OXIDATIVE TRANSFORMATIONS OF CEMBRANE DITERPENOIDS

IV. ~~PHOTOOXIDATION OF CEMBRENE~~

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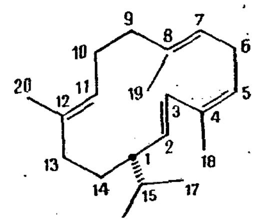
The ~~photooxidation of cembrene~~ by singlet oxygen is a stereoselective reaction and it is stereochemically similar to the epoxidation of cembrene by peracids. From the mixture of the photooxidation products of cembrene after its treatment with sodium tetrahydroborate four allyl alcohols have been isolated and the structures of two of them, previously undescribed, have been established on the basis of their spectral characteristics. The main component of these alcohols is cembra-2E,4Z,7E,10E-tetraen-12S-ol.

The photooxidation of terpenoids is attracting ever increasing attention in connection with its broad synthetic possibilities and also from the point of view of modeling biosynthetic transformations. The latter aspect is acquiring particular significance in view of the detection in plants of terpenoid peroxy compounds which are, apparently, the products of the oxidation of terpenoids by singlet oxygen [1]. Chlorophyll may act as a sensitizer in this reaction in plants [2].

We have investigated the products of the photosensitized oxidation of cembrene (I), which contains three trisubstituted double bonds, two of which (unconjugated) should, according to the well-known laws of the oxidation of olefins by singlet oxygen [3], be the most reactive.

Photooxidation was performed by passing air through a solution of cembrene in methanol until the maximum content of monohydroperoxides in the reaction mixture had been reached (monitoring by TLC). Rose Bengal was used as sensitizer, and the source of light was a high-pressure mercury lamp. The reaction mixture was treated with sodium tetrahydrobroate to decompose hydroperoxides and was chromatographed on silica gel to isolate the monohydric alcohols, formed with a total yield of 67% on the cembrene that had reacted. In addition, a mixture of nonpolar components not containing hydroxy groups (about 2%) and a polar fraction (25.4%) consisting of the products of the more far-reaching oxidation of cembrene were obtained.



I

Chromatography of the mixture of monohydric alcohols yielded four compounds. According to their IR spectra, they all contained a trans-disubstituted double bond (980 cm^{-1}) and, therefore, were products of the oxidation of cembrene at the trisubstituted double bond. One of them was obtained in the form of an oil with n_D^{17} 1.5314 with a yield of 25.4% (here

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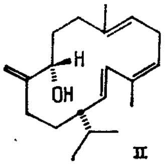
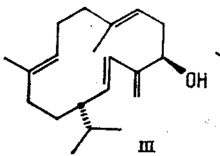
and below, the yields are given on the sum of the monohydric alcohols). A direct comparison with an authentic sample by TLC and by spectroscopy identified this alcohol as cembra-2E,4Z,7E,12(20)-tetraen-11S-ol (II), which has been obtained previously by the isomerization of 11S,12S-epoxycembrene on alumina [4].

The second alcohol, with mp 67-68°C (yield 8.2%), coincided with alcohol (II) in TLC on silica gel but differed from the latter in chromatography on silica gel impregnated with silver nitrate. This product proved to be cembra-2E,4(18),7E,11E-tetraen-5R-ol(III), as was established by a comparison with an authentic sample obtained by the lithium tetrahydroaluminate reduction of the known acetate of this compound [5].

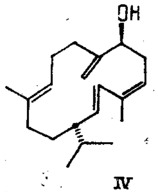
The third alcohol (an oil with n_D^{22} 1.5309, yield 11.5%) was a close isomer of compound (II), since, according to IR and NMR spectra, it contained the same functional groups. In view of the retention in it of a conjugated diene system shown in the UV spectrum (λ_{max} 240 nm, log ε 4.27), it was possible to suggest formula (IV) for this compound and this was confirmed by NMR results using double resonance. It was established that one of the two magnetically nonequivalent protons at C_6 (multiplet at 2.63 ppm) had spin–spin coupling with a proton geminal to a hydroxy group (H_7, doublet of doublets at 4.07 ppm, J = 10 and 4 Hz) and with one olefinic proton (H_5, multiplet at 5.3 ppm). An analogous three-proton system has been found previously in cembra-2E,7E,11E-triene-4S,5R-diol [5].



