THE STEREOCHEMISTRY OF CEMBRENE AND RELATED DITERPENOIDS

V. A. Raldugin, A. I. Rezvukhin,
and V. A. Pentegova

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Cembrane diterpenoids are a comparatively small group of natural compounds. In the present paper we give information on the stereochemistry of the cembrane diterpenoids isolated from the oleoresin of Pinus [1-3].

As has been shown by Dauben [4] and Kobayashi [5], cembrene has the structure (1) with a trans-disubstituted double bond, the S configuration of the asymmetric center, and an undetermined configuration of the trisubstituted double bonds. In the NMR spectrum (60 MHz) of this diterpenoid, they identified the signals from H_3, C_4-Me, and the isopropyl group.

We have performed a fuller assignment of the signals in the NMR spectrum (100 MHz) by using double and triple resonance (Fig. 1). One of the protons of the C_6 methylene group (H_{6a}) resonates at 3.00 ppm, and the signal of the other (H_{6b}) is masked by the signals of the allyl protons. For the low-field part of the spectrum we found the following parameters: H_3 – 6.04 ppm, $J_{2,3}=15.5$ Hz; H_5 – 5.48 ppm, $J_{5,6a}=6.0$ Hz, $J_{5,6b}=9.0$ Hz; H_2^* – 5.07 ppm, doublet of doublets, $J_{1,2}=9.0$ Hz, $J_{2,3}=15.5$ Hz; H_7 – 5.02 ppm, doublet of multiplets, $J_{7,6a}=11$ Hz, $J_{7,6b}=2$ Hz; H_{11} – 4.48 ppm, doublet of multiplets, $J=6$ Hz.

On double resonance with saturation of the H_{11} signal, the amplitude of the methyl singlet at 1.50 ppm increased, with a simultaneous decrease in its width at half-height. The second methyl signal, located at 1.58 ppm, remained unchanged in this experiment. Consequently, the signal at 1.50 ppm relates to the $C_{12}-$Me and that at 1.58 ppm to the C_8-Me.

On saturation of the C_4-Me signal (1.75 ppm), the relative integral intensity of the H_5 signal rose by 15%. The positive intramolecular nuclear Overhauser effect [7] shows the cis configuration of the C_4-C_5 double bond. The $C_{11}-C_{12}$ double bond has the trans configuration, which is shown by the absence of an increase in the integral intensity of the H_{11} signal on saturation of the $C_{12}-$Me signal. To determine the configuration of the C_7-C_8 double bond in (1) we used an indirect method. The hydrogenation of (1) over Raney nickel gave a mixture of two dihydro derivatives containing no trans-disubstituted double bonds (IR spectra). One of them, according to its NMR and NMDR spectra (Fig. 2) contained a $=CH-CH_2-CH=C(CH_3)-$ grouping with magnetically nonequivalent protons of the methyl group, and it is therefore 2,3-dihydrocembrene. The absence from the NMR spectrum of the second dihydro derivative (Fig. 3) of resonance absorption at 2.25-4.00 ppm shows [8] that this compound is 2,5-dihydrocembrene (2). On double resonance with saturation of the combined signal of its three methyl groups (1.54 ppm), the relative integral intensity of the multiplet of the three olefinic protons did not increase, which shows the trans configuration of all the double bonds in (2) and the trans configuration of the C_7-C_8 double bond in (1).

The two other cembrene diterpenoids – isocembrene (3) [2] and isocembrol [2, 6] – have trisubstituted double bonds in the trans configuration, since by the dehydration of isocembrol under mild conditions ($POCl_3$/Py, 0°C) we obtained a mixture of cembrene and isocembrene (85 : 15).

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*The assignment by Kimland and Norin [6] of the multiplet at 5.51 ppm in the NMR spectrum (60 MHz) of cembrene to H_2 is erroneous.

