OXIDATIVE TRANSFORMATIONS OF CEMBRANE DITERPENOIDS

I. OXIDATION OF CEMBRENE WITH CHROMIUM TRIOXIDE

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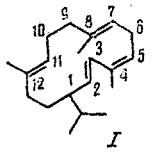
The diterpene hydrocarbon cembrene (I) is known as a component of the oleoresin of a number of conifers of the family Pinaceae Lindl. [1-6]. Its structure was established by Dauben [7] and Kobayashi [8]. Although cembrene is a comparatively accessible compound, its chemical transformations have scarcely been investigated. There is information in the literature on the products of the partial hydrolysis [7, 9], the photolysis [10], the isomerization with iodine [11], and the acid cyclization [10] of cembrene. Great interest is presented by the oxidative transformations of cembrene and related compounds, since they may serve as models for biosynthetic transformations of simple cembrene diterpenoids into the highly oxidized cembrene derivatives found in nature. They also form methods of approach to physiologically active substances and, in particular, to analogs of juvenile hormones.

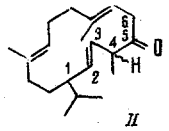
In the present paper we describe the main products formed in the oxidation of cembrene by chromium trioxide under mild conditions (in aqueous acetone) and in a strongly acid medium (oxidation by the Jones reagent).

The oxidation of cembrene with the Jones reagent gave a very complex mixture of compounds from which, after the separation of substances of an acid nature and unchanged cembrene, we isolated six oxygen-containing substances denoted in the order of their elution from a column of SiO_2 as substances A, B, C, D, E, and F. Their yields were 2, 10, 5, 2, 10, and 30%, respectively (calculated on the cembrene that had reacted).

Substances A and B are isomers of the general formula $C_{20}H_{32}O$. Their IR spectra practically coincide and contain the bands of a nonconjugated carbonyl group (1720 cm^{-1}) and of a trans-disubstituted double bond (980 cm^{-1}). According to their UV spectra, which are also very similar, these compounds contain a conjugated dienic or α-enonic system, and in each of them the oxo group is in the β position to a double bond, as is shown by the value of the molar extinction of the absorption band of the carbonyl group [λ_{max} 297 nm (ε 210) and max 297 nm (ε 209), respectively]. In the NMR spectrum of substance B (Fig. 1, the values of the chemical shifts are given for the centers of the signals) there are the signals of the methyls of an isopropyl group (two doublets at 0.74 and 0.78 ppm, J = 7.0 and 7.0 Hz), of a secondary methyl group (doublets at 1.01 ppm, J = 7.0 Hz), of two methyl groups on nonconjugated double bonds (at 1.42 and 1.45 ppm), and also two groups of signals in the 2.6-3.3 and 4.8-5.6-ppm regions the analysis of which was performed by means of double resonance. The spectral information obtained enables us to propose the structure of cembra-2,7,11-trien-5-one (II) for substance B.



I



II

The NMR spectrum of substance A was qualitatively the same as the NMR spectrum of the ketone (II) and differed from the latter only in the values of the chemical shifts of the signal and of the spin–spin coupling constants. In view of this, and also of the fact that when the ketone (II) was treated with sodium ethoxide in ethanol it was partially converted into substance A, it may be concluded that substance A is the epimer of ketone (II) at C_4.