II



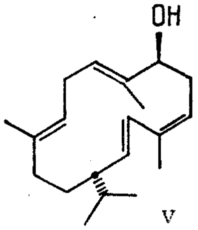
III



IV

The configuration of the asymmetric center at C_7 in alcohol (IV) was established on S on the basis of an observation of a positive Cotton effect in the circular dichromism curve of the o-nitrobenzoate of this alcohol [6].

The $\Delta^{8(9)}$ isomer of alcohol (IV) – (V) – had been obtained previously by the isomerization of 7S,8S-epoxycembrene on alumina having Brockmann activity II. It was found that when more active alumina was used (activity grade I-II) isomerization takes place less actively and a mixture of the alcohols (V) and (IV) (4:3 according to the NMR spectrum) is formed. According to TLC and to NMR spectroscopy, the samples of the alcohol (IV) obtained by the photooxidation of cembrene and by the isomerization of 7S,8S-epoxycembrene were identical.



V

The fourth alcohol among the products of the photooxidation of cembrane was obtained with a yield of 48.5% in the form of an oil with n_D^{20} 1.5290. According to the results of high-resolution mass spectrometry, it had the empirical formula $C_{20}H_{32}O$ and was an isomer of alcohols (II), (III), and (IV). The absence from the NMR spectrum of the compound isolated (Fig. 1) of the signal of a carbinol proton indicated that it was a tertiary alcohol, as was also shown by the presence in its NMR spectrum of the signal of a tertiary methyl group (singlet at 1.16 ppm, 3 H) geminal to a hydroxy group. Three possible structures may be suggested for this alcohol, corresponding to the attack of singlet oxygen on each of the three trisubstituted double bonds of cembrene (VI, VII, and VIII). The choice between them was made in favor of formula (VI) on the basis of the NMR spectrum, in which the signals of allyl protons present in a C=C–CH–C=C grouping were observed in the 2.3-2.9 ppm region (Fig. 1)[7].

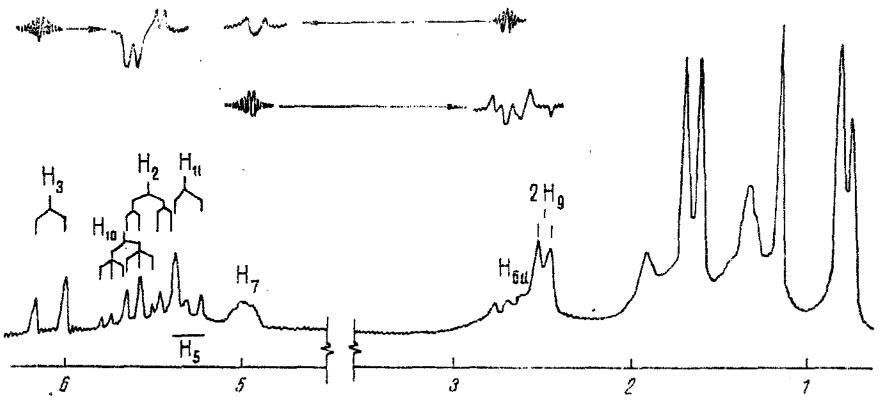
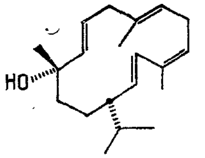
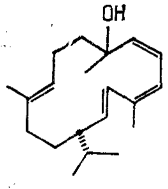


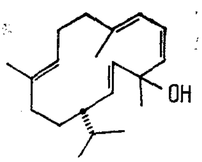
Fig. 1. NMR spectrum of the alcohol (VI) (100 MHz). The results of experiments using double resonance are shown at the top.



