14-HYDROXYCARYOPHYLLENE 4,5-OXIDE — A NEW SESQUITERPENE FROM *Betula pubescens*

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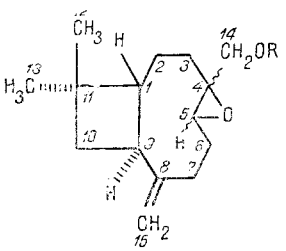
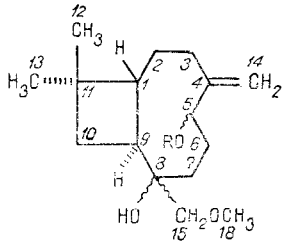
UDC 581.192+547.914

A new sesquiterpene — 14-hydroxycaryophyllene 4,5-oxide — has been isolated from the unsaponifiable part of an ethereal extract of the leaves of *Betula pubescens*, and its structure has been established on the basis of chemical and spectral characteristics.

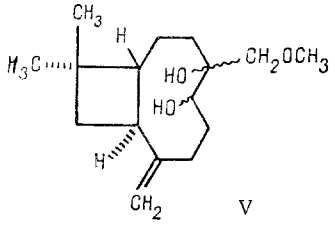
Continuing investigations on the terpenoid composition of the leaves of Siberian species of birch [1], from the unsaponifiable fraction of an ethereal extract of *Betula pubescens* we have isolated a new sesquiterpene (I), $C_{15}H_{24}O_2$. The IR spectrum of (I) in $CHCl_3$ solution (c 6.3 mg/ml) contained three bands, at 896, 1630, and 3078 cm^{-1}, due to the vibrations of a $R_2C{-}CH_2$ group, and a broad band at 3455 cm^{-1} and a narrow one at 3606 cm^{-1} that are characteristic for the stretching vibrations of a hydroxy group. The hydroxy group in (I) is not bound by an intramolecular hydrogen bond, since when the solution was diluted 17-fold the band at 3455 cm^{-1} disappeared and the intensity of the band at 3606 cm^{-1} increased considerably.



I. R = H
II. R = OCOCH$_3$



III. R = H
IV. R = OCOCH$_3$



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Terpene (I) was readily acetylated under mild conditions. The IR spectrum of the acetate (II) showed no bands characteristic for the vibrations of a hydroxy group, which demonstrated the absence of a tertiary hydroxy groups from (I). The fact (I) was a sesquiterpenoid followed from an analysis of the ^{13}C spectrum, which contained the signals of 15 carbon atoms (Table 2). Singlet signals in the ^1H spectrum of (I) (CD_3OD) at 1.00 and 1.03 ppm with an intensity of 3 H each showed the presence in them of two tertiary Me groups in (I), while the presence of only one signal of a quaternary C atom in the ^{13}C spectrum of (I) at 34.4 ppm led to the conclusion that these Me groups were arranged geminally.

The presence in the ^1H spectrum of (I) of signals of the protons of an isolated AB system (the A part in the form of a doublet of doublets (dd) at 3.20 ppm with J = 12.4 and 1.5 Hz,

Pacific Ocean Institute of Bioorganic Chemistry, Far Eastern Scientific Center, Academy of Sciences of the USSR, Vladivostok. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 598-603, September-October, 1984. Original article submitted August 31, 1983.

0009-3130/84/2005-0563$08.50

TABLE 1. ^{1}H Chemical Shifts (CSs) (ppm relative to TMS) and SSCCs (Hz) of Compound (I)

