OXIDATIVE TRANSFORMATIONS OF CEMBRANE DITERPENOIDS.

II. CEMBRA-2,7,11-TRIENE-4,5-DIOLS

V. A. Raldugin, A. I. Rezvukhin,
L. Ya. Korotkikh, and V. A. Pentegova

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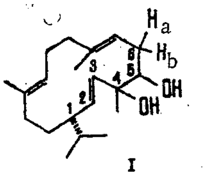
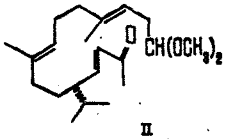
In a preceding communication [1], we described the isolation and determination of the structures of a number of products formed in the oxidation of cembrene with chromium trioxide in two polar media. When the reaction mixture in the oxidation of cembrene with chromium trioxide in aqueous acetone was carefully analyzed by TLC, we detected another product, which was isolated by chromatography on SiO_2. Its yield was comparatively low (about 2% for the reaction performed under the conditions described [1]). The substance obtained crystallized, but analysis by TLC on plates with SiO_2 + 5% of $AgNO_3$ showed that it consisted of a mixture of two similar compounds. The recrystallization of this mixture from hexane yielded the main component (substance A) with mp 61-62°C, $[\alpha]_D^{21}$ +34.4° (c 4.65); $C_{20}H_{34}O_2$ (high-resolution mass spectrometry). The UV spectrum of this compound contained no maxima in the 210-400 nm region, which shows the absence of a conjugated diene system. Its IR spectrum showed the absorption bands of a trans-disubstituted double bond (980 cm^{-1}) and of hydroxy groups (3610 cm^{-1} — free hydroxy group, and 3300-3550 and 3580 cm^{-1} — hydrogen bonds). The acetylation of substance A with acetic anhydride in pyridine gave a product with n_D^{19} 1.5030 and $[\alpha]_D^{20}$ +35.5° (c 7.05), the empirical formula of which ($C_{22}H_{36}O_3$) corresponded to a monoacetate of substance A. The IR spectrum of this monoacetate showed the absorption band of a tertiary hydroxy group (3610 cm^{-1}) and of an acetate carbonyl (1750 cm^{-1}). On the basis of the results obtained and the NMR spectrum of the monoacetate (Fig. 1, the assignment of the H_5, H_{6a}, and H_7 signals was performed with the aid of double resonance), it could be assumed that substance A is a secondary-tertiary diol — the product of the hydroxylation of cembrene at the C_4 double bond and has the structure expressed by formula (I). A proof of the correctness of the proposed structure is the formation of the dimethylacetal (II) when substance A was cleaved with periodic acid in hot methanol (Fig. 2).



I



II

Substance B, accompanying substance A, amounted to about 15% of the mixture of these substances, and its chromatographic isolation was difficult. Since, when the unresolved mixture of the two compounds was treated with periodic acid in methanol the complete conversion of the initial compounds gave a single product — the dimethyl acetal (II) — substance B must be a diastereoisomer of substance A. The monoacetate of substance B, isolated by chromatography of a mixture of the monoacetates of substances A and B on SiO_2 + 5% of $AgNO_3$ and having n_D^{21} 1.5020 and $[\alpha]_D^{21}$ +99° (c 2.47), on dehydration with phosphorus oxychloride in pyridine, gave the same allyl acetate (III) as was obtained by the dehydration of the monoacetate of substance A under the same conditions. Consequently, substances A and B, which were previously called "diol A" and "diol B" are (2E,7E,11E)-cembra-2,7,11-triene-4,5-diols (I) epimeric at C_4. The difference in the configurations at C_4 is clearly reflected in the NMR spectra of the acetates of the two diols. In the NMR spectrum of the acetate of diol B, the signal of the H_3 proton is shifted upfield as compared with that for diol A, which leads to

