NEW DERIVATIVES OF (−)-NEOCEMBRENE FROM THE SOFT CORAL Sarcophyton trocheliophorum

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A hexane extract of the soft coral Sarcophyton trocheliophorum has yielded two new diterpenoids for which the structures of 13S-hydroxy-(−)-neocembrene and 13S-hydroxy-11,12-epoxy-(−)-neocembrene have been established.

As has been established in the last half-decade, terpenoids of many structural types are widely distributed in marine invertebrates — sponges, ascidians, alcyonarians, gorgonians, and others [1, 2]. For alcyonarians (soft corals) of the genera Sarcophyton, Sinularia, and Lobophytum the most typical are macrocyclic diterpenoids of the cembrane series [3, 4].

We have investigated the coral Sarcophyton trocheliophorum collected in 1985 on the reefs of the Seychelle Islands. A coral of the species collected in the same region has already been the object of chemical study. Braekman [5] isolated from it a new epoxyalcohol trocheliophorol (I), the sterochemistry of the molecule of which at C-4, C-11, and C-12 was established by one of the authors of the present paper [6] and, independently and somewhat later, by Carmely [7].

By the chromatography on silica gel of a hexane extract of the lyophilized coral we isolated two new cembrane alcohols with yields of 0.25 and 0.22%, respectively (on the initial raw material). Their structures and stereochemistries, which are shown in formulas (II) and (III), were established in the following way.

The ^{1}H NMR spectrum (Table 1) and ^{13}C and IR spectra (see Experimental) indicated that compound (II) was a monocyclic secondary alcohol in the molecule of which there were four double bonds, one of which was that of an exomethylene group, and four vinyl methyl groups.

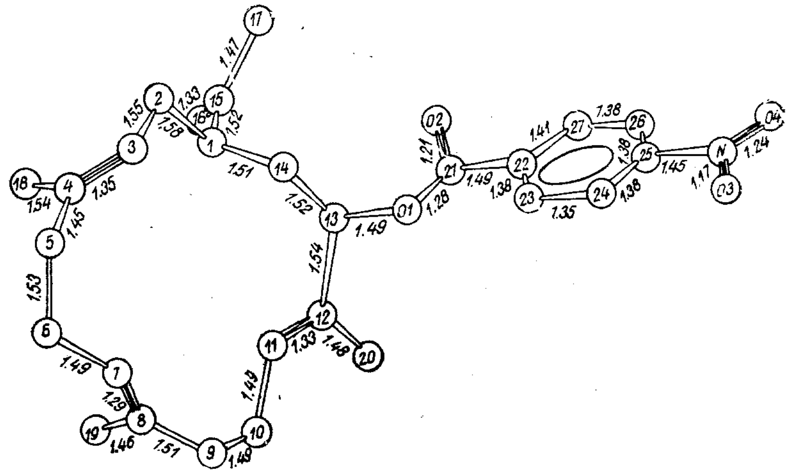

Fig. 1. Structure and relative configuration of the molecule of the p-nitrobenzoate of alcohol (II).

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TABLE 1. Chemical Shifts (ppm) and Spin—Spin Coupling Constant (Hz, shown in parentheses) for the Signals in the PMR Spectra*

Compound	CH_3-17	CH_3-18 CH_3-19	CH_3-20	2H-16	H-3, H-7	H-11	H-13
I	1,72	1,57 1,59	1,67	4,66 4,72	5,13 tm (~6) 4,95 tm (~6)	5.34 t (6)	3,88 dd (8,0; 4,0)
III	1,71	1,53 1,61	1,29s	4,74 4,78	5,05 tm (~6) 5,10 tm (~7)	2,95 dd (6.5; 6,0)	3,56 ddd † (8,0; 4,0; 4,0)
11,12-epi-III	1,71	1,54 1,65	1,21s	4,76 m $W_{\frac{1}{2}}$ =5Hz	5,00 m $W_{\frac{1}{2}}$ = 16 Hz	2,79 dd (9,0; 4,0)	3,43 d‡ (11,0)
V	1,70	1,44	1,41s	4,68 4,75	4,90 tm (6) 5,01 tm (6)	3,01 t (5,5)	—

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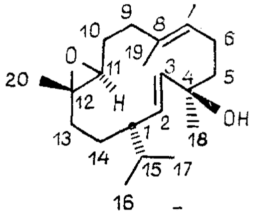
*The CH_3-18 and CH_3-19 signals in the spectra of all the compounds and the CH_3-20 signal in the spectrum of alcohol (II) are broadened singlets, and the signals of the 2H-16 protons in all the spectra are narrow multiplets.