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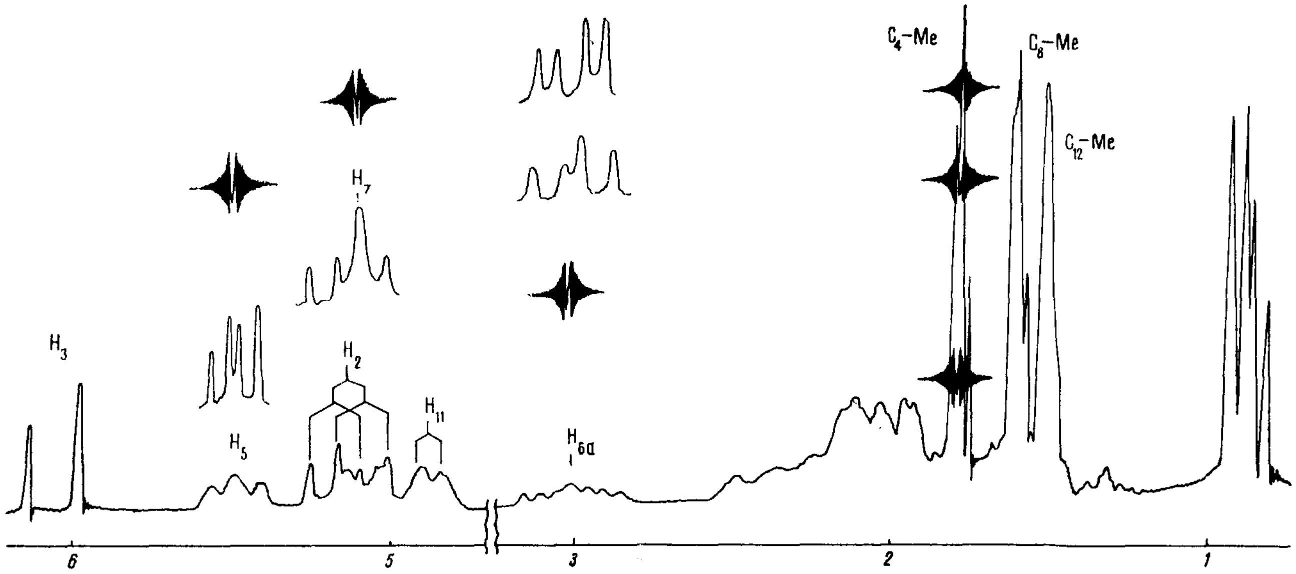


Fig. 1. NMR spectrum of cembrene (1) (100 MHz).

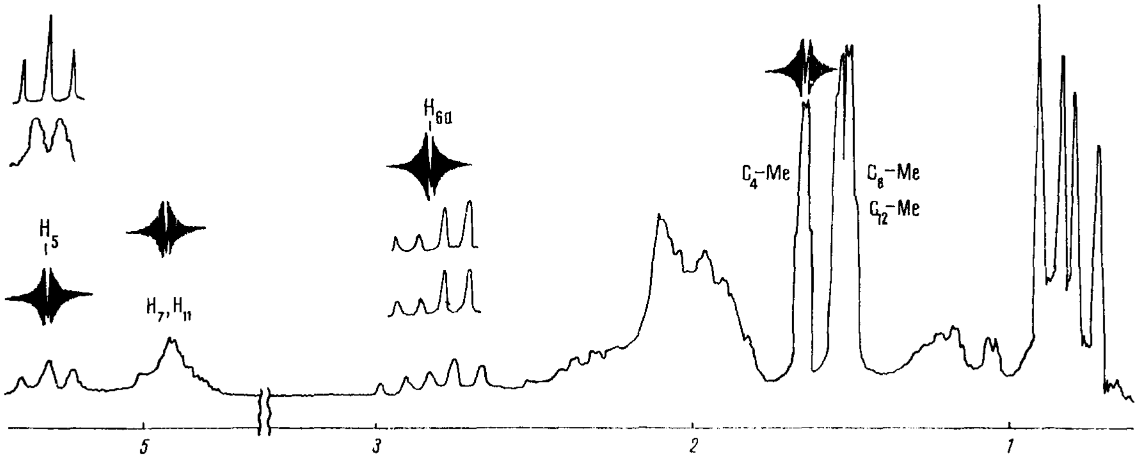


Fig. 2. NMR spectrum of 2,3-dihydrocembrene (100 MHz).

