qualitatively similar to the PMR spectrum of the epoxide (I). It contained the signals of the protons of trans-disubstituted and of trisubstituted double bonds, of an epoxide ring, and of three tertiary methyl groups, one of which was present at a double bond. To demonstrate the structure of this compound we used the same method as for the epoxide (I) [1]. Its dehydration with phosphorus oxychloride in pyridine gave two products corresponding to two directions of the dehydration reaction - the splitting out of a protons from C₅ or C₁₂ (with the formation of epoxycebrene and epoxyisocembrene, respectively).

The epoxycebrene obtained had a PMR spectrum differing from those of the known 7S,8S- and 11S,12S-epoxycebrene [4]. It is therefore the diepimer of one of these epoxides - 7R,8R- or 11R,12R-epoxycebrene. The choice between these structures was made in favor of 7R,8R-epoxycebrene (III) on the basis of its PMR spectrum (Table 1), in which the signal of the allyl proton at 2.51 ppm (H_{5a}) is part of a bound spin system simultaneously including epoxidic (2.94 ppm, H₇) and olefinic (5.45 ppm, H₃) protons (established with the aid of double resonance). Thus, the initial epoxide is 7R,8R-epoxyisocembreol (IV).



A product coinciding on TLC with the epoxide (IV) was obtained only in the form of its mixture with the latter. In the PMR spectrum of this mixture (Fig. 1), the signals from the two products were observed separately. In them, only the signals of the methyl group present at the double bond coincide (Table 1). A comparison of the spectra obtained with the spectrum of the pure epoxide (IV) revealed the signals belonging to the second epoxide. This epoxide was 7S,8S-epoxyisocembreol (V), since on dehydration with phosphorus pentoxide in pyridine it gave the known 7S,8S-epoxycebrene [4], identified by a comparison with an authentic sample by TLC, GLC, and PMR spectroscopy.

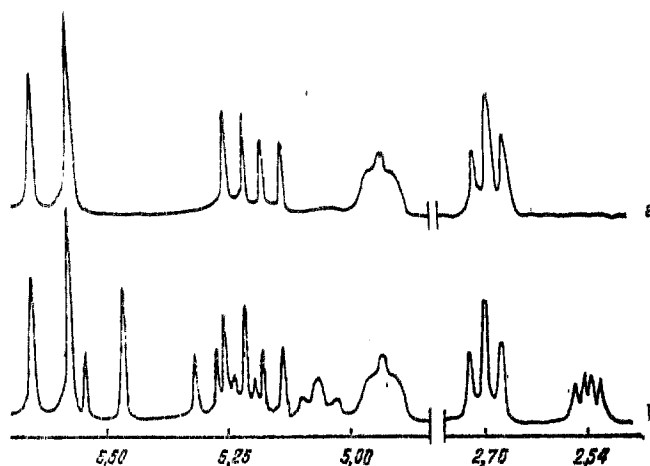
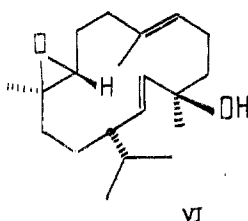


Fig. 1. Fragments of PMR spectra: a) the epoxyisocembrol (IV); b) mixture of the epoxyisocembrols (IV) and (V).



Finally, for the last monoepoxide (R_f 0.72), containing, according to its IR and PMR spectra, a trans-disubstituted double bond, the only possible structure remaining is (VI) (11R,12R-epoxyisocembrol).

All the monoepoxides isolated correspond in their reactions to the trisubstituted double bonds of isocembrol. The disubstituted double bond is apparently inert with respect to the reagent used. 2,3-Epoxyisocembrol has been described previously only as a product of the reaction of isocembrol with the Jones reagent [5].