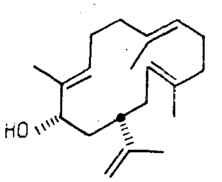
†One of the constants (4.0 Hz) is J.

‡The components of the doublet are broadened and have $W_{1/2}$ values of up to 5 Hz.

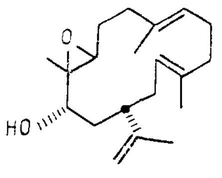
Since it did not appear possible to deduce the structure unambiguously from the spectral characteristics, we made an x-ray-structural analysis of the well-crystallizing p-nitrobenzoate obtained by the reaction of the compound under investigation with p-nitrobenzoyl chloride in pyridine. Figure 1 shows the relative configuration of the molecule of the p-nitrobenzoate of alcohol (II) and the bond lengths. The standard deviations for the bond lengths were 0.013-0.027 Å. The bond lengths within the 3σ limits corresponded to the usual values, with the exception of the O1—C21 and O1—C13 distances which differed from the normal by 4σ. The phenyl ring is planar with an accuracy of ±0.03 Å. The nitro group lies in the plane of the phenyl ring (interplanar angle 1.7°), while the ester group is twisted by 16.6%.



I



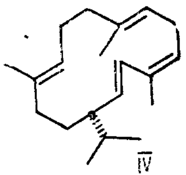
II



III

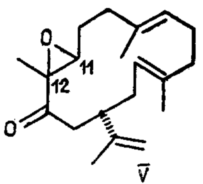
The absolute configuration of the molecule of the alcohol under investigation is the opposite of that shown in Fig. 1 for the p-nitrobenzoate, since, as was established by Horeau's method [8] the asymmetric center at C-13 has the S-configuration. The confirmation of the macrocyclic ring differs from that for cembrene (IV) [9], which may be due to the absence from the molecule of p-nitrobenzoate of alcohol (II) of a conjugated dienic system and the presence of an ester group at C-13. Nevertheless, the structurally coinciding part of the ring from C-5 to C-12 has similar spatial structures in the two molecules, as can be seen from a comparison of the torsional angles (Table 2). Thus, alcohol (II) is (1S,3E,7E,11E,13S)-cembra-3,7,11,15-tetraen-13-ol (13S-hydroxyneocembrene).

The second diterpenoid isolated, judging from its ^{13}C NMR spectrum, contained in its molecule two sp^2-hybridized carbon atoms less than compound (II) and in place of them the signals of two carbon atoms linked with noncarbonyl oxygen were observed (doublet at 59.5 ppm and singlet at 63.3 ppm). In view of the fact that the mass of the molecular ion in the mass spectrum of the compound under investigation differed from that of the alcohol (II) by 16 m.u., it could be assumed that it was an epoxy derivative of the latter. The spectral characteristics (for the PMR spectrum, see Table 1; Experimental) were in harmony with this hypothesis. It was confirmed additionally by the isolation of the epoxy derivative of the alcohol from a mixture of the products of the epoxidation of compound (II) with peracetic acid in chloroform.



IV

The position of the epoxy group was established on the basis of a study of the products of the interaction of alcohol (II) with pyridinium chlorochromate in methylene chloride [10]. By chromatographing the mixture of products obtained in this reaction, we isolated the main component — the epoxyketone (V) — and two epoxyalcohols, one of which proved to be identical (according to TLC, PMR spectrum, and optical rotation) with the natural compound. It must be mentioned that epoxidation proceeding as a competing reaction in the oxidation of allyl alcohols with chromium trioxide in the presence of mineral acids is well known [11] and it takes place at a double bond located in the α-position to a hydroxy group. In actual fact, the carbonyl group in the molecule of the epoxyketone (V) was not, according to its IR spectrum (1730 cm^{-1}), conjugated with a double bond. When ketone (V) was reduced with sodium tetrahydroborate in ethanol we obtained two corresponding epimeric alcohols (TLC), the main one of which was isolated by chromatography and proved to be identical according to TLC and its PMR spectrum with the natural compound. Consequently, the epoxy group was present at C-11—C-12, and the configuration of the asymmetric centers at C-1 and C-13 in the molecule of the epoxyalcohol (III) was the same as in the alcohol (II).



