DEPENDENCE OF THE GROWTH-REGULATING ACTIVITY OF MACROCYCLIC ALLYL ALCOHOLS OF THE CEMBRANE SERIES ON THE STEREOCHEMISTRY OF THE DISUBSTITUTED DOUBLE BOND

A. V. Vorob'ev, N. A. Larionova, and V. A. Raldugin

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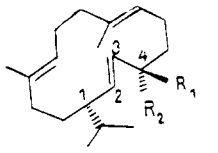
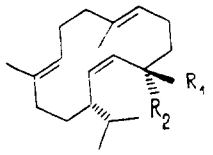
With the use of a number of known and two specially synthesized cembranoids it was established that the growth-inhibiting activity of membrane alcohols does not change appreciably on the inversion of the configuration of the Δ^2 double bond in their molecule.

Growth-inhibiting activity, revealed in the biotest on wheat coleoptiles, is known for cembrane alcohols the structure of the molecules of which is based on that of isocembrol (I) [1, 2]. The change in this activity with a variation in the number and position of oxygen-containing substituents in the molecule has been investigated previously, and it has been established that it is connected with the presence of an allyl hydroxy group at C-4 adjacent to a trans-disubstituted double bond [2]. The unnatural 2-cis isomers of isocembrol and of 4-epiisocembrol (II) have recently been synthesized [3], and it appeared of interest to us to determine whether growth-inhibiting activity was retained in them. In addition to these compounds ((III) and (IV)), we have obtained the previously unknown 18-nor derivatives (V) and (VI) by the reduction of ketone (VII) [3] with lithium tetrahydroaluminate in diethyl ether.



I $R_1 = OH$; $R_2 = CH_3$

II $R_1 = CH_3$; $R_2 = OH$



III. $R_1 = OH$; $R_2 = CH_3$

IV $R_1 = CH_3$; $R_2 = OH$

V $R_1 = OH$; $R_2 = H$

VI. $R_1 = H$; $R_2 = OH$

VII. $R_1 + R_2 = O$

Alcohols (V) and (VI), formed in a ratio of 9:10, were separated by chromatography on silica gel and were characterized by their spectral properties (see the Experimental part). The absolute configurations of their molecules at C-4 were determined from the sign of the Cotton effect at 330 nm on the ORD curve for the corresponding ortho-nitrobenzoates (negative sign for (V), positive for (VI)) in agreement with the rule put forward in [4].

The results of trials of compounds (I-VI) (working solutions with a concentration of $1 \cdot 10^{-3}$ M were used) on the inhibition of the growth of sections of wheat coleoptiles in the standard biotest are given below:

Wheat variety	Increase in length, % on the control taken as 100%					
	I	II	III	IV	V	VI
Mironovskaya 808	49	44	34	21	42	31
Skala	44	36	44	31	34	39

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Two main conclusions can be drawn from these results: growth-inhibiting activity is retained without appreciable changes for the 2-cis isomers of isocembrol and of 4-epiisocembrol, and the replacement of the 4-methyl group in the molecule of each of these isomers by a hydrogen atom likewise does not affect the activity shown.

EXPERIMENTAL

NMR spectra were recorded on a Bruker AM-400 instrument (400 MHz for ^1H and 100.62 MHz for ^{13}C) for solutions in deuterochloroform, δ-scale. Conventional symbols for describing the PMR spectra: s) singlet; d) doublet; t) triplet; m) multiplet. IR spectra were recorded on a UR-20 instrument for solutions in CCl_4, and ORD curves (for solutions in methanol) on a Spectropol 1 spectropolarimeter.

For chromatography we used air-dry silica gel of type KSK with a grain size of 0.05-0.14 mm at a ratio of substance to sorbent of ~1:30.

The determination of growth-inhibiting activity on wheat coleoptiles was performed by the procedure of [5]. Tween-80 was used to dissolve the samples, the ratio of substance to emulsifying agent being 1:3.

Under the conditions of the trial, the compounds under investigation did not undergo cis-trans isomerization and epimerization.

Preparation of Alcohols (V) and (VI). At room temperature, 0.05 g of lithium tetrahydroaluminate was added to a solution of 0.210 g of ketone (VII) in 5 ml of diethyl ether and, after stirring, the mixture was left at the same temperature for 5 min. The usual working up and chromatography yielded, successively, 0.095 g of the alcohol (V) and 0.110 g of the alcohol (VI).