VI



VII



VIII

The correctness of structure (VI) for the compound isolated was confirmed by a more detailed analysis of the NMR spectrum using double resonance and the INDOR method and by comparing the spectra recorded on instruments with different working frequencies (60 and 100 MHz). The interpretation of the signals of the olefinic protons was considerably simplified by using a shift reagent — europium dipivaloylmethanate (Fig. 2). A comparison of the NMR spectra of the compound obtained with that for cembrene [8] showed that it retained the characteristic systems of cembrene protons H_5—H_{6a}—H_7 and H_2—H_3 (AB part of a ABX system). The doublet at 2.58 ppm (2 H, J = 6.5 Hz) due to the two magnetically equivalent protons at C_9 was converted into a singlet on double resonance with saturation of the signal at 5.65 ppm (1 H, H_{10}, doublet of triplets, $J_{10,9}$ = 6.5 Hz, $J_{10,11}$ = 16 Hz). In its turn, the proton giving a signal at 5.65 ppm (H_{10}) forms an AB system with the proton the signal of which appears in the form of a doublet with its center at 5.31 ppm (H_{11}, see Fig. 2). The value of the coupling constant in these protons (16 Hz) shows that they are present at a trans-disubstituted double bond. Thus, in this compound the second disubstituted double bond has the trans configuration. The presence of this bond adjacent to the hydroxy grup is confirmed by the pronounced downfield shift of the H_{10} and H_{11} signals in the NMR spectrum (Fig. 2) observed on the addition of the shift reagent.

The results obtained show that the photooxidation of cembrene takes place extremely selectively — it is its nonconjugated double bonds that are mainly involved in the reaction. The conjugated double bonds either do not take part in the reaction (bond at C_2) or are affected to a small degree (bond at C_4, yield of product (III) 8.2%). On the other hand, the selectivity of the reaction is also shown in the amounts of products formed. With attack of the three trisubstituted double bonds it is possible to expect the formation of 18 isomeric monohydroperoxides although in actual fact only four compounds are formed in appreciable amounts. Alcohols (II), (IV), and (VI) correspond to the splitting out of allyl hydrogen atoms from that side of the plane of the double bond on which the two alkyl substituents are located. This observation is in harmony with literature information on the direction of the shift of a double bond on photooxidation [9]. An important stereochemical aspect of the reaction is the formation in each case of one of the two possible epimers with respect to the asymmetric center including the hydroxy group, which indicates its high stereospecificity.

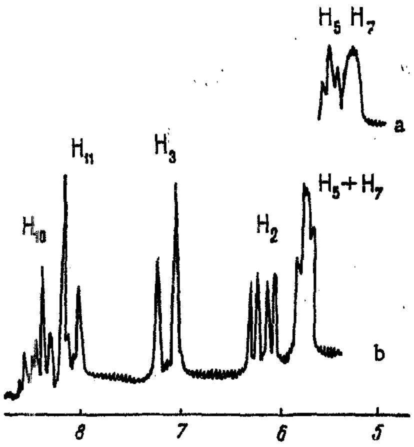


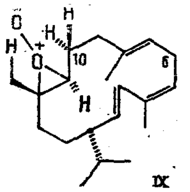
Fig. 2. Fragments of the NMR spectrum of the alcohol (VI) (100 MHz) recorded with the addition of 20 mg (a) and of 50 mg (b) of the shift reagent (europium trisdipivaloylmethanate) to 50 mg of the alcohol (VI).

The mechanism of the oxidation of olefins by singlet oxygen to allylic hydroperoxides giving alcohols after reduction have been the subject of broad discussion for many years [10]. In early papers it was assumed that the formation of hydroperoxides takes place through a six-membered transition state (concerted "ene" mechanisms) [11]. However, the results of investigations performed recently using labeled compounds have permitted other authors to give their preference to a perepoxide mechanism [12]. The formation of an intermediate or quasi-intermediate perepoxide particle in reactions of olefins with singlet oxygen is also confirmed by quantum-mechanical calculations [13], and the polar nature of the perepoxide appears, for example, in the formation of cyclic oxides in the photooxidation of cis-abienol [14].