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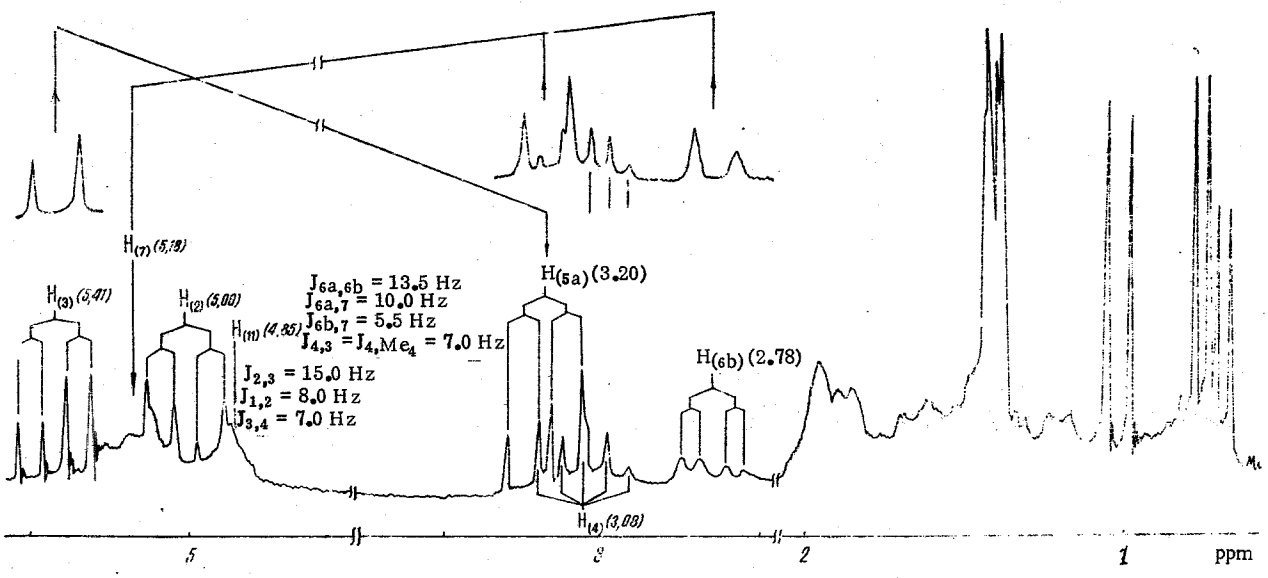
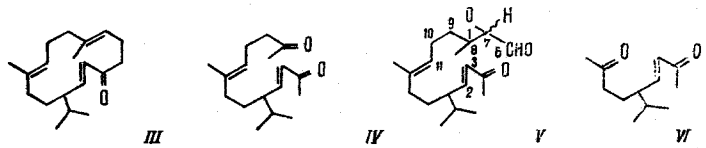


Fig. 1. NMR spectrum of substance B (II) (100 MHz, in benzene).

Substance C with $[\alpha]_D^{20}$ + 44° (c 2.0) and n_D^{22} 1.5070 proved to be identical with the norcembrane ketone (III) which we obtained previously [12] by the autooxidation of isocembrene, and also by its oxidation with potassium permanganate in aqueous pyridine. The ketone (III) is apparently a product of the oxidation of the isocembrene formed from cembrene as a result of reversible acid isomerization.

Substance D, according to its NMR, IR, and UV spectra, was identical with (3E, 8E)-5-isopropyl-8-methyltrideca-3,8-dien-2,12-dione (IV) obtained previously by Roberts [13] from the cleavage of α-duva-4,8,13-trien-1,3-diol (cembra-2,7,11-trien-4,6-diol). Roberts assigned the cis configuration to the C_8 double bond of α-duva-4,8,13-trien-1,3-diol, which, as Courtney [14] found, is erroneous.



Substance E, having the molecular formula $C_{19}H_{30}O_3$, appeared to be an individual substance according to TLC on SiO_2 and SiO_2 + 5% of $AgNO_3$, but its NMR spectrum (Fig. 2) shows that it is a mixture of two diastereoisomeric compounds of the general formula (V)* differing by the configuration of one of the two asymmetric centers at C_7 and C_8. It is interesting to note that the signals of the H_2 proton in the diastereoisomers (V) appear at different resonance frequencies in spite of the considerable remoteness of this proton from the asymmetric centers at C_7 and C_8. The IR and UV spectra confirm the structure (V)† for these compounds [λ_{max} 228 nm (log ε 4.22) – α-enone; ν_{max}, cm^{-1}: 1720, 2730 (CHO), 1360, 1685 (α-enone), 995 (trans-disubstituted double bond)].