(1S,4R)-18-Norcembra-2Z,7E,11E-trien-4-ol (V). Colorless oil with $[\alpha]_D^{18}$ + 43.4° (c 4.15; $CHCl_3$); IR spectrum: 3620 cm^{-1} (OH). PMR spectrum (ppm): 0.81 and 0.87 (3 H each, doublets with J = 7 Hz each, $-CH(CH_3)_2$), 1.52 and 1.58 (3 H each, broadened singlets, Me-8 and Me-12), 4.24 (1 H, H-4, dm $J_{4,3} = J_{4,5a} = 9.5$ Hz, $J_{4,2} \approx J_{4,5b} \approx 1$ Hz), 4.95 and 5.16 (1 H each, multiplets, H-7 and H-11), 5.15 (1 H, H-2, ddd, $J_{2,3} = J_{2,1} = 10.5$ Hz, $J_{2,4} = 1$ Hz), 5.50 (1 H, H-3, dd, $J_{3,2} = 10.5$ Hz, $J_{3,4} = 9.5$ Hz). In double resonance with suppression of the H-4 signal (4.24 ppm), the H-3 signal was converted into a doublet with J = 10.5 Hz, and the H-2 signal into a triplet with J = 10.5 Hz, ^{13}C NMR spectrum (ppm): quartets at 14.97, 15.67, 18.26, and 20.87; triplets at 23.10, 24.05, 29.28, 35.72, 38.00, and 38.64; doublets at 31.51 (C-15), 40.06 (C-1), 64.69 (C-4), 124.60, 125.87, 133.69, and 134.73; singlets at 133.72 and 134.54.

(1S,4S)-18-Norcembra-2Z,7E,11E-trien-4-ol (VI). Colorless oil with $[\alpha]_D^{18}$ − 149.0° (c 5.57; $CHCl_3$). IR spectrum: 3620 cm^{-1} (OH). PMR spectrum: 0.84 and 0.86 (3 H each, doublets with J = 7 Hz each, $-CH(C\underline{H}_3)_2$); 1.56 and 1.62 (3 H each, broadened singlets, Me-8 and Me-12); 4.36 (1 H, dddd, H-4, $J_{4,3} = 7.5$ Hz, $J_{4,5a} = 10.5$ Hz, $J_{4,2} = J_{4,5b} = 1.5$ Hz); 4.95 (2 H, m, H-7 and H-11); 5.07 (1 H, ddd, H-2, $J_{2,3} = J_{2,1} = 11$ Hz, $J_{2,4} = 1.5$ Hz); 5.51 (1 H, dd, H-3, $J_{3,2} = 11$ Hz, $J_{3,4} = 7.5$ Hz). On double resonance with suppression of the H-3 signal (5.51 ppm), the H-2 and H-4 signals were converted into a doublet (J = 11 Hz) with broadened components and into a double of multiplets (J = 10.5 Hz), respectively. ^{13}C NMR spectrum (ppm); quartets at 14.76, 16.30, 19.13, and 20.56; triplets at 23.76, 24.92, 27.88, 35.08, 37.12, and 40.12; doublets at 31.30 (C-15), 40.21 (C-1), 67.14 (C-4), 123.72, 125.31, 131.54, and 135.01; singlets at 134.23 and 135.58.

o-Nitrobenzoates of the Alcohols (V) and (VI). A solution of 0.02 g of the alcohol (V) and 0.2 g of o-nitrobenzoyl chloride in 5 ml of pyridine was heated at 70-80°C for 10 min. After the usual working up and chromatography of the product, 0.02 g of the o-nitrobenzoate of the alcohol (V) was obtained in the form of a pale yellow oil. IR spectrum (cm^{-1}): 917 (=CH), 1080 and 1130 (O–C–O), 1450 (C=C, aromatic), 1550 (NO_2), and 1730 (C=O). PMR spectrum (ppm): 0.81 and 0.85 (3 H each, doublets with J = 7 H each, $-CH(C\underline{H}_3)_2$); 1.58 and 1.60 (3 H each, broadened singlets, Me-8 and Me-12); 5.04 and 5.22 (1 H each, multiplets, H-7 and H-11); 5.35 (1 H, t, J = 10.5 Hz, H-2); 5.44 (1 H, dd, J = 9.5 and 10.5 Hz, H-3); 5.78 (1 H, broadened t, J ~ 9.5 Hz, H-4); 7.2-7.9 (4 H, protons of the aromatic ring). ORD: +22.7° (589 nm), +42° (440 nm), +10.5° (375 nm), +714° (304 nm), +609° (289 nm), +819° (270 nm) (s 0.23).