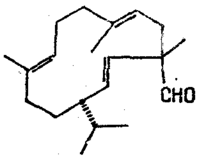
Taking into account the preservation of the orientation of the double bonds in the cembrene molecule with respect to the ring on its passage from the solid state to solutions [4] and assuming that the interaction of cembrene with singlet oxygen takes place by the perepoxide mechanism, it may be expected that the intermediate or quasi-intermediate perepoxide particles corresponding to the attack of singlet oxygen on the C_7 and C_{11} double bonds of cembrene will have the 7S,8S and 11S,12S configurations, leading in the final account to alcohols with the S configuration. In actual fact, alcohols (II) and (IV) have the 11S and 7S configurations, respectively, and for alcohol (VI) the configuration is assumed to be S on the basis of the photooxidation mechanism and the known [4, 15] orientation of the C_{11} double bond in the conformation of cembrene.

It is interesting to note that the oxidation of cembrene at the C_7 double bond takes place selectively with the formation of the product of the detachment of a hydrogen atom only from a methyl group, although analogous aliphatic trisubstituted olefins usually give a mixture of secondary and tertiary alcohols [9]. The C_{11} double bond of cembrene exhibits normal behavior in this respect, in spite of the fact that the cembrene molecule is conformationally immobile. An explanation of these facts can be obtained by considering the geometric parameters of the cembrene molecule calculated from Drew's results [15]. It was found that the hydrogen atoms at C_6 and C_{10} are oriented differently with respect to the plane of the neighboring bonds (Fig. 3, projections a and b). While the α-hydrogen atom at C_{10} is in a very favorable position for its participation in the reaction [16] (IX), both hydrogen atoms at C_6 are located less favorably.

In addition to the alcohols isolated, their initial mixture was shown by TLC to contain in the form of traces an unidentified compound chromatographically very close to the alcohol (IV). It is possibly the allyl isomer analogous to the alcohol (VI).



IX



X

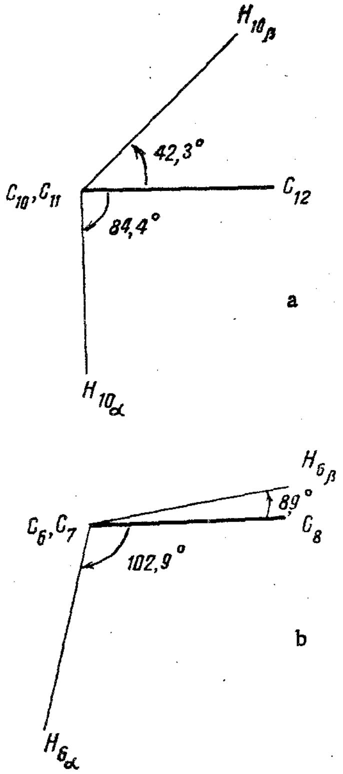


Fig. 3. Orientation of the allyl methylene groups with respect to the plane of the neighboring double bonds in the cembrene molecule: a) C_{10} methylene group; b) C_6 methylene group.