V

Since the epoxyalcohol (III) was formed in the epoxidation of the alcohol (II), having the 11E configuration of the double bond, it must have either the 11S,12S or the 11R,12R configuration. It is difficult to make an unambiguous choice between them on the basis of spectral characteristics alone because of the conformational mobility of the cembrane ring. On the assumption of approximately equally preferred conformations of the p-nitrobenzoate of alcohol (II) (in solution) and of the intermediate chromate of the same alcohol in the reaction with pyridinium chlorochromate the most probable is, as shown below, the 11S,12S-configuration. On the circular dichroism curve of the p-nitrobenzoate of alcohol (II) a negative Cotton effect was observed at 259 nm (Δε −7.5) which shows the left-handed helicity of the allyl benzoate chromophore [12, 13] in the molecule of this compound. With such an orientation of the double bond at C-11—C-12 in the chromate of alcohol (II), intramolecular epoxidation which, as is well known, is stereoselective [11], must lead to the 11S,12S-epoxy derivative of alcohol (II).

TABLE 2. Torsional Angles in the Molecules of Compounds (II) and (IV)

Angle	Size of the angle, deg.	
	II	IV
C14C1C2C3	—74,2	121,4
C1C2C3C4	—91,5	—177,2
C2C3C4C5	—178,5	178,1
C3C4C5C6	—118,7	—2.1
C4C5C6C7	68,6	—67,2
C5C6C7C8	—123,6	130,9
C6C7C8C9	—177,1	—175.7
C7C8C9C10	—117.2	116,3
C8C9C10C11	56,5	—60,9
C9C10C11C12	169,8	—161,3
C10C11C12C13	—179,1	178,8
C11C12C13C14	—7,1	121.3
C12C13C14C1	—75,3	—54.9
C13C14C1C2	176,8	—64,4

TABLE 3. Coordinates of the Atoms (in fractions of a cell) of the p-Nitrobenzoate of Alcohol (II)

Atom	$x\times10^3$	$y\times10^3$	$z\times10^4$	Atom	$x\times10^3$	$y\times10^3$	$z\times10^4$
C1	0941(14)	6184(8)	8488(3)	C17	—1206(24)	4753(15)	8790(6)
C2	1099(19)	5739(10)	7958(4)	C18	0338(22)	7607(12)	7341(7)
C3	2596(19)	6310(10)	7673(4)	C19	2798(28)	10061(14)	8108(6)
C4	2262(22)	7162(10)	7400(5)	C20	2782(21)	7790(10)	9868(5)
C5	3745(23)	7629(13)	7137(5)	C21	3118(14)	4894(10)	9854(4)
C6	4182(27)	8755(15)	7276(6)	C22	4501(17)	4280(9)	10122(4)
C7	4953(23)	8849(12)	7774(8)	C23	3928(20)	3639(12)	10492(5)
C8	4391(23)	9395(11)	8134(6)	C24	5109(21)	3087(13)	10764(5)
C9	5349(24)	9459(11)	8614(6)	C25	6912(21)	3094(9)	10640(4)
C10	4356(25)	9059(10)	9044(5)	C26	7580(17)	3721(10)	10277(4)
C11	3747(19)	7953(11)	9005(4)	C27	6359(17)	4308(9)	10018(4)
C12	3077(14)	7400(10)	9369(4)	N	8305(19)	2523(10)	10900(5)
C13	2507(15)	6255(10)	9296(4)	O1	3784(10)	5631(6)	9596(2)
C14	2518(15)	5805(8)	8788(4)	O2	1537(10)	4657(7)	9883(3)
C15	—0857(19)	5870(14)	8706(4)	O3	9842(17)	2555(11)	10805(4)
C16	—2111(22)	6558(15)	8831(7)	O4	7769(15)	1984(9)	11244(4)

The stereoselectivity in the reaction of the alcohol (II) with pyridinium chlorochromate was fully expressed – the stereoisomer of ketone (V) (11,12-diepimer) was formed in small amount and could not be isolated, the ratio of the epoxy alcohol (III) and 11,12-diepi-(III) being approximately 2:1.

The extract investigated contained, in addition to compounds (II) and (III), another series of so-far-unidentified components. As has been established by TLC and PMR spectroscopy using 11S,12S-epoxyisocembrol (trocheliophorol) (I) as marker, the latter was not present among them.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on Bruker HX-90E (90 MHz for ^{1}H) and Bruker WH-250 (250 MHz for ^{1}H) instruments using solutions in deuterochloroform (TMS, δ-scale). IR spectra were obtained for solutions in carbon tetrachloride on UR-20 and Specord-751 instruments. Specific optical rotations were measured on a Perkin–Elmer polarimeter and a Spectropol I spectropolarimeter. Mass spectra were recorded on a LKB-900 chromato-mass spectrometer using direct introduction at an ionization energy of 20 eV. CD curves were recorded on the Spectropol I instrument for solutions in methanol.