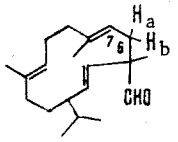
Substance F with $[\alpha]_D^{21}$ +6.05° (c 4.45) and n_D^{30} 1.4710 is, according to its spectra, identical with norsolanadione (VI), the product of the autooxidation of (+)-solanone [15].

The oxidation of cembrene with chromium trioxide in aqueous acetone also leads to a complex mixture of products from which we isolated the epimeric ketones (II), the diketone (V), an unresolvable mixture of the epoxy aldehyde (V), and also two new compounds which we have called substances G and H. The yields and ratios of the reaction products vary with slight changes in the experimental conditions, but the main components of the

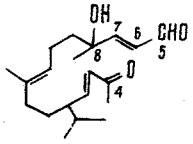
*Here and below the numbering of the atom remains the same as in the normal cembrene hydrocarbon skeleton.
†The epoxyaldehydes (V) are also formed by the oxidation of cembrene with chromium trioxide in pyridine. Under these conditions the possibility of the occurrence of acid-catalyzed rearrangements and isomerizations with the participation of the $C_{11}-C_{12}$ double bond is excluded.

mixture are always the ketones (II), the epoxy aldehydes (V), and substance H. Compounds (III) and (VI) were not detected in the reaction mixture.

Substance G with $[\lambda]_D^{23}$ + 10.5° (c 2.87) and n_D^{24} 1.5056 has the molecular formula $C_{20}H_{32}O$ and is an aldehyde (ν_{max}: 1730 and 2720 cm^{-1}) containing a transdisubstituted double bond (980 cm^{-1}) and a β-enone chromophore [λ_{max} 298 nm (ε 150)]. The NMR spectrum of this substance has the signals of the methyls of an isopropyl group (two doublets at 0.72 and 0.78 ppm, J = 6.3 and 6.3 Hz), of two methyl groups on nonconjugated double bonds (1.47 and 1.55 ppm), of a tertiary methyl group (single at 1.17 ppm), of six olefinic protons (unsymmetrical multiplet in the 4.65-5.40 ppm region), and of the proton of an aldehyde group attached to a quaternary carbon atom (single at 9.25 ppm). The spectral information obtained permits structure (VII) with a contracted cembrene ring to be put forward for substance G. The signal of one of the C_6 protons (H_{6a}) in the NMR spectrum of substance G is in a weaker field (doublet of doublets at 2.60 ppm, $J_{6a,7}$ = 11.0 Hz, $J_{6a,6b}$ = 14.0 Hz) than the signals of the other allyl protons. On doublet resonance with the superimposition of a second radio frequency field at 5.10 ppm (the region of the resonance of the H_7 proton), this signal is converted into a doublet with $J_{6a,6b}$ = 14.0 Hz, which is an additional confirmation of the correctness of structure (VII).



VII



VIII

Substance H with $[\alpha]_D^{28}$ − 8.35° (c 5.40) and n_D^{28} 1.5000 has the molecular formula $C_{20}H_{32}O_3$. According to its IR spectrum, it contains a tertiary hydroxy group (3615 cm^{-1}), an aldehyde group (2730 cm^{-1}), a conjugated carbonyl group (1675 cm^{-1}), and a trans-disubstituted double bond (980 cm^{-1}). The UV spectrum [λ_{max} 223 nm (log ε 4.14)] shows the existence of conjugation. It follows from these facts and from the NMR spectrum (Fig. 3, the values of the chemical shifts are given for the centers of the signals) that substance H possesses the structure (VIII), containing two trans-disubstituted double bonds. The identification of the proton multiplets in the 5.8-7.0 ppm region (Fig. 3) was performed by recording the NMR spectrum on an instrument with a working frequency of 60 MHz, and the assignment of the one-proton doublet of doublets with its center at 6.2 ppm to H_6 was confirmed by double resonance with the suppression of the signal of the aldehyde proton at 9.56 ppm.