The nonpolar fraction of the photooxidation products contained more than 50% of a compound which, after its purification, was identified as the aldehyde (X), which has been obtained previously by the isomerization of 4S,5R-epoxycembrene on silica gel [4]. The aldehyde (X) cannot be a product of the photooxidation of cembrene, since it should be reduced when the reaction mixture is treated with sodium tetrahydroborate, as was confirmed in a model experiment. Consequently, it is formed from a noncarbonyl precursor during the chromatography of the photooxidation products after their treatment with sodium tetrahydroborate. This precursor is, most probably, 4S,5R-epoxycembrene formed by the oxidation of cembrene by molecules of triplet oxygen. As has been shown by Shimizu [17], this process does in fact lead to epoxides. In the decomposition of the unstable 4S,5R-epoxycembrene during its chromatography on silica gel, the aldehyde (X) is not the main product [4], the main directions of the reaction being hydration at the epoxy ring and a hydride shift from C_5 to C_4. The increased content of the aldehyde in the reaction mixture after its passage through silica gel [4] as compared with the other products of the decomposition of 4S,5R-epoxycembrene is due to the influence of the solvent — methanol — in which the reaction mixture was transferred to the column of silica gel after its treatment with sodium tetrahdroborate. In actual fact, a model mixture of epoxycembrenes obtained as described previously [4] gives a 2.6 times greater yield of the aldehyde (X) if it is transferred to the silica gel column in methanol solution and not in petroleum ether. This increase in the yield of the aldehyde (X) was determined after the recording of the NMR spectra of the mixtures of products obtained after the passage of the total epoxycembrenes through a column filled with silica gel (using diethyl ether as eluent). It was expressed in a 2.6-fold increase of the integral intensity of the signal of the aldehydic proton (9.25 ppm) of the aldehyde (X) with respect to the integral intensity of the signals of unchanged 7,8- and 11,12-epoxycembrenes [4] on passing from the mixture of epoxycembrenes transferred to the column in the form of a solution in petroleum ether to that transferred in methanol solution.

EXPERIMENTAL

The instruments and chromatographic methods used have been described previously [18]. Angles of optical rotation were measured for solutions in chloroform, NMR spectra were obtained for solutions in carbon tetrachloride (with hexamethyldisiloxane as internal standard; δ scale); UV spectra were recorded for solutions in ethanol, and IR spectra for solutions in carbon tetrachloride.

Photooxidation of Cembrene. A mixture of 3.00 g of cembrene and 0.30 g of Rose Bengal in 100 ml of methanol was irradiated at 22°C in a quartz cell with the light of a high-pressure mercury lamp (DRSh-500) with the passage of air through the reaction mixture for 4 h. The solution obtained was evaporated in a rotary evaporator at 35°C to 1/3 of its original volume and was then cooled to 0°C and over 30 min 0.70 g of sodium tetrahydroborate was added to it in portions. The resulting reaction mixture was evaporated in the rotary evaporator to a volume of 10 ml and was transferred to a chromatographic column filled with 100 g of air-dry silica gel. Washing the column with petroleum ether–diethyl ether (1:1) eluted a mixture of reaction products (monitoring by TLC). The sodium hydroxide and the bulk of the Rose Bengal remained in the column. The reaction products (3.50 g) were chromatographed on silica gel. This gave successively 1.20 g of unchanged cembrene, 0.05 g of a fraction of nonpolar compounds, 1.22 g of a fraction of monohydric alcohols (alcohol II, III, IV, and VI), and 0.71 g of a fraction of polar compounds which was not investigated further.

Separation of the Fraction of Monohydric Alcohols. The chromatography of the fraction of monohydric alcohols (1.22 g) on 100 g of air-dry silica gel gave successively 0.47 g of a mixture of the alcohols (II) and (III), 0.59 g of the alcohol (VI) (yield 48.5%; here and below the yields are given on the cembrene that reacted), and 0.14 g of the alcohol (IV) (yield 11.5%).

The mixture of alcohols (II) and (III) was separated by chromatography on silica gel impregnated with silver nitrate (5%). This gave successively 0.21 g of the alcohol (II) (yield 25.4%) in the form of an oil with n_D^{17} 1.5314. $[\alpha]_D^{17}$ + 47.3° (c 5.92), the IR, UV, and PMR spectra of which coincided with those for an authentic sample, and 0.07 g of the alcohol (III) (yield 8.2%) in the form of colorless crystals with mp 67-68°C (from hexane) and $[\alpha]_D^{17}$ + 48.8° (c 1.64), giving no depression of the melting point with an authentic sample.

