

## OXIDATIVE TRANSFORMATIONS OF CEMBRANE DITERPENOIDS

### III. EPOXYCEMBRENES

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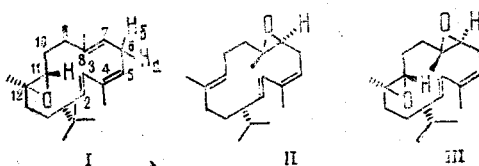
UDC 547.595.9

The epoxidation of cembrene is one of the possible routes for the introduction of functional groups into the cembrene carbon skeleton and of approach to analogs of physiologically active highly oxidized cembrene diterpenoids found in nature [1-3]. Cembrene epoxides are also of interest as possible intermediates in the biosynthesis of complex cembrene derivatives.

We have studied the products of the interaction of cembrene with equimolecular amounts of peroxyacetic acid in chloroform and of perbenzoic acid in benzene in the presence of an excess of sodium bicarbonate, preventing the decomposition of the unstable epoxides. According to TLC, the reaction mixtures in both cases consisted of unchanged cembrene, three monoepoxides difficult to separate, and a small amount of polar compounds.

The most polar monoepoxide proved to be extremely unstable in relation to the usual adsorbents - silica gel and alumina. Air-dry silica gel containing 5% of sodium bicarbonate caused no decomposition of the compound, but the selectivity of this adsorbent was sufficient only to separate the combined monoepoxides from the unchanged cembrene and from more polar products. The absence of the absorption bands of carbonyl and hydroxy groups in the IR spectrum of monoepoxide fractions obtained in this way showed that all three of its components were epoxides.

The two more polar monoepoxides were isolated by chromatography and were provisionally called epoxides A and B in the order of their elution from a column of silica gel. They are isomers of the general formula  $C_{20}H_{32}O$  and contain a conjugated dienic system [UV spectra:  $\lambda_{max}$  243 and 240 nm ( $\log \epsilon$  4.20 and 4.19, respectively)]. The presence of the signals of the  $H_5$ ,  $H_{6a}$ , and  $H_7$  protons in the NMR spectrum of epoxide B (Fig. 1) shows that this compound is 11,12-epoxycembrene (I). The absence from the NMR spectrum of epoxide A of the signal of the  $H_{6a}$  proton (in the 2.6-3.1 ppm region) that is characteristic for cembrene, 2,3-dihydrocembrene [4], and epoxide B, permits epoxide A to be assigned the structure of 7,8-epoxycembrene (II). This conclusion is confirmed by the formation of the same diepoxide (III) on the epoxidation of both epoxide A and epoxide B with peroxybenzoic acid.



As has been shown by Joshi et al. [5], epoxides isomerize on active alumina into secondary allyl alcohols with the retention of the configuration of one of the asymmetric centers. We have made use of this fact to determine the absolute configuration of the monoepoxycembrenes. When epoxides (I) and (II) were isomerized on alkaline alumina (activity grade II according to Brockmann), the secondary alcohols (IV) and (V), respectively, were formed. The configurations of the hydroxyl-containing asymmetric centers in the alcohols (IV) and (V) were established on the basis of relationship between the sign of the long-wave circular dichroism band of the *o*-nitrobenzoate of the secondary alcohol and the configuration of the corresponding asymmetric center [6].