In the chain of proofs of the structure (1) described by Dauben [4], an experiment was performed on the preparation of 2,3-dihydrocembrene by the hydrogenation of (1) over Pd/C. However, the specific rotation of 2,3-dihydrocembrene given by Dauben $[\alpha]_D^{24}$ −28°, (chloroform)] showed that he apparently took 2,5-dihydrocembrene with only a low content of 2,3-dihydrocembrene. For (2) we found $[\alpha]_D^{18}$ −29.3°, and for 2,3-dihydrocembrene $[\alpha]_D^{23}$ +130° (chloroform). In addition to this, 2,3-dihydrocembrene is a compound which crystallizes readily, while Dauben's dihydrocembrene was a liquid, like our sample of (2). By the hydrogenation of (1) over Pd/$CaCO_3$ in ethyl acetate, as on hydrogenation over Pd/C, we obtained (2) as the predominating product.

According to the UV spectrum [2], the conjugated diene system in (3) is in the S-trans conformation. The S-trans conformation of the conjugated diene system in (1) follows from the absence of a positive intramolecular Overhauser effect between H_3 and the C_4−Me (on saturation of the C_4−Me signal) and is confirmed by the value of ε at 245 nm in the UV spectrum of (1). These facts are in harmony with Haagen-Smit's hypothesis [1] of the S-trans conformation of the diene systems (1) made correspondingly from the absence of a reaction of (1) with maleic anhydride. Taking into account the S-trans conformation of the diene system in (1), from a consideration of a Dreiding model Dauben [4] assumed that the molecule of (1) with the trans configuration of all the double bonds was less preferred than a molecule with one cis bond.

In substance (2), the C_3−C_4 double bond has the trans configuration, which is interesting from the point of view of the stereochemistry of the 1,4- addition of hydrogen to 1,3-dienes. Wilson [9], studying

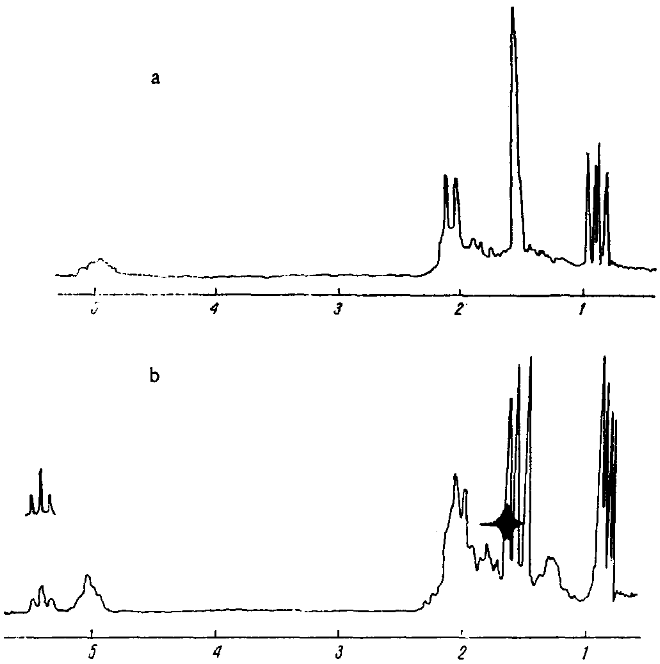
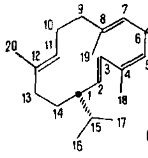
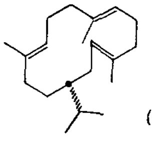


Fig. 3. NMR spectra (100 MHz) of 2,5-dihydrocembrene (2) (a) and of 2,18-dihydroisocembrene (4) (b).