Synthesis of 5R-Cembra-2E,4(18),7E,11E-tetraen-4-ol (III). The acetate of the alcohol (III) (0.01 g), obtained from cembrene by a published method [5], was dissolved in 20 ml of absolute diethyl ether, and 0.1 g of lithium tetrahydroaluminate was added to the resulting solution. After the reaction mixture had been kept for 1 h at room temperature and had been worked up in the usual way, 0.08 g of the alcohol (III) was obtained in the form of colorless crystals with mp 67-68°C (from hexane) $[\alpha]^{20}$ + 40α (c 8.1), the IR, UV, and NMR spectra of which coincided with those for a sample of the alcohol (III) obtained by the photooxidation of cembrene.

The Alcohol (IV) (1S,7S-Cembra-2E,4A,8(19),11E-tetraen-7-ol). Colorless oil with n_D^{22} 1.5309 and $[\alpha]_D^{23}$ – 16.1° (c 4.96), UV spectrum, λ_{max}: 240 nm (log ε 4.27), IR spectrum, ν_{max}, cm^{-1}: 3080, 1650, 905 (>C=CH$_2$), 980 (trans-disubstituted double bond), 3620 (OH). NMR spectrum, ppm: 1.50 and 1.71, 3 H each, singlet, C_{12}—CH_3 and C_4—CH_3, respectively, 4.07 ppm, 1 H, doublet of doublets, H_7, $J_{7,6a}$ = 10.0 Hz, $J_{7,6b}$ = 4.5 Hz, 4.72 and 4.82, narrow multiplets, 1 H each, protons of an exomethylene group, 4.90-5.40, multiplet, 2 H, H_5 and H_{11}, 5.02, doublet of doublets, 1 H, H_2, $J_{2,1}$ = 8 Hz, $J_{2,3}$ = 15 Hz, 6.09 ppm, doublet, 1 H, H_3, $J_{3,2}$ = 15 Hz, 2.4-2.9 ppm, multiplet, 1 H, H_{6a}.

The Alcohol (VI) (1S,12S-Cembra-2E,4Z,7E,10E-tetraen-12-ol). Colorless oil with n_D^{20} 1.5290 and $[\alpha]_D^{20}$ + 1 — 26.2°(c 12.2). NMR spectrum — Figs. 1 and 2. UV spectrum, λ_{max}: 244 nm (log ε 4.10). IR spectrum, ν_{max}, cm^{-1}: 980 (trans-disubstituted double bond, the band has approximately twice the integral intensity of that for the alcohol (IV)), 3620 (OH).

The Aldehyde (X). The chromatography of 0.05 of the fraction of nonpolar products of the photooxidation of cembrene on 20 g of silica gel yielded 0.03 g of the aldehyde (X) in the form of an oil which was identical according to TLC, and IR and NMR spectroscopy with an authentic sample of the aldehyde (X) obtained by a method described previously [4].

SUMMARY

1. The photooxidation of cembrene by singlet oxygen is a stereoselective reaction and is analogous stereochemically to the epoxidation of cembrene with peracids.

2. In the photooxidation of cembrene by singlet oxygen all the trisubstituted double bonds of cembrene are affected, but the dominating direction of the reaction is an attack of the singlet oxygen on the C_{11} double bond.

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TRITERPENE GLYCOSIDES OF *Astragalus* AND THEIR GENINS.
II. THE STRUCTURE OF CYCLOSIEVERSIGENIN

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The bitter plant *Astragalus sieversianus* has yielded a new isoprenoid cyclosieversigenin the structure of which has been established on the basis of spectral characteristics and chemical transformations as 20(S),24(R)-epoxycycloartane-3β,6α,16β,25-tetraol.

The wide genus *Astragalus* (family Leguminosae), which is represented in the flora of the USSR by almost 850 species, has been studied little in the chemical respect. Of its low-molecular weight compounds, there is only a certain amount of information on the flavonoids [1]. We have now investigated the isoprenoids of the Central Asian plant *Astragalus sieversianus* Pall.

The sum of the extractive compounds obtained from the roots by extraction with methanol was subjected to hydrolysis with 8% sulfuric acid. From the reaction products we isolated substances (I) and (IV) with close R_f values — 0.35 and 0.42 respectively.

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