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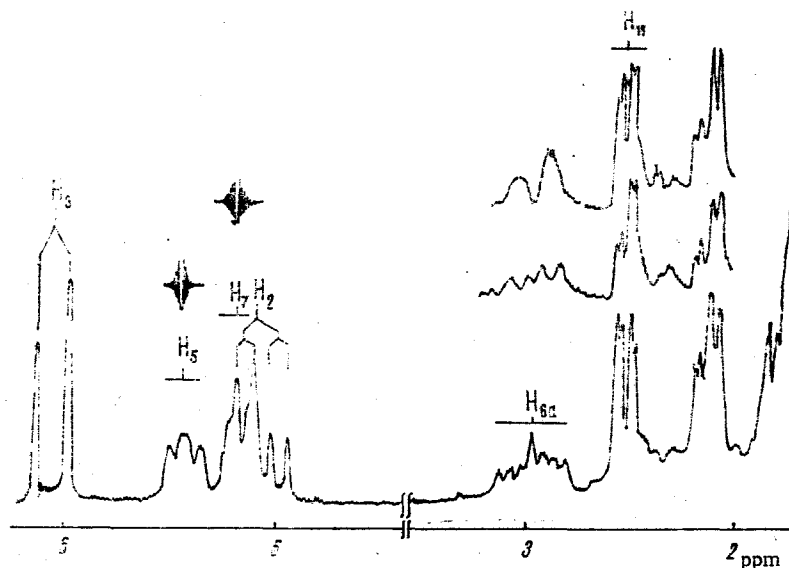
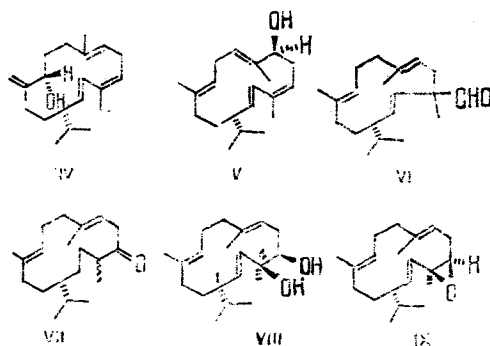


Fig. 1. NMR spectrum of 11,12-epoxycembrene (I) (100 MHz, in  $\text{CCl}_4$ ).

The *o*-nitrobenzoates of the alcohols (IV) and (V) obtained by the reaction of these alcohols with *o*-nitrobenzoyl chloride in pyridine gave a positive Cotton effect at 335 nm (in methanol solution), which shows the *S* configuration of the asymmetric centers in the alcohols. In view of the stereospecificity of the opening of the epoxide ring when it is isomerized on alumina and the *trans* configuration of the nonconjugated double bonds of cembrene [4, 7], it may be concluded that epoxides (I) and (II) have the 11*S*,12*S* and 7*S*,8*S* configurations, respectively, and the diepoxide (III) the 7*S*,8*S*,11*S*,12*S* configuration.

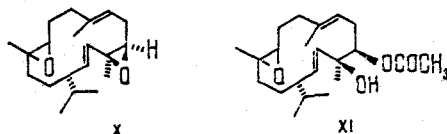


The third, least polar, cembrene epoxide decomposed completely when the mixture of monoepoxides was chromatographed on air-dry silica gel with the formation of the aldehyde (VI) and a mixture of two epimeric ketones (VII), which we had obtained previously by oxidizing with chromium trioxide in aqueous acetone [8], and also the diol (VIII) and its  $C_4$  epimer, which we have also described previously [9]. These products were formed in a ratio of 3:26:55:13. Their structures permit the conclusion that the third epoxide is (4*S*,5*R*)-4,5-epoxycembrene (IX). Although the epoxide (IX) was not isolated in the individual state, the NMR spectrum (100 MHz) of the monoepoxide fraction clearly showed its most characteristic signals ( $\delta$ ):  $H_2$ , doublet of doublets with components at 5.20, 5.28, 5.36, and 5.44 ppm,  $J_{1,2} = 8.0$  Hz,  $J_{2,3} = 15.5$  Hz;  $H_3$ , doublet with components at 4.85 and 5.00 ppm,  $J_{3,2} = 15.5$  Hz;  $H_5$ , doublet of doublets at 2.90 ppm,  $J_{5,6a} = 8.0$  Hz,  $J_{5,6b} = 5.5$  Hz;  $\text{Me}_4$ , singlet at 1.32 ppm. In the NMR spectrum of the mixture of products obtained by the passage of the monoepoxide fraction through a column containing air-dry silica gel the signals of the epoxide (IX) disappeared, and the signals of the ketones (VII) and of the diol (VIII) — the main components of the mixture of decomposition products of the epoxide (IX) — appeared.