The formation of all the compounds obtained can be explained within the framework of existing ideas on the oxidation of olefins by chromium trioxide [16, 17]. In a strongly acid medium (oxidation with the Jones reagent), the reaction takes place at all the trisubstituted double bonds of cembrene, and in a weakly acid medium the process is regiospecific – the $C_{11}-C_{12}$ double bond is not affected.

EXPERIMENTAL

The molecular formulas of all the compounds obtained were determined mass-spectrometrically on an MS 902 instrument; the IR spectra were recorded on a UR-20 spectrometer using solutions in carbon tetrachloride; the UV spectra (for solutions in ethanol) were obtained on a "Specord UV-VIS" spectrometer; and the NMR spectra on Varian HA-100 and Varian A-56-60 A instruments (using solutions in carbon tetrachloride with HMDS as internal standard, δ scale). The angles of optical rotation were determined on a Zeiss polarimeter for solutions in chloroform. Chromatography was performed with air-dry silica gel using mixtures of petroleum ether with increasing proportions of diethyl ether as the eluents.

Oxidation of Cembrene by the Jones Reagent. Cembrene (5 g) was dissolved in 70 ml of acetone, 7 ml of water were added, the solution was cooled to 0°C, and 20 ml of the Jones reagent were added slowly, dropwise. After being stirred for 30 min at 0°C, the reaction mixture was poured into 200 ml of a saturated aqueous solution of sodium chloride cooled to 0°C and was rapidly extracted with diethyl ether. The ethereal extract was washed with 5% aqueous sodium bicarbonate and dried with sodium sulfate, and the solvent was distilled off from it. The product (3 g) was chromatographed on 60 g of SiO_2. Petroleum ether eluted 1.5 g of unchanged cembrene and then the first epimeric ketone (II) (substance A) (0.07 g), $[\alpha]_D^{23}$ + 253.8° (c 1.3) and n_D^{25} 1.5055. NMR spectrum, ppm: 0.74 and 0.78, 3 H each, doublets, J = 6.7 and 6.7 Hz- methyls of an isopropyl group; 1.10 ppm, 3 H, doublet, J = 6.5 Hz – C_4-CH_3; 1.45 and 1.60, 3 H each, C_8-CH_3 and $C_{12}-CH_3$; 3.39 ppm, 1 H, doublet of doublets, J = 10.5 and 12.5 Hz, H_{6a}; 3.12 and 2.78 ppm, 1 H each, multiplets broadened because of long-range spin – spin coupling, H_4 and H_{6b}; 4.59 and 5.00 ppm, broad multiplets – H_{11} and H_7; 4.88 ppm, 1 H, doublet of doublets, H_2, $J_{1,2}$ = 8.0 Hz, $J_{2,3}$ = 15.5 Hz, $J_{2,4}$ = 2.0 Hz; and 5.43 ppm, 1 H, doublet of doublets, H_3, $J_{3,2}$ = 15.5 Hz, $J_{3,4}$ = 4.5 Hz.