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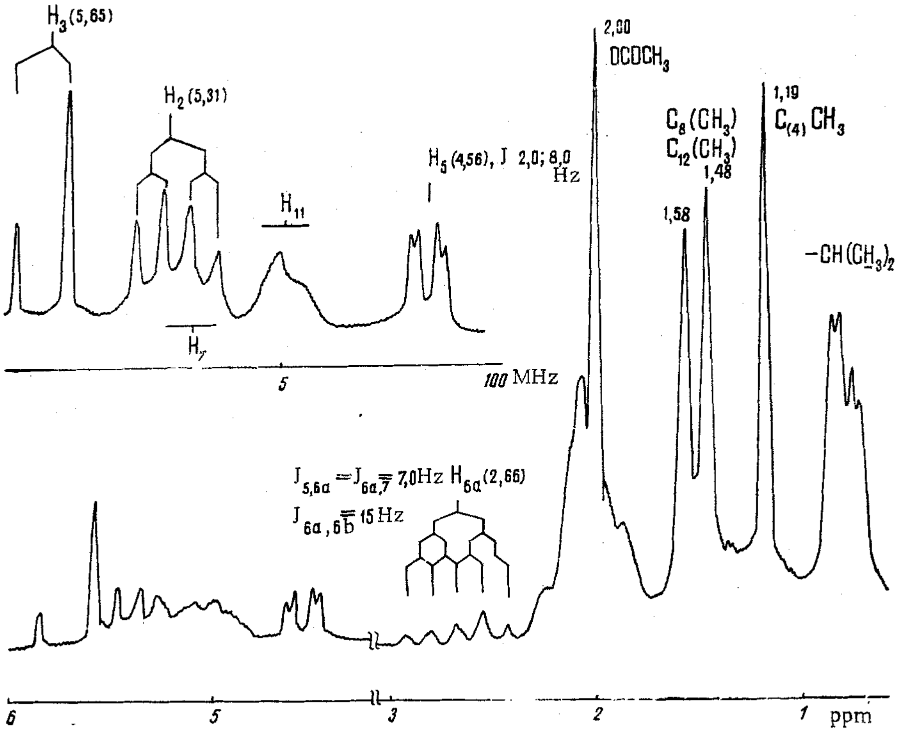


Fig. 1. NMR spectrum of the monoacetate of the diol A (I) (60 MHz, CCl_4).

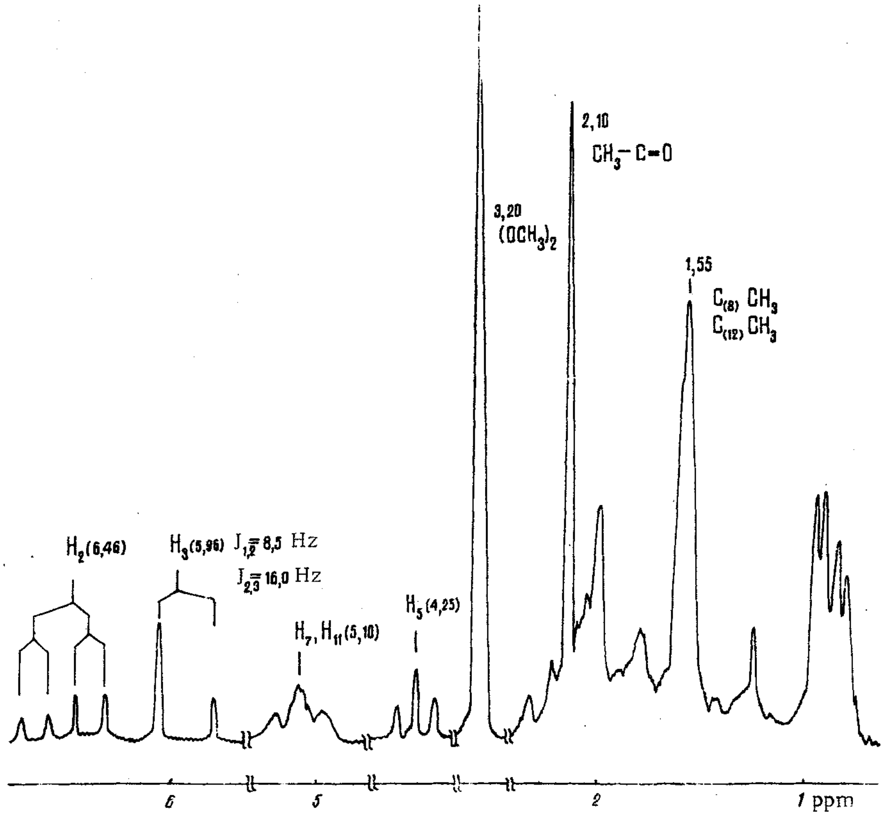
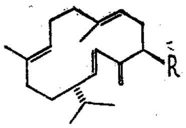


Fig. 2. NMR spectrum of the dimethyl acetal (II) (60 MHz, in CCl_4).