The stereoisomers of the epoxides (I) (II) and (IX) did not appear in the reaction mixtures in appreciable amount, which shows the high stereospecificity of the epoxidation of cembrene. Furthermore, cembrene epoxidizes at each of the three double bonds in the same conformation in which it exists in the crystal, since for this

conformation [7] (see also reference [7] in the paper of Schmitz et al. [10]) the directions leading to the formation of epoxides with the stereochemistry that we have established are favorable for attack by peroxyacetic acid. For the epoxidation of cembrene at the nonconjugated double bonds, a definite regiospecificity expressed in predominant attack on the C<sub>11</sub>-C<sub>12</sub> double bond is also observed. Thus, the ratio of the epoxides (I) and (II) determined from the integral intensities of the signals of the H<sub>3</sub> protons of the NMR spectra if the monoepoxide fractions was 1.7:1 (epoxidation by perbenzoic acid in benzene) and 2:1 (epoxidation by perbenzoic acid in chloroform). In both cases, the epoxide (IX) made up ~60% of the mixture of monoepoxides, as was determined from the yield of its decomposition products.

The components of the polar (diepoxide) fraction of the products of the epoxidation of cembrene could be isolated in reasonable amounts from reaction mixtures by the reaction of cembrene with two equivalents of perbenzoic or peracetic acid. When these mixtures were chromatographed on silica gel containing 5% of sodium bicarbonate, the liquid diepoxide (X) was eluted first after the monoepoxides; its NMR spectrum contains signals similar to those observed for the epoxide (IX) in the NMR spectrum of the mixture of cembrene monoepoxides. When chromatographed on air-dry silica gel, this diepoxide decomposed in the same way as epoxide (IX) with the formation of the corresponding epoxydiol as the main product. In the NMR spectrum of the acetate of this epoxydiol (XI) the signal of the H<sub>6a</sub> proton is found at 2.82 ppm, its assignment being made by means of double resonance with suppression of the H<sub>5</sub> and H<sub>7</sub> signals. This shows the position of the epoxide ring in the diepoxide (X) and in the acetate of the corresponding epoxydiol. The stereochemistry of compounds (X) and (XI) at C<sub>4</sub> and C<sub>5</sub> was shown by the formation of the acetate (XI) by the epoxidation of the monoacetate of the diol (VII) with perbenzoic acid in benzene in the presence of an excess of sodium bicarbonate.



The second component of the diepoxide fraction, eluted immediately after the diepoxide (X), was identical with the 7,8:11,12-diepoxycembrene (III) obtained by the epoxidation of epoxides A and B (I and II). The stereoisomers of the diepoxide (III) were not present in appreciable amounts in the reaction mixtures, which gives grounds for assuming that epoxides (I and II) epoxidize in conformations analogous to the conformation of cembrene in the same solvents.

The third component of the diepoxide fraction obtained in the epoxidation of cembrene with peracetic acid was identified as the 5-O-acetate of the diol (VIII), and the corresponding substance isolated from the mixture of products of the reaction of cembrene with perbenzoic acid was identified as the 5-O-benzoate of the same diol. This benzoate was identical with the product of the benzylation of the diol (VIII) with benzoyl chloride in pyridine.

The formation of the esters obtained can be explained by the assumption that acetic acid or benzoic acid, as the case may be, is present in the heterogeneous reaction mixture in small amount and adds to the reactive monoepoxide (IX). The 4-O-acyl derivative of the diols would be expected as the normal product of the addition of the acid to this monoepoxide. The fact that the 5-O-acyl derivative was actually formed is apparently explained by the side reaction of the migration of the acyl residue from the tertiary hydroxyl to the secondary with the formation of the sterically more stable acetate or benzoate. A similar isomerization takes place in the reaction of  $\alpha$ -aryl epoxides with carboxylic acids [11].

The third expected diepoxycembrene - 4,5:7,8-diepoxycembrene - was not detected in the mixture of cembrene epoxidation products. It was apparently formed in very small amount and on chromatography was masked by the diepoxide (X).

#### EXPERIMENTAL

The instruments and methods have been described previously [8]. The molecular formulas of substances (III-V) were determined mass-spectrometrically on a MS 902 instrument. The elementary analyses of substances (I), (II), (IX), and the 5-O-benzoate of the diol (VIII) corresponded to the calculated figures.