On comparing the results of the epoxidation of isocembrol and the cembrene [4], it can be seen that the attack of the reagent on each trisubstituted double bond of cembrene takes place with complete stereospecificity, leading to only one of the two possible epoxides. For isocembrol the formation of both possible stereoisomers is observed in each case. Reaction at the C_{11} double bond takes place with pronounced stereospecificity, leading mainly to a product with the same stereochemistry as on the epoxidation of cembrene [4]. Reaction at the C_7 double bond of isocembrol takes place somewhat preferentially in the direction of the formation of the 7R,8R-isomer.

The ratio of the monoepoxyisocembrols formed does not change appreciably with a variation in the temperature of the reaction or on the replacement of peracetic acid by monoperphthalic acid (Table 2).

The further epoxidation of 11S,12S-epoxyisocembrol (I) with peracetic acid led to a mixture (3:1 PMR spectrum) of two diepoxyisocembrols isomeric at C_7 and C_8 . The main diepoxide eluted first from a column of silica gel gave, on dehydration with phosphorus oxychloride in pyridine, 7S,8S:11S,12S-diepoxyisocembrene [4]. It was therefore 7S,8S:11S,12S-diepoxyisocembrol (VII). The fact that the second diepoxide was a stereoisomer of the epoxide (VII) was established by comparing the PMR spectra of a mixture of these compounds and of the pure diepoxide (VII). This showed that the second diepoxide contained an unaffected trans-disubstituted double bond and, consequently, the second epoxy group was located at C_7 - C_8 . In view of the formation of the diepoxide (VII) as the main product of the epoxidation of substance (I), it may be mentioned that replacement of the C_{11} double bond of isocembrol by

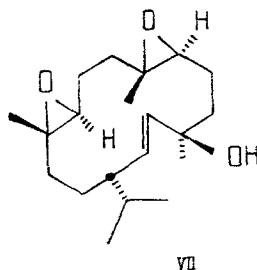
TABLE 2. Ratio of the Monoepoxyisocembrols Formed under Various Conditions of the Epoxidation of Isocembrol

Reaction conditions	Degree of conversion of the isocembrol, %	Yield of monoepoxides in sum, %*	Amounts of the monoepoxides in their mixtures, %†			
			I	IV	V	VI
1. Peracetic acid (1.5 eq.) in methylene chloride solution, +19°C, 2 h	79	71	72.9	1.8	5.5	19.8
2. The same, 0°C	79	86	67.6	1.9	6.8	23.7
3. The same, -25°C	58	98	76.7	2.3	4.7	16.3
4. Monoperphthalic acid (2 eq.) in diethyl ether, 0 to -5°C, 48 h	55	91	60.0	5.2	10.0	24.8

*Calculated based on the isocembrol that reacted.

†The amount of epoxide (I) was calculated from the results of column chromatography and the amounts of epoxides (IV-VI) from the results of the GLC of their mixture eluted from the column after the pure epoxide (I).

an epoxy group changes into its opposite the predominant direction of the attack of a peracid on the remaining C, double bond.



We isolated 11S,12S-epoxyisocembrol (trocheliophorol) (I) by chromatography from the neutral fraction of the oleoresin of the Siberian stone pine (*Pinus sibirica* R. Mayr.), in which its concentration is very low, amounting to about 0.1% (on the oleoresin). One of the main components of this oleoresin is isocembrol (tunbergol [6]). Isocembrol accompanies trocheliophorol in soft corals [3]. The presence of this pair of compounds in a coniferous plant and in a marine coral indicates a similarity of the routes of the secondary metabolism of the cembrane diterpenoids in these so widely differing living organisms.

EXPERIMENTAL

PMR spectra were obtained on a Bruker WP-200 (200 Hz) instrument for solutions in carbon tetrachloride with hexamethyldisiloxane as internal standard, the signal of which was taken as 0.04 ppm, δ -scale; 0.1 ml of perdeuterocyclohexane was added to each of the solutions of the samples

Gas-liquid chromatography was carried out on a Chrom 41 instrument with a glass capillary column, 30 m \times 0.25 mm, liquid phase SKFT-50, column temperature 180°C, evaporator temperature 240°C.