H atom*	CS	SSCCs
1	1,88	$J_{1,2}$=1,2; $J_{1,2}$=10,3; $J_{1,9}$=10,4
2	1,51	$J_{1,2}$=10,3; $J_{2,2}$=—14,9; $J_{2,3}$=4,5; $J_{2,3}$=13,0
2	1,67	$J_{1,2}$=1,2; $J_{2,2}$=—14,9; $J_{2,3}$=5,6; $J_{2,3}$=3,0
3	0,76	$J_{3,2}$=13 0; $J_{3,2}$=5,6; $J_{3,3}$=—13,0; $J_{3,14}$=1,5
3	2,54	$J_{3,2}$=3,0; $J_{3,2}$=4,5; $J_{3,3}$=—13,0; $J_{3,6}$=1,0
5	3,02	$J_{5,6}$=4,3; $J_{5,6}$=10,9
6	1,33	$J_{6,5}$=4,3; $J_{6,7}$=3,6; $J_{6,7}$=8,9
6	2,23	$J_{6,5}$=10,9; $J_{6,7}$=3,8; $J_{6,7}$=6,5; $J_{6,3}$=1,0
7	2,11	$J_{7,6}$=3,8; $J_{7,6}$=6,5; $J_{7,7}$=—12,5; $J_{7,15}$=0,8
7	2,33	$J_{7,6}$=3,6; $J_{7,6}$=8,9; $J_{7,7}$=—12,5; $J_{7,15}$=$J_{7,15}$=0,8
9	2,70	$J_{9,1}$=10,4; $J_{9,10}$=10,5; $J_{9,10}$=8,6; $J_{9,15}$=0,8
10	1,60	$J_{10,9}$=10,5; $J_{10,10}$=—10,5
10	1,66	$J_{10,9}$=8,6; $J_{10,10}$=—10,5
12 (CH_3)	1,03	—
13 (CH_3)	1,00	—
14	3,20	$J_{14,14}$=—12,4; $J_{14,3}$=1,5
14	3,92	$J_{14,14}$=—12,4
15	4,82	$J_{15,15}$=1,7; $J_{15,7}$=$J_{15,7}$=0,8
15	4,97	$J_{15,15}$=1,7; $J_{15,7}$=0,8; $J_{15,9}$=0,8

*The numbering of the protons corresponds to the numbering of the carbon atoms in the structural formula of (I).

and a B part in the form of a doublet at 3,92 ppm with J = 12,4 Hz) the protons of which were greatly descreened on acetylation (the A part as a doublet of doublets at 3.62 ppm with J = 12.0 and 1.8 Hz, and B part as a doublet at 4,57 ppm with J = 12.0 Hz in the ^{1}H spectrum of (II) (singlet at 2.11 ppm) showed the presence in (I) of a primary alcohol group attached to a quaternary carbon atom. The signal of a methine proton was observed in the weak-field section of the ^{1}H spectrum of (I) at 3.02 ppm (dd, J = 4,3 and 10.9 Hz) and it did not change its position on passage to the ^{1}H spectrum of (II) (dd, J = 4,2 and 10.5 Hz).

The ^{13}C spectrum of (I) contained three signals of carbinyl C atoms at 62.1 ppm (triplet), 62.8 ppm (singlet), and 64.9 ppm (doublet), the form of which together with the features of the ^{1}H spectra of (I) and (II) given above permits the conclusion that an epoxy ring and a hydroxymethyl group are present in (I) at the same carbon atom. The existence in the molecule of (I) of an exomethylene double bond follows from the presence of ^{1}H spectrum of (I) of multiplet signals of unit intensity at 4.82 ppm (J = 0.7, 0,7, and 1.7 Hz), and 4.97 ppm (J (J = 0.9, 0.9, and 1.7 Hz), and also from the presence in the ^{13}C spectrum of (I) of the signals of a methylene C atom at 113.1 ppm and of a quaternary C atom at 151.6 ppm.

On the basis of the results of the investigation of (I) by physicochemical methods that have been given and also in the light of biogenetic considerations, the sesquiterpene (I) was assigned the structure of 14-hydroxycaryophyllene 4,5-oxide. A fairly reliable confirmation of the proposed structure of (I) was provided by results of proton-proton double-resonance and INDOR (250 MHz) experiments permitting the determination of the SSCCs and the complete assignment of the signals of the protons in the ^{1}H spectrum of (I) (Table 1). The high degree of coupling of the protons at C-6 did not permit the value of their geminal SSCC to be determined or the vicinal SSCCs of the nuclei to be assigned unambiguously. The INDOR experiments showed weak spin-spin coupling of the proton at C-1 with the protons of the CH_3 group