**Epoxidation of Cembrene.** With vigorous stirring and ice cooling 1.75 ml (9.2 mmole) of 40% peroxyacetic acid obtained by Greenspan's method [12] was added dropwise to a solution of 2.5 g (9.2 mmole) of cembrene in 25 ml of chloroform containing 5 g of anhydrous sodium carbonate in suspension. After the addition of the whole

of the peroxyacetic acid, the reaction mixture was stirred at the same temperature for another hour and was poured into a cold saturated aqueous solution of sodium bicarbonate. The organic layer was washed with water and dried with sodium sulfate, and the solvent was driven off from it to give 2.4 g of a mixture of products which was chromatographed on 300 g of silica gel. Petroleum ether and mixtures of petroleum ether and diethyl ether containing from 0 to 100% of the latter eluted successively 1.0 g of cembrene, 0.02 g of the aldehyde (VI), 0.40 g of a mixture of the epoxide (II) and the epimeric ketones (VII), 0.45 g of the epoxide (I), 0.05 g of a diepoxide fraction, 0.02 g of the 5-O-acetate of the diol (VIII), 0.26 g of the mixture of the diol (VIII) and its C<sub>4</sub> epimer, and 0.2 g of a polar fraction. The diol (VIII) and its epimer were separated by the chromatography of their acetates [9].

**7,8-Epoxyembrene (II).** This epoxide was separated from the ketones (VII) by chromatographing 0.40 g of a mixture of these substances on 10 g of silica gel containing 10% of silver nitrate. This yielded 0.04 g and 0.11 g of the epimeric ketones (VII), identical with those described previously [8], and 0.23 g of the epoxide (II) with mp 80–81°C (from ethanol),  $[\alpha]_D^{22} - 17.9^\circ$  (c 2.79). NMR spectrum (here and below, the  $\delta$  scale is used, ppm): 0.76 and 0.81 (3H each, doublets with  $J = 5.5$  Hz each, methyls of an isopropyl group), 1.20 (3H, singlet, Me<sub>8</sub>), 1.46 and 1.78 (3H each, singlets, Me<sub>12</sub> and Me<sub>4</sub>, respectively), 4.95 and 5.55 (1H each, doublet and triplet of multiplets, respectively, H<sub>11</sub> and H<sub>5</sub>), 5.55 (1H, doublet of doublets,  $J = 15.5$  and 9.4 Hz, H<sub>2</sub>), and 6.10 ppm (1H, doublet,  $J = 15.5$  Hz, H<sub>3</sub>).

**11,12-Epoxyembrene (I).** Colorless needles from ethanol, mp 70–71°C,  $[\alpha]_D^{22} + 90.7^\circ$  (c 3.86). NMR spectrum: 1.04 (3H, singlet, Me<sub>12</sub>), 1.63 and 1.68 ppm (3H each, triplets,  $J = 1.5$  Hz each, Me<sub>8</sub> and Me<sub>4</sub>). The interpretation of the other signals is given in Fig. 1.

**Isomerization of Epoxides (I) and (II) on Alumina.** A solution of 0.5 g of one of these epoxides in 2 ml of pentane was transferred to a column containing 10 g alkaline alumina (Brockmann activity grade II, filled by the wet method with pentane as solvent) and was left for a day beneath a layer of solvent. The products were eluted with diethyl ether and were chromatographed on 10 g of silica gel. This gave the alcohols (IV) (from the epoxide (I)) and (V) [from the epoxide (II)] with yields of 80 and 70%, respectively.

The alcohol (IV) formed a colorless oil with  $n_D^{20} 1.5260$ ,  $[\alpha]_D^{20} + 27.5$  (c 6.55). IR spectrum (cm<sup>-1</sup>): 3625 (free secondary hydroxy group), 3090, 1655, 905, ( $>C=CH_2$ ), 980 (trans-disubstituted double bond). NMR spectrum, ppm: 1.61 and 1.75 (3H each, singlets, Me<sub>8</sub> and Me<sub>4</sub>), 2.71 (2H, triplet of multiplets, protons at C<sub>6</sub>), 3.84 (1H, doublet of doublets,  $J = 3.5$  and 7.5 Hz, H<sub>11</sub>), 4.71 and 4.92 (1H each, narrow multiplets,  $W_{1/2} = 4$  Hz each,  $>C=CH_2$ ).