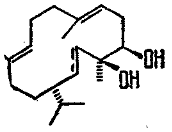
a considerable complication of the appearance of the AB part of the ABX system formed by the H_2, H_3, and H_1 protons. This complication appears in the fact that H_2 and H_3 protons give one unsymmetrical multiplet at 5.38 ppm.



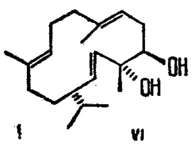
III. R=$OCOCH_3$
IV. R=$OCOC_6H_4-NO_2-O$

The configuration of the asymmetric center at C_5, which is the same in the two diols, was established on the basis of the 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 [2]. The o-nitrobenzoate (IV) obtained by the reduction of the allyl acetate (III) with lithium tetrahydroaluminate followed by acylation of the product with o-nitrobenzoyl chloride (in pyridine, 1 h at 120°C) gives a negative Cotton effect at 335 nm in methanolic solution, which shows the R configuration of the asymmetric center at C_5.

The configurations of the diols A and B at C_4 were established on the basis that in the hydroxylation of cembrene with potassium permanganate in acetone (0°C, in the presence of an excess of caustic soda), the diol A is formed. In view of the fact that this reaction is a cis addition and the asymmetric center at C_5 has the R configuration, it may be concluded that diol A has the 4S configuration (formula V) and its C_4 epimer, the diol B, the 4R configuration (formula VI). The IR spectra for the epimeric diols are in harmony with the stereochemistries proposed for them. Thus, diol A in carbon tetrachloride solution has a strong intramolecular hydrogen bond (band at 3580 cm^{-1} that does not change when the solution is diluted to a concentration of 0.025% but the relative intensity of which is approximately twice that of the bands of the free hydroxy group at 3610 cm^{-1}). The similar intramolecular hydrogen bond in the IR spectrum of diol B amounts to about 15%, in integral intensity, of the band of the free hydroxy group present at 3610 cm^{-1}.



V



VI

In the light of existing ideas on the mechanism of the oxidation of olefins with chromium trioxide [3, 4], diols A and B are normal primary products of the oxidation of cembrene (C_4 double bond). The reagent attacks the cembrene stereospecifically, since diols with one of the two possible configurations at C_5 are formed. As mentioned above, the same stereochemical result was obtained in the hydroxylation of cembrene with potassium permanganate.

EXPERIMENTAL

The instruments and methods have been described in a preceding communication [1].

The Diol A (V). Chromatography on SiO_2 of the combined reaction products from the oxidation of cembrene with chromium trioxide in aqueous acetone gave a polar fraction which was eluted from the column after substance D [1]. Chromatography of this fraction (1.0 g) on 40 g of SiO_2 yielded 0.4 g of a mixture of the diols A and B (eluent — petroleum ether with 20% of diethyl ether). The recrystallization of the mixture from 10 ml of hexane yielded 0.2 g of the diol A; NMR spectrum, ppm: 1.26 (3H, singlet, Me_4), 1.47 and 1.57 (3H each, singlets, Me_8 and Me_{12}), 3.84 (1H, doublet of doublets, J = 8 and 2 Hz, H_5), and 4.78-5.45 ppm (2H, multiplet, H_7 and H_{11}). The H_2 and H_3 protons form a AB system with J_{AB} = 16.0 Hz, δ_A (H_3) = 5.65 ppm, δ_B (H_2) = 5.36 ppm, $J_{1,2}$ = 6.5 Hz.

Monoacetates of the Diols A and B. A mixture of the diols A and B (0.50 g) was dissolved in 20 ml of pyridine, and 5 ml of acetic anhydride was added. After the mixture had been kept at room temperature for 12 h and had been worked up in the usual way, a product was obtained (0.49 g) which was chromatographed on 30 g of SiO_2 + 5% of $AgNO_3$. Petroleum ether containing 30% of diethyl ether eluted 0.41 g of the monoacetate of diol A. A mixture of petroleum ether with 30% of diethyl ether eluted 0.07 g of the monoacetate of diol B; IR spectrum, cm^{-1}: 980 (trans-disubstituted double bond), 1750 (C=O), 3610 (tertiary hydroxy group); PMR spectrum, ppm: 1.20 (3H, singlet, Me_4), 1.47 and 1.56 (3H each, singlets Me_8

and Me_{12}), 4.52 (1H, doublet of doublets, J = 7.5 and 4.0 Hz, H_5), 4.86-5.33 (2H, multiplet, H_7 and H_{11}), 5.38 (2H, narrow multiplet, $W_{1/2}$ = 7 Hz, H_2 and H_3).