TABLE 2. ^{13}C Chemical Shifts of Compounds (I-IV) (ppm relative to TMS, $CDCl_3$)

Compound	C atom								
	1	2	3	4	5	6	7	8	9
I	48,9	26 6	29,1*	62,8	64,9	30,1*	33,6	151,6	49,9
II	49,0	26,5	29,0*	59,9	64 1	30,3*	33,6	151,3	49,7
III	44,0	23,8	34,2	151,2	73,2	32,6	34 1	75,7	53,4
IV	43,1	23,1	35,6	150,7	75,5	29,5	34,1	75,6	55,0

Compound	C atom								
	10	11	12	13	14	15	16	17	18
I	40,0	34 4	21,5	29,9	62,1	113,1	—	—	—
II	39,9	34,4	21,5	29,9	63,7	113 4	171,1	20,8	
III	36 2	33,7	21,9	30,0	109,6	79,3	—	—	59,4
IV	36 0	33,8	21,7	29,7	110,7	77,2	170,7	20,8	59,1

*The assignment of the signals may be reversed.

at C-11 (1.03 ppm) and of one of the protons (1,60 ppm) at C-10 with the protons of the other CH_3 group, at C-11 (1.00 ppm), but it was impossible to measure the coupling constants. It is interesting to note also the reliably established spin-spin coupling between one of the protons (2.54 ppm) at C-3 and one of the protons (2,23 ppm) at C-6 (^5J = 1.0 Hz).

The results of investigations of terpene (I) by the ^1H and ^{13}C NMR methods unfortunately did not permit an unambiguous conclusion to be drawn concerning the stereochemistry of the epoxy ring in (I).

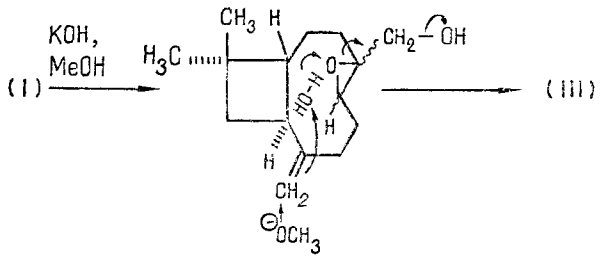
The treatment of (I) with a saturated solution of KOH in CH_3OH led to the formation in moderate yield (35%) of 5,8-dihydroxy-8-methoxy-4-methylenecaryophyllane (III). The IR spectrum of (III) in $CHCl_3$ solution (c 7.1 mg/ml) showed three bands, at 891, 1635, and 3081 cm^{-1}, due to the vibrations of a $R_2C{=}CH_2$ group, two broad intense bands at 3469 and 3571 cm^{-1}, and a narrow band at 3605 cm^{-1}. On 20-fold dilution of the solution, the band at 3469 cm^{-1} disappeared while the band at 3571 cm^{-1} did not change its position and intensity, which shows the existence of an intramolecular hydrogen bond in (III) either between the OH groups at C-5 and C-8 or between the proton of the OH group at C-5 and the oxygen atom of the methoxy group.

When (III) was acetylated under mild conditions, the monoacetate (IV) was obtained. The IR spectrum of (IV) in $CHCl_3$ solution (c 5,7 mg/ml) showed a broad strong band at 3465 cm^{-1} and a narrow band at 3605 cm^{-1}. On 18-fold dilution of the solution the band at 3465 cm^{-1} disappeared and the intensity of the band at 3605 cm^{-1} increased. The results of the acetylation of (III) unambiguously showed the presence of a tertiary OH group in (IV) which permits alternative structures containing no such groups to be rejected. The presence in (IV) of an isolated methoxymethyl group was confirmed by the results of the ^1H and ^{13}C NMR spectra. The ^1H spectrum of (III) showed a singlet at 3,40 ppm (OCH_3) and signals of the protons of an isolated AB system: two doublets at 3,40 and 3.55 ppm with J_{gem} = 9.2 Hz. Since only three signals of methine carbon atoms were observed in the ^{13}C spectrum of (III), two of which belonged to C-1 and C-3, and the third to C-5, and only one weak-field signal of a quaternary carbon atom, at 75,7 ppm, the hydroxy group not undergoing acetylation and the methoxymethyl group must be attached to the same carbon atom. The fact that this atom is C-8 was confirmed by the downfield shift by 3.5 ppm of the C-9 signal in the ^{13}C spectrum of (III) and the upfield shift by 4.9 ppm of the C-1 signal in comparison with the positions of these signals in the spectrum of (I). The upfield shift of the C-1 signal in the ^{13}C spectrum of (III) was apparently due both to the disappearance of the γ-anti effect of the double bond (what is in view is the 8.15 double bond in (I)) on the CS of C-1 [2] and also to the negative γ-effect of the OH group at C-8.