The alcohol (V) formed a colorless oil with  $n_D^{21} 1.5290$ ,  $[\alpha]_D^{21} - 39.2^\circ$  (c 5.11). IR spectrum, cm<sup>-1</sup>: 3620 (secondary hydroxy group), 970 (trans-disubstituted double bond). NMR spectrum (ppm): 1.51 (6H, singlet with weak splitting, Me<sub>8</sub> and Me<sub>12</sub>), 1.70 (3H, triplet,  $J = 1.4$  Hz, Me<sub>4</sub>), 3.76 (1H, doublet of doublets,  $J = 10.0$  and 3.5 Hz, H<sub>7</sub>).

**4,5:11,12-Diepoxymbrene (X)** formed a colorless oil with  $n_D^{23} 1.5030$ ,  $[\alpha]_D^{23} + 32.6^\circ$  (c 4.9). IR spectrum, cm<sup>-1</sup>: 975 (trans-disubstituted double bond). The UV spectrum showed no absorption maximum in the 215–400 nm region. PMR spectrum, ppm: 1.03, 1.30, and 1.53 (3H each, singlets, Me<sub>8</sub>, Me<sub>4</sub>, and Me<sub>12</sub>, respectively), 2.89 (1H, doublets,  $J = 5.5$  and 8.5 Hz, H<sub>5</sub>), 4.89 (1H, multiplet, H<sub>7</sub>), 4.90 (1H, doublet,  $J = 16.5$  Hz, H<sub>3</sub>), 5.20 (1H, doublet of doublets,  $J = 16.5$  and 7.5 Hz, H<sub>2</sub>).

**7,8:11,12-Diepoxymbrene (III)** formed colorless needles from carbon tetrachloride with mp 111–112°C,  $[\alpha]_D^{22} - 10.0^\circ$  (c 7.16). IR spectrum, cm<sup>-1</sup>: 980 (trans-disubstituted double bond). UV spectrum (in heptane):  $\lambda_{max} 242$  nm (log  $\epsilon$  4.2). NMR spectrum, ppm: 1.06, 1.28, and 1.75 (3H each, singlets, Me<sub>12</sub>, Me<sub>8</sub>, and Me<sub>4</sub>, respectively), 2.0–2.8 (3H, multiplet, H<sub>7</sub>, H<sub>11</sub>, and, apparently, one of the protons at C<sub>6</sub>), 5.50 (1H, triplet of multiplets,  $J = 8$  Hz, H<sub>5</sub>), 5.21 (1H, doublet of doublets,  $J = 15.0$  and 8.0 Hz, H<sub>2</sub>), 5.87 (1H, doublet,  $J = 15.0$  Hz, H<sub>3</sub>).

**5-O-Benzoate of the Diol (VIII).** Colorless oil with  $n_D^{19} 1.5250$ ,  $[\alpha]_D^{19} - 21.4^\circ$  (c 4.56). IR spectrum, cm<sup>-1</sup>: 980 (trans-disubstituted double bond), 1030, 1070, 1130, 1280, 1500, 1590, 1610, 1700 (benzoyloxy group) 3600 (hydroxy group). The UV spectrum qualitatively coincided with the UV spectrum of ethyl benzoate.

**5-O-Acetate of the 11,12-Epoxydiol (XI).** The polar fraction (0.2 g) obtained in the separation of the oxidation products of cembrene (see above) was acetylated with acetic anhydride (0.5 ml) in pyridine (5 ml) at 20°C for 5 h. After the usual working up and chromatography of the product on 10 g of silica gel, 0.1 g of the 5-O-acetate of the 11,12-epoxydiol was obtained with  $n_D^{23} 1.5028$  and  $[\alpha]_D^{23} + 38.2^\circ$  (c 5.24). IR spectrum, cm<sup>-1</sup>: 980 (trans-disubstituted double bond), 1240, 1750 (OCOCH<sub>3</sub>), 3600 (hydroxy group). There was no maximum in