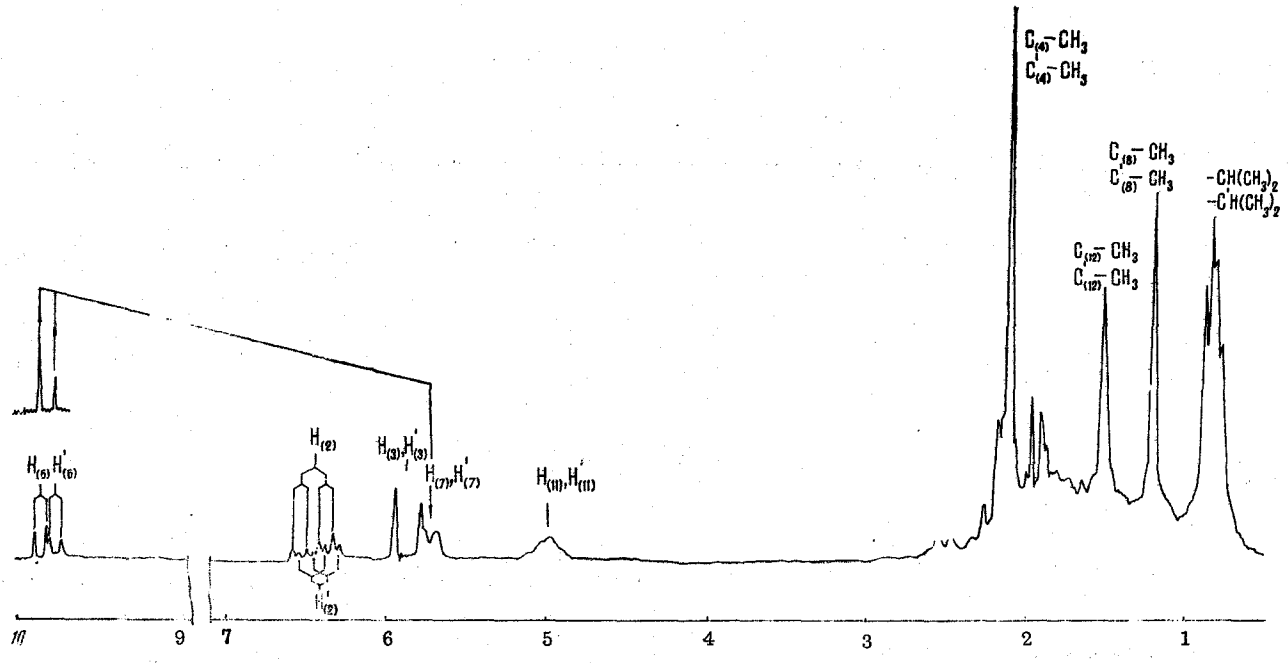


Fig. 2. NMR spectrum of substance E (V) (100 MHz).