Thus, on considering the structure of the initial compound, the product of the reaction of (I) with KOH in CH_3OH was assigned structure (III). The alternative structure (V), agreeing with many spectral characteristics of compound (III), was rejected because at least the C-9 CS in the ^{13}C spectrum of (V) should not have been appreciably changed in comparison with

the C-9 CS in the spectrum of (I). In the experimental ^{13}C spectrum of (III), however, the C-9 signal had shifted downfield by 3.5 ppm in comparison with its position in the spectrum of (I). The facts available to us do not yet enable us reliably to establish the configurations of the C-5 and C-8 asymmetric centers in (III). The diol (III) is probably formed as the result of an attack by the methoxide anion on the protonated carbon atom of the exocyclic double bond and the simultaneous transannular interaction of a water molecule with the quaternary carbon atom of the same double bond and the oxygen atom of the epoxide ring (scheme 1).

Scheme 1



The base-catalyzed rearrangement of caryophyllene oxides have been studied in fairly great detail in [3], but no rearrangements similar to the transformation of (I) into (III) that we have described have been observed.

EXPERIMENTAL

IR spectra were recorded on a Specord 75 IR spectrometer in $CHCl_3$ solution, and mass spectra of a LKB 9000 spectrometer at an ionizing energy of 70 eV. The ^1H and ^{13}C NMR spectra were measured on a Bruker WM-250 Fourier spectrometer with a working frequency of 250 MHz for ^1H and 62.9 MHz for ^{13}C. The solvents used were $CDCl_3$ and CD_3OD in the ^1H experiments and $CDCl_3$ in the ^{13}C experiments. The chemical shifts are expressed in the δ scale relative to TMS. The accuracy of the measurement was ±1.5 Hz for ^{13}Hz and ±0.15 Hz for ^1H. In the assignment of the signals in the ^{13}C spectra of compounds (I-IV) we used the method of off-resonance spin decoupling and comparison with literature information [4-9]. Optical rotations were determined on a Perkin-Elmer instrument in a cell 10 cm long, and melting points on a Boetius stage.

Isolation of the Terpene (I). The air-dry leaves of *Betula pubescens* (collected in June, 1981, in the Selenga region of the Buryat ASSR) (3 kg) were exhaustively extracted with diethyl ether at room temperature. The extract was evaporated to dryness and the residue was treated further by the method of Fischer and Seiler [10]. Then 21.5 g of the unsaponifiable fraction of the ethereal extract was chromatographed on a column containing SiO_2 L (80-125 μm) with elution by the petroleum ether—acetone (30:1) system. This gave 490 mg of the noncrystalline sesquiterpene (I), $[\alpha]_D^{18}$ −34.6° (c 0.5; chloroform).