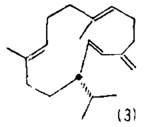
the mechanism of the hydrogenation of butadiene over Pd, concluded that cis- and trans-but-2-enes are formed, respectively, from the S-cis and S-trans conformers of butadiene.



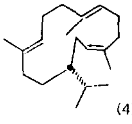
(1)



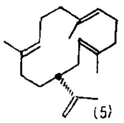
(2)



(3)



(4)



(5)

If the absence of conformational transformations of the semihydrogenated intermediates on Pd catalysts is the rule for the hydrogenation of 1,3-dienes (in neutral media at room temperature and atmospheric pressure), the formation of (2) from (1) and of the C_3-cis isomer (4) from (3) may be expected. In actual fact, we obtained 2,18-dihydroisocembrene (4) together with 2,3-dihydroisocembrene by the hydrogenation of (3) both over Pd/$CaCO_3$ and over Raney nickel, the isomer (2) not being detected in appreciable amounts. Structure (4) was also confirmed, as for (2), by the NMR spectrum (Fig. 3b), and the cis configuration of the newly formed C_3-C_4 double bond by the positive intramolecular Overhauser effect between C_4–Me and H_3. (The relative integral intensity of the triplet at 5.35 ppm increased by 20% on saturation of the methyl signal at 1.65 ppm, the chemical shift of which shows, according to Bates' rule [10], the presence of this methyl group on a double bond in the cis configuration.) The absence of isomerizing activity in the nickel catalyst used is shown by the fact that (4) was isolated unchanged when it was treated with hydrogen under the conditions of the hydrogenation of (1). The hydrogenation of (1) and (3) over Pd/$CaCO_3$ in the presence of piperidine, which inhibits the migration of double bonds [11], led to the same results as in the absence of piperidine.

Thus, the formation of (2) and (4) from (1) and (3), respectively, shows that the stereochemistry of the product of the addition of hydrogen reflects the S-trans conformation of the initial diene.

The recently described [3] cembrene diterpenoid neocembrene (5), on hydrogenation over $Pd/CaCO_3$, gave substance (2), identical with that obtained by the hydrogenation of (1) under the same conditions. Since for the hydrogenation of an unknown compound it is impossible to exclude the possibility of the migration of double bonds [11, 12], we performed a supplementary experiment on the correlation of (5) with (1). The use of Raney nickel [11] for the hydrogenation of (5) led to the same dihydro derivative (2) with $[\alpha]_D^{24}$ −20°. Consequently, neocembrene possesses the 1R configuration, like the other cembrane diterpenoids of Pinus, and all the trisubstituted double bonds in it have the trans configuration. This is the first time that neocembrene (5) has been isolated from the oleoresin of Pinus sibirica R. Mayr.

EXPERIMENTAL

The IR spectra were obtained on a UR-20 instrument in CCl_4; the specific rotations were determined on a Zeiss polarimeter and a Spectropol I spectropolarimeter in $CHCl_3$; and the NMR spectra were recorded of solutions in CCl_4 on Varian A-56-60A and Varian HA-100 instruments (with HMDS as the internal standard, its signal being taken as 0.05 ppm on the δ scale). The preparation of the samples (10-20% solutions in CCl_4; HMDS or $CHCl_3$ for the reference signal) and the experimental conditions of the observation of the nuclear Overhauser effect (on the Varian HA-100 instrument) were the same as in the work of Anet and Bourn [7]. The hydrogenations of (1) and (3) were performed at room temperature and atmospheric pressure until 1 mole of hydrogen had been absorbed (0.5-1 h). None of the dihydro derivatives obtained had maxima in the 210-400 nm region. The analyses of all the compounds corresponded to the calculated figures.