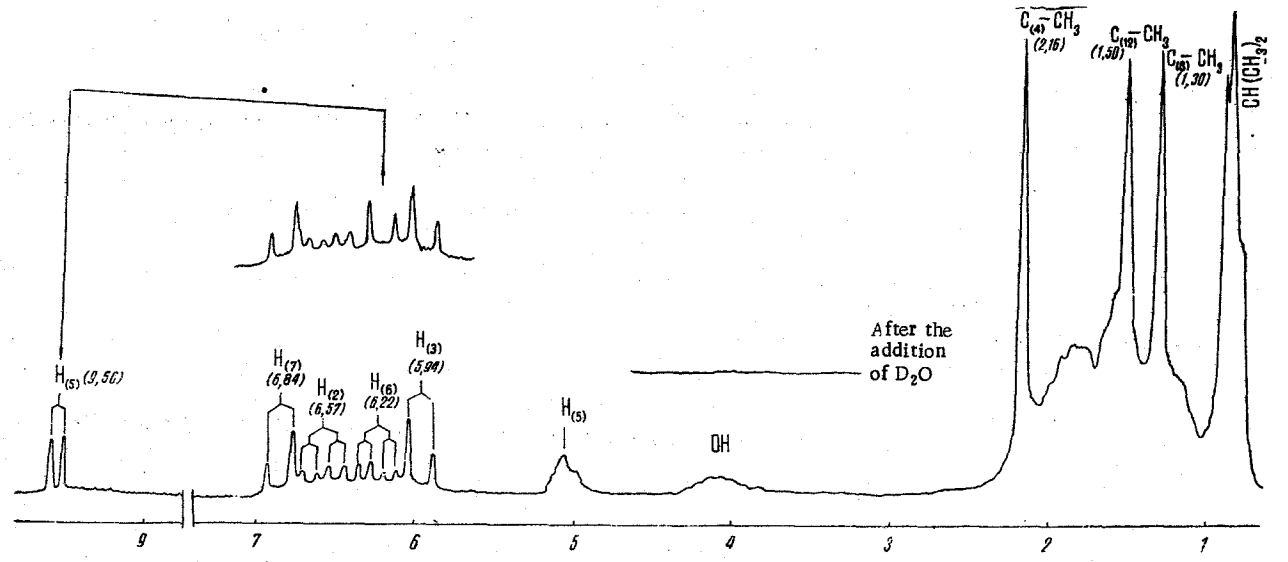


Fig. 3. NMR spectrum of substance H (VIII) (100 MHz).

Further elution yielded 0.35 g of substance B (epimer II) with $[\alpha]_D^{30}$ + 169.6° (c 6.0) and n_D^{20} 1.5080; 0.18 g of the ketone (III); 0.07 g of the diketone (IV) with n_D^{20} 1.4850; 0.35 g of a mixture of the epoxy oxo aldehyde (V) (colorless viscous oil); and 1.15 g of norsolanadione (VI).

Oxidation of Cembrene with Chromium Trioxide in Aqueous Acetone. A solution of 2.4 g of chromium trioxide in 7 ml of water was added to a solution of 5 g of cembrene in 70 ml of acetone cooled to 0°C. The vigorously stirred mixture was heated to room temperature and was then left for 18 h. After the same working up as in the preceding case, 4.6 g of a product were obtained which was chromatographed on 70 g of SiO_2. The following substances were eluted successively: 1.4 g of cembrene, 0.1 g of the aldehyde (VII), 0.5 g of a mixture of the epimeric ketones (II) with a predominance of the more polar epimer (substance B), 0.25 g of a mixture of unidentified substances, 0.07 g of the diketone (IV), 0.5 g of a mixture of the epoxy oxo aldehydes (V), 0.6 g of a complex mixture of unidentified substances, and 0.8 g of the hydroxy oxo aldehyde (VIII).

SUMMARY

1. The oxidation of cembrene with chromium trioxide in aqueous sulfuric acid (the Jones reagent) and in aqueous acetone has given norcembra-2,7,11-trien-4-one, norsolanadione, (3E, 8E)-5-isopropyl-8-methyltrideca-3,8-diene-2,12-dione, and five new compounds the structures of which have been established on the basis of their spectra.

2. Oxidation with chromium trioxide in aqueous acetone, in contrast to oxidation with the Jones reagent, takes place stereospecifically—the $C_{11}-C_{12}$ double bond of cembrene is not affected.

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ALKALOIDS OF Haplophyllum perforatum

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We are studying for the first time the alkaloids of the epigeal part of the plant Haplophyllum perforatum growing in the Dzhungarian Ala-Tau, Kazakh SSR. The plant, collected in the flowering period, was extracted with methanol. The methanolic extract was separated into acid, neutral, and basic fractions. From the basic fraction, comprising 0.32% of the weight of the dry plant, we obtained evoxine (I) [1], and the new alkaloids glycoperine (II) [2], and methylevoxine (III) [3], and from a neutral fraction the lignane eudesmin, the known alkaloids flindersine (IV) [4] and 7-isopentenyloxy-γ-fagarine (V) [5], and a new base—haplamine (VI) [6], which proved to be the main component (0.143% of the dry weight of the plant) of the mixture of bases. No alkaloids were found in the acid fraction. The total amount of bases obtained was 0.48% of the weight of the dry plant, and of these 1/3 was represented by the alkaloids isolated from the neutral fraction of the extract. Thus, the combined alkaloids of this plant can be evaluated both qualitatively and quantitatively only after separation of the basic and the neutral fractions of the extract.

Of the substances isolated, only evoxine and the lignane eudesmin had been obtained from this plant previously [7, 8]. Furthermore, we did not detect skimmianine, which is present in the plant H. perforatum

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