Acetylation of the Terpene (I). A solution of 100 mg of (I) in 3 ml of pyridine was treated with 1.5 ml of acetic anhydride. The reaction mixture was left overnight at room temperature. After the usual working up, 114 mg of 14-acetoxycaryophyllene 4,5-oxide (II) was obtained with $[\alpha]_D^{18}$ −58.4° (c 0.5; chloroform). IR spectrum (ν, cm^{-1}): 898, 1630, 1734, 3080. ^1H spectrum (ppm): 1.00 (s, 3 H), 1.02 (s, 3 H), 2.11 (s, 3 H, OAc), 3.02 (dd, 1 H, J = 4.2 and 10.5 Hz, H^5), 3.62 (dd, 1 H, J = 1.8 and 12.0 Hz, H^{14}), 4.57 (d, 1 H, J = 12.0 Hz, H^{14}), 4.87 (d, 1 H, J = 1.7 Hz, H^{15}), 5.03 (d, 1 H, J = 1.7 Hz, H^{15}).

Rearrangement of (I) into (III). A solution of 400 mg of (I) in 55 ml of methanol was boiled with 8 g of KOH for 3 h. The reaction mixture was diluted with water and extracted with ether. After the usual working up of the ethereal extract, the residue was chromatographed on a column of SiO_2 L with elution by mixtures of petroleum ether and acetone. This gave 150 mg of the initial (I) and 100 mg of the sesquiterpene (III) with the composition $C_{16}H_{28}O_3$, mp 66-68°C (petroleum ether), $[\alpha]_D^{18}$ −39.6α (c 0.5; chloroform). ^1H spectrum (ppm): 0.98 (s, 3 H), 1.00 (s, 3 H), 2.72 (s, 1 H, C^8—OH), 3.03 (d, 1 H, J = 4.0 Hz, C^5—OH), 3.40 (s, 3 H, OCH_3), 3.40 (d, 1 H, J = 9.2 Hz, H^{15}), 3.55 (d, 1 H, J = 9.2 Hz, H^{15}), 3.84 (m, 1 H, J = 4.0, 4.0, and 7.5 Hz, H^5), 4.87 (s, 1 H, H^{14}), 4.89 (s, 1 H, H^{14}).

Mass spectrum, m/z (%): 250 (0.4; M − H_2O), 223 (4.3 M − CH_2OCH_3), 205 (30.9), 187 (24.4), 175 (15.7), 161 (10.8), 149 (25.4), 137 (15.2), 135 (16.1), 131 (16.5), 123 (26.5),

121 (29.4), 119 (21.6), 111 (35.2), 109 (29.4), 108 (25.5), 107 (57.8), 105 (27.5), 95 (51.3), 93 (55.3), 91 (29.4), 83 (33.3), 81 (55.8), 79 (50.0), 71 (23.5), 69 (100), 67 (37.3), 55 (49.1), 45 (60.8), 43 (40.1), 41 (92.2).

Acetylation of the Terpene (III). Under conditions similar to those described for (I), 40 mg of (III) yielded 48 mg of 5-acetoxy-8-hydroxy-8-methoxy-4-methylenecaryophyllane (IV), $[\alpha]_D^{18}$ −8.8° (c 0.5; chloroform). IR spectrum (ν, cm^{-1}): 895, 1636, 1729, 3078, 3465, 3605. ^1H spectrum (ppm): 0.99 (s, 3 H), 1.01 (s, 3 H), 2.06 (s, 3 H, OAc), 3.25 (AB spectrum, 2H, J_{gem} = 9.5 Hz, $\Delta\delta$ = 0.02 ppm, 2 × H^{15}), 3.32 (s, 3 H, OCH_3), 3.96 (broad singlet, 1 H, C^8—OH), 4.80 (d, 1 H, J ≈ 1.0 Hz, H^{14}), 4.87 (d, 1 H, J ≈ 1.0 Hz, H^{14}), 5.25 (dd, 1 H, J = 5.0 and 6.0 Hz, H^5).

CONCLUSIONS

1. A new sesquiterpene — 14-hydroxycaryophyllene 4,5-oxide (I) — has been isolated from the unsaponifiable fractions of an ethereal extract of the leaves of *Betula pubescens*.

2. The treatment of (I) with a methanolic solution of caustic soda led to the formation of 5,8-dihydroxy-8-methoxy-4-methylenemethylcaryophyllane (III), probably as the result of the transannular interaction of the exocyclic double bond with the oxygen atom of the epoxy ring taking place with the participation of a molecule of water and a methoxide anion.

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