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HYDROLYSIS AND REARRANGEMENT REACTIONS  
OF CARYOPHYLLENE OXIDE

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**ABSTRACT.**—Caryophyllene oxide [**2**] undergoes hydrolysis and rearrangements in aqueous solution buffered at pH 4. Six major reaction products have been isolated and identified. The production of ketone **1**, aldehyde **3** and elimination products **4** and **5** indicates that a carbocation intermediate is involved. Hydrolysis of the epoxide also produced diols **6** and **7**.

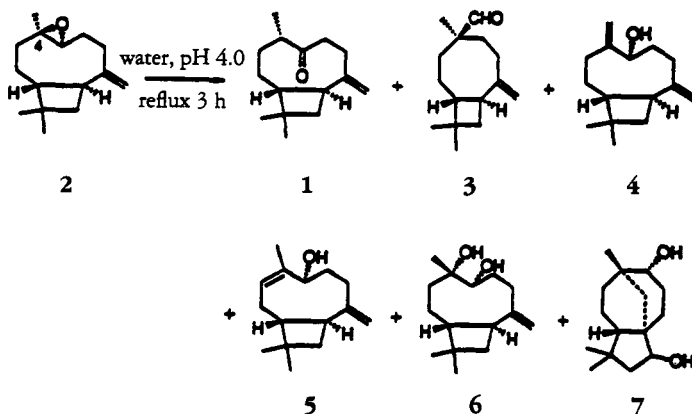
Caryophyllene oxide is one of the most widespread sesquiterpenoids in plants. Its precursor, caryophyllene, also is one of the important sesquiterpenes found in hops. In the present investigation caryophyllene oxide was heated under reflux for 3 h in buffered solution consisting of NaOAc/HOAc (pH 4.0). The reaction mixture was extracted and monitored by gas chromatography over a period of 10 min to 3 h for disappearance of the starting material. Seven major compounds (gc peak area larger than 2%) were present after 3 h.

Compounds **1–6** were extracted with pentane and compound **7** was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The individual compounds were purified by flash chromatography and hplc and analyzed. Analysis by gas chromatography-chemical ionization mass spectrometry (gc-cims) indicated that compounds **1–5** have molecular ion peaks with *m/z* 220, while those for compounds **6** and **7** have peaks with *m/z* 238. High-resolution ms showed that compounds **1**, **3–5** have the empirical formula C<sub>15</sub>H<sub>24</sub>O, and that compounds **6** and **7** have the empirical formula C<sub>15</sub>H<sub>26</sub>O<sub>2</sub>. The numbers of hydroxyl groups in the reaction products were determined by gc-ms analysis of the silylated derivatives. When treated with trimethylsilyl imidazole, compounds **4–7** yielded derivatives that showed intense ion peaks with *m/z* 73 for (CH<sub>3</sub>)<sub>3</sub>Si<sup>+</sup>. Compounds **4** and **5** have a molecular ion peak at *m/z* 292 which corresponds to one hydroxyl group, while silylated **6** and **7** both have a molecular ion peak at *m/z*

382, indicating that **6** and **7** are diols. In addition, the spectrum of **6** showed a peak at *m/z* 147 due to the formation of [(CH<sub>3</sub>)<sub>2</sub>SiOSi(CH<sub>3</sub>)<sub>3</sub>]<sup>+</sup>, which indicates that two hydroxyl groups are on adjacent carbon atoms or are in close proximity to one another.

The nmr data for **1–5** and **7** are consistent with those reported in the literature (1–5) (Scheme 1). The <sup>13</sup>C-nmr resonances of **6**, a compound that has not been reported previously, indicate that the exomethylene double-bond from caryophyllene oxide remained unchanged. Compound **6** has two <sup>13</sup>C-nmr resonances in the 70–90 ppm region for the carbinol carbon atoms. The hydroxyl protons also were identified in the 1.5–2.5 ppm region of the <sup>1</sup>H-nmr spectrum. The connectivities were determined from <sup>1</sup>H-<sup>1</sup>H and <sup>1</sup>H-<sup>13</sup>C nmr correlation data, and the stereochemistry of diol **6** was established based on expected inversion of configuration at C-4.

Compound **7** (clovane diol) has been observed as a by-product in the oxidation of caryophyllene by H<sub>2</sub>O<sub>2</sub> (6). Compounds **6** and **7** were the major products in the hydrolysis of caryophyllene oxide, and constituted 42% of the total gc peak area and 73% of the isolated products by weight. Compounds **4** and **5** have previously been reported as by-products in the oxidation of caryophyllene by lead tetraacetate (1). They are apparently the elimination products of the carbocation with the charge at C-4. Similar elimination products were found in the hydrolysis of humulene epoxides (6). Compounds



SCHEME 1

**1** and **3** are rearrangement products of caryophyllene oxide. They were previously found as products of boron trifluoride etherate-catalyzed rearrangement of caryophyllene oxide (**2**). As expected, ring opening takes place on the more substituted C-4 which can better stabilize the positive charge. The concentrations of all products increased with reaction time and considerable amounts of **4** and **5** already were present after refluxing for 10 min. When compounds **1**, **3**, **6**, and **7** were separately refluxed for 3 h, little change was observed in the products. Elimination and rearrangement products also were produced under hydrolytic conditions after the double-bond of caryophyllene oxide was hydrogenated. The carbocation, therefore, is likely formed directly from ring opening of the epoxide.