Hydrogenation of Cembrene (1). The hydrogenation of 100 mg of (1) in 5 ml of absolute EtOAc was performed over 20 mg of Raney nickel. The mixture of products contained, in addition to 2,3-dihydrocembrene and (2), present in a ratio of 2 : 3 (NMR spectrum), about 5% of tetrahydro derivatives. Chromatography on SiO_2 +5% of $AgNO_3$ yielded 30 mg of 2,3-dihydrocembrene, $C_{20}H_{34}$, and 50 mg of (2). The melting point of the 2,3-dihydrocembrene was 49-50°C (from ethanol), $[\alpha]_D^{23}$ +130° (c 3.68), IR spectrum, cm^{-1}: 855, 920, 1376, 1675, 3040. NMR spectrum, ppm: 0.75 and 0.86 (3H each, doublet, $J \approx 7.0$ Hz, methyls of an isopropyl group), 1.51 (6H, C_8-Me and $C_{12}-Me$), 1.64 (3H, C_4-Me), 2.68-3.00 (1H, H_{6a}), 4.71-5.10 (2H, H_7 and H_{11}), and 5.23 (1H, triplet of multiplets, $J=8$ Hz, H_5). Mol. wt. 274 (mass spectrometry).

2,5-Dihydrocembrene, $C_{20}H_{34}$ (2): n_D^{22} 1.5016, $[\alpha]_D^{18}$ −29.3° (c 3.07). IR spectrum, cm^{-1}: 850, 876, 1350, 1392, 1675, 3050. Mol. wt. 274 (mass spectrometry).

Hydrogenation of Isocembrene (3). The hydrogenation of 100 mg of (3) was performed in 10 ml of absolute ethanol containing 0.04 ml of piperidine over 15 mg of $Pd/CaCO_3$ (containing 5% of Pd). The mixture of products contained about 95% of 2,3-dihydrocembrene and (4) (3 : 2) (NMR spectrum). Chromatography of the mixture on SiO_2 +5% of $AgNO_3$ yielded 45 mg of 2,3-dihydrocembrene, $C_{20}H_{34}$, and 40 mg of (4). 2,3-Dihydrocembrene: n_D^{20} 1.5015, $[\alpha]_D^{24}$ +25.8° (c 7.28); IR spectrum, cm^{-1}: 894, 1650, 3080 $\left(\gt C=CH_2\right)$, 1677 $\left(\gt C=CH-\right)$, 1375, 1390; NMR spectrum, ppm: 0.78 and 0.81 (3H each, doublets, $J=7$ Hz, methyls of an isopropyl group), 1.52 and 1.57 (3H, resolved singlets, C_8-Me and $C_{12}-Me$), 4.73 (2H, narrow multiplet $\gt C=CH_2$), 4.74-5.24 (2H, multiplet, H_7 and H_{11}). Mol. wt. 274 (mass spectrometry).

2,18-Dihydroisocembrene, $C_{20}H_{34}$ (4): n_D^{20} 1.5020, $[\alpha]_D^{24}$ −85° (c 8.04); IR spectrum, cm^{-1}: 1375, 1390, 1675. Mol. wt. 274 (mass spectrometry).

Hydrogenation of Neocembrene (5). The compound isolated from the oleoresin of Pinus sibirica R. Mayr by a method analogous to that described previously [3] and having n_D^{24} 1.5090, $[\alpha]_D^{20}$ −2.1°, $[\alpha]_{383}^{20}$ −14.5° (c 0.934), (200 mg) was hydrogenated for 6 h over 100 mg of Raney nickel in 10 ml of a mixture of absolute EtOAc and absolute EtOH (1 : 1). Chromatography of the product on 30 g of SiO_2 yielded 90 mg of unchanged (5) and 80 mg of (2) with $[\alpha]_D^{24}$ −20° (c 9.48).

SUMMARY

1. It has been shown that the nonconjugated trisubstituted double bonds of cembrene, isocembrene, neocembrene, and isocembrol have the trans configuration, and the conjugated trisubstituted double bond of cembrene possesses the cis configuration.

2. The asymmetric center of neocembrene has the R configuration.

3. The stereochemistry of the product of the addition of hydrogen to cembrene and isocembrene on Pd and Ni catalysts is apparently determined solely by the conformation of the conjugated diene system in these diterpenoids.

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