For chromatography we used type L silica gel (Czechoslovakia) with a grain size of 0.100-0.160 mm at a ratio of substance to sorbent of ~1:20 with, as eluent, petroleum ether (bp 40-70°C) containing amounts of diethyl ether increasing from 0 to 100%.

Isolation of the Alcohol (II) and the Epoxyalcohol (III). The ground lyophilized coral (420.00 g) was extracted with hexane in a Soxhlet apparatus for 50 h. The yield of extract was 19.00 g. Its chromatography yielded successively 4.32 of a mixture of hydrocarbons and unidentified oxygen-containing compounds, 1.06 g of alcohol (II) (eluted by petroleum ether with 30% of diethyl ether), 0.91 g of the epoxyalcohol (III) (with the same eluent), and 9.75 g of a mixture of polar compounds (eluted by diethyl ether).

(1S,3E,7E,11E,13S)-Cembra-3,7,11,15-tetraen-13-ol (II). Colorless oil with $[\alpha]_D^{20}$ −150° (c 0.2). IR spectrum, cm^{-1}: 920, 1640, 3050 $(-\underset{|}{C}=CH_2)$, 3620 (OH). Mass spectrum (m/z): 288 (M$^+$), 271 (M$^+$ − H$_2$O). The PMR spectrum is given in Table 1. ^{13}C NMR spectrum, ppm: quartets at 14.2, 14.8, 15.6, and 19.1; triplets at 23.8, 25.0, 29.8, 32.6, 37.5, 38.8, and 110.5; doublets at 45.3, 75.0, 122.8, 124.7, and 125.8; singlets at 133.1, 135.4, 136.8, and 149.0.

(1S,3E,7E,13S)-11,12-Epoxycembra-3,7,15-triene-13-ol (III). Colorless oil with $[\alpha]_D^{20}$ −85° (c 0.5). IR spectrum, cm^{-1}: 950,1640, 3050 $(-\underset{|}{C}=CH_2)$, 3620 (OH). Mass spectrum (m/z): 304 (M$^+$). For the PMR spectrum, see Table 1. ^{13}C NMR spectrum, ppm: quartets at 15.9, 15.9, 16.6, and 19.8; triplets at 24.8, 25.0, 29.8, 33.2, 36.2, 38.8, and 111.1; doublets at 45.2, 59.5, 70.8, 123.8, and 126.2; singlets at 63.3, 132.8, 135.8, and 148.2.

p-Nitrobenzoate of the Alcohol (II). A solution of 0.20 g of the alcohol (II) and 0.15 g of p-nitrobenzoyl chloride in 15 ml of pyridine was heated at 70-80°C for 1 h. After the usual working up and chromatography of the product, 0.15 g of the p-nitrobenzoate of alcohol (II) was obtained with mp 88-88.5°C (from a mixture of hexane and diethyl ether). CD ($c = 2.53 \cdot 10^{-4}$ M): $\Delta\varepsilon = -7.5$ (259 nm).

The x-ray structural experiment with the p-nitrobenzoate of alcohol (II) was performed on a Syntex $P2_1$ diffractometer (λ Mo K_α, $\mu = 0.8\ \text{cm}^{-1}$). Crystallographic characteristics: $a = 7.409(2)$, $b = 12.820(3)$, $c = 27.636(6)$ Å, $z = 4$; space group $P2_12_12_1$; $d_{calc} = 1.10\ \text{g/cm}^3$. The intensities of 2640 independent reflections were measured by the ω-scanning method in the $2\theta < 50°$ region. The calculations were performed with 1222 reflections having $I > 3\sigma$. The structure was interpreted by the direct method using the MULTAN program and was refined with the SHELX 76 program by the method of least squares in the anisotropic-isotropic (for the hydrogen atoms) approximation to $R = 0.094$ and $R_\omega = 0.098$, where $\omega^{-1} = (\sigma_F^2 + 0.000458F^2)$. The positions of the hydrogen atoms in each cycle of refinement were calculated geometrically. The coordinates of the nonhydrogen atoms are given in Table 3.