Analogously, 0.028 g of the alcohol (VI) yielded 0.025 g of the oily o-nitrobenzoate. IR spectrum, cm^{-1}: 920 (=CH), 1080 and 1130 (O–C–O), 1450 (aromatic C=C), 1550 (NO_2), 1730

(C=O). PMR spectrum (ppm): 0.87 and 0.88 (3 H each, doublets with J = 7 Hz each, $-CH(C\underline{H}_3)_2$); 1.57 and 1.65 (3 H each, broadened singlets, Me-8 and Me-12); 5.01 (1 H, broadened d, J ~ 12 Hz, H-7 or H-11); 5.18 (1 H, broadened t, J = 7 Hz, H-11 or H-7); 5.28 (1 H, dd, J = 11 and 9.5 Hz, H-2); 5.47-5.54 (2 H, m, H-3 and H-4); 7.58-7.88 (4 H, protons of the aromatic ring). ORD: −52.6° (589 nm), −108° (410 nm), −60° (375 nm), −595° (315 nm) (s 0.33).

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STRUCTURE OF A NEW TRITERPENOID FROM THE BARK OF THE SIBERIAN LARCH

G. F. Chernenko, I. Yu. Bagryanskaya, and É. N. Shmidt

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A petroleum ether extract of the bark of the Siberian larch has yielded a new triterpenoid – the methyl ester of 3α-hydroxy-24S,25R-epoxylanost-9(11)-en-27-oic acid, the structure of which has been established on the basis of spectral characteristics, chemical transformations, and x-ray structural analysis.

In the study of the chemical composition of a petroleum ether extract of the bark of the Siberian larch, substance (I) with the composition $C_{31}H_{50}O_4$ (high-resolution mass spectrometry) of unknown structure was detected in the fraction containing sterols.

According to its PMR spectrum, compound (I) with mp 184.5-186°C, contained a trisubstituted double bond (multiplet at 5.23 ppm), a free hydroxyl (multiplet at 3.4 ppm), a methoxycarbonyl group (singlet at 3.7 ppm), an oxide ring (multiplet at 3.12 ppm), and seven methyl groups one of which was secondary doublet at 0.88 ppm, J = 6 Hz). The acetylation of the substance confirmed the presence of a secondary hydroxy group. A comparison of the spectra (^1H and ^{13}C NMR spectra) of compound (I) with the spectra of abieslactone and its derivatives showed that they were related [1]. From these facts it was possible to assume that the compound (I) that had been isolated was a triterpenoid of the lanostane type. To determine the structure of the new substance more accurately we performed an x-ray structural analysis (XSA). The structure, the relative configuration, the spatial arrangement, the length of the bonds are shown in Fig. 1.

The geometry of the molecule is characteristic for structures of this type [2]. The six-membered rings in the molecule have the chair-chair and half-chair form, and the five-membered ring the twist form. The long side chain can be divided into three planar fragments: the ester group, with a maximum departure from the plane of 0.01 Å (A); the epoxide ring (B); and the C_{17}, C_{20}, C_{22}, and C_{23} atoms (C) which lie in one plane with a maximum departure of 0.02 Å. The dihedral angle between A and B amounts to 101.2° and that between B and C to 110.7°. The geometry of the oxide ring is as follows: the mean bond length is 1.45 Å and the mean value of the angles 60° [4]. In the crystal a strong intermolecular hydrogen bond is observed. According to the XSA results, compound (I) has the structure of the methyl ester of 3α-hydroxy-24S,25R-epoxylanost-9(11)-en-27-oic acid.

Institute of Organic Chemistry, Siberian Branch Academy of Sciences of the USSR, Novosibirsk.

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