The Dimethyl Acetal (II). A solution of 0.10 g of a mixture of the diols A and B in 10 ml of methanol and 0.5 ml of water was treated with 0.2 g of periodic acid, and the mixture was stirred at room temperature for 10 min and then at +40°C for another 3 min. After the usual working up, 0.08 g of the dimethyl acetal (II) was obtained with n_D^{22} 1.4870, $[\alpha]_D^{22}$ −6.5° (c 6.1). The results of elementary analysis agreed with the figures calculated for $C_{22}H_{38}O_3$. UV spectrum: λ_{max} 225 nm (log ε 3.94); IR spectrum, cm^{-1}: 995 (trans-disubstituted double bond, 1635, 1690 (α-enone), 1070, 1130 (C=O); the NMR spectrum is given in Fig. 2. The mass spectrum recorded at an energy of the ionizing electrons of 12 V showed only one ion (m/e 318.2531), formed as the result of the ejection of a methanol molecule from the molecular ion.

The oxidation of 0.1 g of the diol A gave the dimethyl acetal (II) with the same yield.

The Allyl Acetate (III). At 0°C, 0.5 ml of phosphorus oxychloride was added dropwise to a solution of 0.31 g of the monoacetate of the diol A in 20 ml of pyridine, and the mixture was left to stand at 0°C for 24 h. After the usual working up and chromatography of the product on 15 g of SiO_2, 0.1 g was obtained of the acetate III with n_D^{20} 1.5029, $[\alpha]_D^{20}$ +57.2° (c 3.5); UV spectrum: λ_{max} 239 nm (log ε 3.85); IR spectrum, cm^{-1}: 900 $\left(CH_2{=}C\langle\right)$, 970 (trans-disubstituted double bond), 1750 (C=O); NMR spectrum, ppm; 1.41 and 1.51 (3H each, singlets, Me_8 and Me_{12}, 1.87 (3H, singlet, OAc), 4.75-5.0 (2H, multiplet, H_7 and H_{11}), 5.05 and 5.09 (1H, each, narrow multiplets, $W_{1/2}$ = 3 Hz each, $\left(C\underline{H_2}{=}C\langle\right)$, 5.33 (1H, doublet of doublets, J = 6.0 and 8.0 Hz, H_5). H_2 and H_3 protons forming an AB system with J_{AB} = 15.5 Hz, δ_A (H_3) = 5.83 ppm, $\delta_B(H_2)$ = 5.52 ppm, $J_{1,1}$ = 8.0 Hz.

Hydroxylation of Cembrene with Potassium Permanganate. A solution of 2 g of caustic potash in 10 ml of water and 0.7 g of dry potassium permanganate were added to a solution of 1 g of cembrene in 100 ml of acetone cooled to 0°C. The mixture was stirred vigorously at 0°C for 1 h. After the usual working up, the product (0.8 g) was chromatographed on 20 g of SiO_2. Petroleum ether eluted 0.3 g of unchanged cembrene; a mixture of petroleum ether with 5% of diethyl ether eluted 0.15 g of a mixture of unidentified ketones (IR spectrum; 1710 cm^{-1}); and a mixture of petroleum ether with 30% of diethyl ether eluted 0.1 g of an unidentified compound and 0.1 g of the diol A. According to ELC, diol B was absent from the reaction mixture in appreciable amounts.

SUMMARY

1. The oxidation of cembrene with chromium trioxide in aqueous acetone forms, together with other compounds, the products of its hydroxylation at the C_4 double bond — cembra-2,-7,11-triene-4,5-diols epimeric at the C_4 double bond.

2. On the basis of chemical and spectral characteristics, it has been established that these diols have the 4S, 5R and 4R, 5R configurations, respectively.

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