Oxidation of the Alcohol (II). To a solution of pyridinium chlorochromate (0.01 g) in 5 ml of methylene chloride were added 0.05 g of anhydrous sodium acetate and a solution of 0.10 g of the alcohol (II) in 5 ml of methylene chloride. After the reaction mixture had been stirred for 2 h at 20°C and the combined products had been chromatographed, 0.02 g of the ketoepoxide (V), 0.04 g of the epoxyalcohol (III), and 0.02 g of the 11,12-diepimer of the epoxyalcohol (III) were obtained.

The ketoepoxide (V) was isolated in the form of crystals with mp 75°C (from pentane); IR spectrum: 1720 cm^{-1} (C=O). The PMR spectrum is given in Table 1.

The epoxyalcohol (III) was identified from its TLC behavior and PMR spectrum.

The 11,12-diepimer of the epoxyalcohol (III) [11,12-diepi-(III)] was isolated in the form of an oil; IR spectrum (cm^{-1}): 903, 1650, 3080 ($C{=}CH_2$); 3615 (OH). PMR spectrum is given in Table 1.

The determination of the absolute configuration of the alcohol (II) molecule at C-13 was carried out by a procedure similar to that described in [8]. The α-phenylbutyric acid isolated had $[\alpha]_D$ −7° (c 1.14; benzene).

Epoxidation of the Alcohol (II). A solution of 0.62 g of the alcohol (II) in 30 ml of methylene chloride was treated with 0.50 g of anhydrous sodium acetate; and then, with stirring, 5 ml of a solution of peracetic acid (100 mg/ml) in chloroform was added dropwise. After the usual working up and chromatography, 0.03 g of the epoxyalcohol (III) was isolated, being eluted first from a complex mixture with other epoxy derivatives of alcohol (II).

Reduction of the Epoxyketone (V). A solution of 0.02 g of the epoxyketone (V) in 2 ml of ethanol was treated with 0.05 g of sodium tetrahydroborate, and the resulting mixture was stirred at room temperature for 15 min. After the usual working up, a mixture of two products (according to GLC) was obtained, by the chromatography of which on silica gel the main one was isolated – the epoxyalcohol (III) (yield 0.01 g), agreeing in TLC and PMR spectrum with a natural sample.

CONCLUSIONS

Two new cembranoids have been isolated from an extract of the soft coral Sarcophyton trocheliophorum, and their structures have been established as (1S,3E,7E,11E,13S)-cembra-3,7,11,15-tetraen-13-ol and (1S,3E,7E,13S)-11,12-epoxycembra-3,7,15-trien-13-ol, respectively.

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TRITERPENE GLYCOSIDES OF Astragalus AND THEIR GENINS.

XXVII. X-RAY STRUCTURAL INVESTIGATION OF CYCLOGALEGIGENIN

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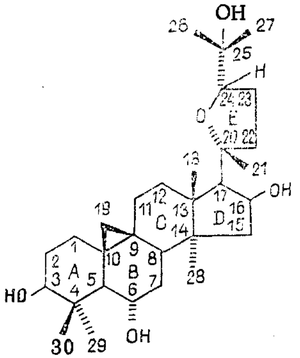
It has been shown by x-ray structural analysis that cyclogalegigenin has the 20S,24R stereochemistry and, consequently, is 20S,24R-epoxycycloartane-3β,6α,16β,25-tetraol. Cyclosieversigenin is 20R,24S-epoxycycloartane-3β,6α,16β,25-tetraol.

Cyclosieversigenin (I) and cyclogalegigenin (II) are genins of the cycloartane series of similar structure that have been isolated from various species of <u>Astragalus</u> [1-4].



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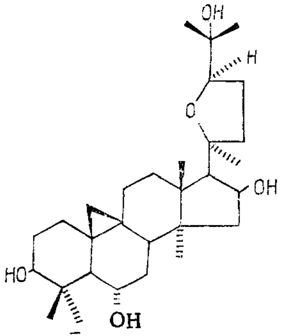

II

Cyclosieversigenin was previously ascribed the structure of 20S,24R-epoxycycloartane-3β,6α,16β,25-tetraol [1]. On the basis of spectral characteristics, and also of chemical transformations permitting a correlation to be made of its structure with that of cyclosieversigenin, cyclogalegigenin was characterized as 20R,24S-epoxycycloartane-3β,6α,16β,25-tetraol [4]. It can be seen from this that these two genins differ only by the configurations of the C20 and C24 chiral centers. In the present paper we give the results of an x-ray structural analysis of cyclogalegigenin (II), which has permitted the stereochemistry of the C20 and C24 atoms to be defined more accurately.

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