the UV spectrum in the 210–400 nm region. NMR spectrum, (ppm): 1.08, 1.17, 1.62, and 1.98 (3H each, singlets, Me<sub>12</sub>, Me<sub>4</sub>, Me<sub>8</sub>, and OCOCH<sub>3</sub>, respectively), 2.82 (1H, multiplet, H<sub>6a</sub>), 4.45 (1H, doublet of doublets, J = 2 and 8 Hz, H<sub>4</sub>), 5.3 (1H, multiplet, H<sub>7</sub>), 5.38 (2H, singlet, H<sub>2</sub> and H<sub>3</sub>).

The same acetate was obtained similarly from the mixture of products formed from the diepoxide (X) when it was chromatographed on air-dry silica gel.

#### SUMMARY

1. It has been established that the epoxidation of cembrene with perbenzoic and peracetic acids takes place stereospecifically at each of the trisubstituted double bonds with the formation of 4S,5R-, 7S,8S-, and 11S,12S-monoepoxycembrenes, the structures and absolute configurations of which have been established by spectral methods.

2. Epoxidation of cembrene at the C<sub>11</sub>-C<sub>12</sub> double bonds under the conditions used takes place preferentially as compared with epoxidation at the C<sub>7</sub>-C<sub>8</sub> double bond.

#### LITERATURE CITED

1. A. J. Weinheimer, R. E. Middlebrook, J. O. Bledsoe, and W. E. Marsico, *J. Chem. Soc., (D)*, 384 (1968).
2. M. B. Hossain and D. van der Helm, *Rec. Trav. Chim.*, **88**, 1413 (1969).
3. J. P. Springer, J. Clardy, R. H. Cox, H. G. Gutler, and R. J. Cole, *Tetrahedron Lett.*, 2737 (1975).
4. V. A. Raldugin, A. I. Rezvukhin, and V. A. Pentegova, *Khim. Prirodn. Soedin.*, 598 (1971).
5. V. S. Joshi, N. P. Damodaran, and Sukh Dev., *Tetrahedron*, **24**, 5817 (1968).
6. U. Nagai and H. Iga, *Tetrahedron*, **26**, 725 (1970).
7. M. G. B. Drew, D. H. Templeton, and A. Zalkin, *Acta Cryst.*, **25B**, 261 (1969).
8. V. A. Raldugin, V. K. Fedorov, and V. A. Penterova, *Khim. Prirodn. Soedin.*, 391 (1976).
9. V. A. Raldugin, A. I. Rezvukhin, L. Ya. Korotkikh, and V. A. Pentegova, *Khim. Prirodn. Soedin.*, 54 (1977).
10. F. J. Schmitz, D. J. Vanderah, and L. S. Ciereszko, *J. Chem. Soc., D*, 407 (1974).
11. G. Berti, F. Bottari, B. Macchia, and F. Macchia, *Tetrahedron*, **21**, 3277 (1965).
12. F. P. Greenspan, *J. Am. Chem. Soc.*, **68**, 907 (1946).

#### WITHANOLIDES OF *Physalis*

##### I. PHYSALACTONE

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UDC 547.926

The first results of a chemical study of *Physalis alkekengi* L. were published more than a century ago [1] when a bitter substance, which was called physalin, was isolated from the leaves of this plant. No structural investigations were carried out at that time. Beginning only in 1969 have communications appeared on the chemical structure of the steroid compounds contained in *Physalis*; in particular, physalins A [2], B [3], and C [4], having the structure of 13,14-seco-16,24-cyclosteroids, have been found (collected in Japan) in *P. alkekengi* var. Franchetti. In addition to those mentioned, withaphysalins A, B, and C have been isolated from *Ph. minima* [5], withaphysacarpin from *Ph. ixocarpa* Brot. [6], and withanolide B and 4β-hydroxywithanolide E from *Ph. peruviana* [7, 8].

Different chemotypes of the same plant species contain withanolides differing from one another by their chemical structure and amount [9, 10] and therefore we considered it desirable to study the withano-

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