Specific optical rotations were measured for solutions in chloroform, IR spectra were taken for solutions in carbon tetrachloride. Column chromatography was carried out on silica gel (0.140-0.315 mm) of the KSK type with a ratio of substance to adsorbent of 1:20, the eluent in all cases being petroleum ether with increasing (from 0 to 80%) amounts of diethyl ether.

Epoxidation of Isocembrol. A stirred solution of 4.66 g of isocembrol in 100 ml of methylene chloride was treated with 5 h of dry sodium bicarbonate, and then 6.5 ml of a solution of peracetic acid (pure peracetic acid - 1.28 g) in methylene chloride was added dropwise over 0.5 h at room temperature, after which the mixture was stirred at the same tempera-

ture for another 1.5 h. After the usual working up and chromatography of the product, 0.95 g of unchanged isocembrol, 2.02 g of the epoxide (I) [oil with $[\alpha]_D^{26} +45.6^\circ$ (c 5.7)] and 0.75 g of a mixture of the epoxides (IV), (V), and (VI) were obtained.

Rechromatography of the mixture of epoxides (IV), (V), and (VI) gave 0.05 g of the epoxide (VI) and 0.70 g of a mixture of the epoxides (IV) and (V) [this mixture gave a single spot in TLC on Silufol with petroleum ether-diethyl ether (2:3) as eluent]. The mixture of epoxides (IV) and (V) was chromatographed once more, whereupon 0.40 g of a mixture of the epoxides (IV) and (V) and 0.25 g of the pure epoxide (IV) were obtained.

The relative retention times of the epoxyisocembrols on GLC were (the retention time of the epoxide (I) was taken as 1.00): the epoxide (IV) 1.18; the epoxide (V) 1.00; the epoxide (VI) 1.06.

The Epoxide (VI) (11R,12R-Epoxyisocembrol). Colorless oil with n_D^{28} 1.4940, $[\alpha]_D^{27} +11.3^\circ$ (c 4.4). IR spectrum, cm^{-1} : 3615 (OH), 985 (trans-disubstituted double bond); 920 (epoxide ring). For the PMR spectrum, see Table 1.

The Epoxide (IV) (7R,8R-Epoxyisocembrol). Colorless oil with n_D^{15} 1.4987 $[\alpha]_D^{15} -3.06^\circ$ (c 6.54). IR spectrum, cm^{-1} : 3610 (OH), 985 (trans-disubstituted double bond), 920 (epoxide ring). For the PMR spectrum, see Table 1.

7R,8R-Epoxycebrene (III). A solution of 0.18 g of the epoxide (IV) in 5 ml of pyridine cooled to 0°C , was treated with 0.2 ml of phosphorus oxychloride and the mixture was left at the same temperature for 20 h. After the usually working up and chromatography of the product, 0.05 g of the epoxide (III) was obtained in the form of an oil the IR spectrum of which was very similar to that for 7S,8S-epoxycebrene [4]. UV spectrum: $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 243 nm (log ϵ 4.2). In the PMR spectrum of this compound, in addition to the signals shown in Table 1, individual signals were observed at 5.45 ppm (1 H, multiplet having the form of a triplet with slightly broadened components, $J \sim 7$ Hz, H_5) and at 2.51 ppm (1 H, doublet of triplets with $J = 14.4$ and 5 Hz, H_{6a}). On double resonance with the suppression of the H_{6a} signal, the H_7 signal (2.94 ppm, see Table 1) was converted into a doublet with $J = 7.5$ Hz, and the H_5 signal into a doublet ($J \sim 7$ Hz) with broadened components.

The second product of the dehydration of the epoxide (IV) — the $\Delta^{18(4)}$ isomer of the epoxide (III) was isolated by chromatographing the mixture of products of the dehydration of the epoxide (IV) and was eluted after the epoxide (III) with a yield of 0.05 g. IR spectrum, cm^{-1} : 980, 1650, 3080 (exomethylene group), 980, (trans-disubstituted double bond), 920 (epoxide ring).

The mixture of epoxides (IV) and (V) obtained as described above (0.40 g) was dehydrated similarly. After the usually working up and chromatography, a product (0.2 g) homogeneous according to TLC was isolated from the reaction mixture which coincided on TLC with samples of the epoxide (III) and of 7S,8S-epoxycebrene. According to its PMR spectrum, the product consisted of a mixture of the epoxide (III) and 7S,8S-epoxycebrene present in a ratio of 1:1 (determined from the ratio of the integral intensities of the signals of the H_3 proton which, for these diepimers, appear at 6.27 ppm (Table 1) and 6.10 ppm [4], respectively).

7S,8S:11S,12S-Diepoxyisocembrol (VII). A stirred solution of 0.30 g of the epoxide (I) in 20 ml of methylene chloride was treated with 3 g of dry sodium bicarbonate, and then a solution of peracetic acid in methylene chloride was added at room temperature until the epoxide (I) had disappeared from the solution (monitored by TLC). After the usual working up, a product (0.25 g) was obtained which gave a single spot on TLC. According to its PMR spectrum, it was a mixture of two diepoxides with an unaffected trans-disubstituted double bond, present in a ratio of 3:1 (determined from the relative integral intensities of the signals of the H_3 proton, which is present in both compounds at a trans disubstituted double bond (5.49 and 5.57 ppm; doublet with $J \sim 15.5$ Hz in each case).

On chromatography, the main component was eluted first, with a yield of 0.1 g; oil with $[\alpha]_D^{25} +28.7^\circ$ (c 6.87). IR spectrum, cm^{-1} : 3610 (OH), 985 (trans-disubstituted double bond), 940 (epoxide). PMR spectrum, ppm: 0.82 and 0.88 (3 H each, doublets, $J = 7$ Hz, each, methyls of an isopropyl group); 1.15, 1.29, and 1.31 (3 H, singlets, $\text{Me}_{1,2}$, Me_8 , and Me_4); 2.64 (2 H, multiplet, H_7 and H_{11}); 5.18 (1 H, doublet of doublets, $J = 16.0$ and 9.0 Hz, H_2); and 5.49 (1 H, doublet, $J = 16.0$ Hz, H_3). For a solution in deuterobenzene, the signals of the H_7 and H_{11} protons were observed separately at 2.60 and 2.87 ppm.

Dehydration of the Diepoxide (VII). The dehydration of the diepoxide (VII) (0.22 g) was carried out in a similar manner to that described above for the epoxide (IV). Chromatography of the product (0.17 g) gave 0.1 g of 7S,8S:11S,12S-diepoxycembrene with mp 109-110°C (according to the literature [4]: mp 111-112°C); the IR and PMR spectra of which coincided with those for an authentic sample.

Isolation of 11S,12S-Epoxyisocembrol (I) from the Oleoresin. The oleoresin of the Siberian stone pine was separated by the group separation scheme [7]. The fraction of neutral polyfunctional compounds (3.30 g, yield 5% on the oleoresin) was chromatographed with the use of a sample of epoxide (I) to monitor the composition of the eluates. The fractions containing the epoxide (I) were combined and rechromatographed. This gave 0.06 g of the epoxide (I) in the form of an oil with $[\alpha]_D^{25} +46^\circ$ (c 5.0), identical with the sample according to TLC, GLC, and PMR spectroscopy.

SUMMARY

1. The epoxidation of isocembrol by peracids takes place at the trisubstituted double bonds, leading to all four possible monoepoxides.
2. The predominant direction of the epoxidation of isocembrol at the C₁₁ double bond is the formation of the 11S,12S-epoxide, and at the C₇ double bond it is the formation of the 7R,8R-epoxide.
3. 11S,12S-Epoxyisocembrol has been isolated from the oleoresin of the Siberian stone pine.

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