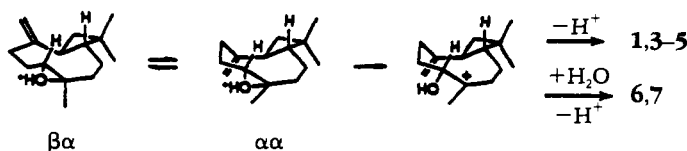
All six products could arise from the hydrolysis of the precursor conformation via the same tertiary carbocation (Scheme 2). Compounds **1**, and **3–5** can arise through proton loss after rearrangement, and **6** and **7** can be produced by addition

of H<sub>2</sub>O (after rearrangement in the case of **7**) followed by proton loss. There is the possibility that **1** undergoes acid-catalyzed equilibration via the enol in which case the initial stereochemical information at C-4 would be lost.

## EXPERIMENTAL

**HYDROLYSIS OF CARYOPHYLLENE OXIDE [2].**—Caryophyllene oxide (**2**, 95%) was purchased from Aldrich Chemical Company. One liter of distilled H<sub>2</sub>O buffered at pH 4.0 by 0.02 M NaOAc/HOAc was added to 30 ml EtOH solution containing 1 g of **2** with vigorous stirring. This mixture was boiled for 3 h under reflux. After cooling, the solution was extracted with pentane and then with CH<sub>2</sub>Cl<sub>2</sub>. The solvent was removed. Yield: 0.55 g viscous liquid from the pentane phase, 0.54 g white solid from the CH<sub>2</sub>Cl<sub>2</sub> phase.

**PRODUCT ISOLATION.**—The pentane extract of the hydrolysis product mixture, containing compounds **1–5** and part of **6** was fractionated by flash cc using a 1.5 × 50 cm Si gel column (Si gel 60, 32–63 μm) at a flow rate of 7 ml/min. The solvent system used was 100 ml hexane-CH<sub>2</sub>Cl<sub>2</sub> (3:1), 100 ml hexane-CH<sub>2</sub>Cl<sub>2</sub> (2:1), 200 ml hexane-CH<sub>2</sub>Cl<sub>2</sub> (1:1), 200 ml hexane-CH<sub>2</sub>Cl<sub>2</sub> (1:2), 200 ml CH<sub>2</sub>Cl<sub>2</sub>, 100 ml CH<sub>2</sub>Cl<sub>2</sub>-EtOAc (1:1), and 100 ml EtOAc. Fractions (15 ml) were collected. Elution was monitored by tlc, which was visual-



SCHEME 2

ized by  $I_2$  vapor or by concentrated  $H_2SO_4$ . After combining the fractions into six portions, the compounds were further purified by reversed-phase hplc with a  $250 \times 10$  mm column (C18, 5  $\mu$ m), using MeOH and MeOH/ $H_2O$  as solvent. Compound purity was checked by gc/fid. Yield: 16 mg of **1**, 16 mg of **2**, 19 mg of **3**, 13 mg of **4**, 68 mg of **5**, 69 mg of **6**. The  $CH_2Cl_2$  extract containing compound **7** was purified by cc with a  $2.5 \times 25$  cm Si gel column (Si gel 60, 32–63  $\mu$ m) at a flow rate of 5 ml/min, with 15 ml fractions being collected. The solvent systems used were: 100 ml  $CH_2Cl_2$ , 100 ml  $CH_2Cl_2$ -EtOAc (4:1), 100 ml  $CH_2Cl_2$ -EtOAc (2:1), 100 ml  $CH_2Cl_2$ -EtOAc (1:1), 100 ml  $CH_2Cl_2$ -EtOAc (1:2) and 200 ml EtOAc. Yield: 54 mg of **7** from 100 mg  $CH_2Cl_2$  extract.

#### SILYLATION OF THE REACTION PRODUCTS.—

The hydrolysis product mixture and the isolated pure compounds were treated with *N*-trimethylsilylimidazole-pyridine (1:1) for 30 min at 60°. The reaction mixture was then injected directly onto a gc column.

**STRUCTURE ANALYSIS.**—Gc-ms analyses were carried out with a 0.32 mm i.d.  $\times$  30 m DB-5 fused silica capillary column (J&W Scientific, Inc., Rancho Cordova, CA) for the trimethylsilylimidazole derivatized samples and a 0.32 mm i.d.  $\times$  30 m Supelcowax 10 fused silica capillary column (Supelco, Inc., Bellefonte, PA) for the hydrolysis products. Helium was used as carrier gas at a flow rate of 25 ml/min. Silylated samples were injected with a split ratio of 1:50. Temperature program: 120° (2 min); 120 to 250° at 2°/min; the electron energy was 70 eV.

The molecular ions in the ms were confirmed by chemical ionization. Ci spectra were obtained in the positive-ion mode using  $NH_3$  as reagent gas at a pressure of 0.6 Torr. The purified compounds were analyzed by hrms. The molecular mass for compounds **1–5** was 220.1828, which corresponds to the composition  $C_{15}H_{24}O$  (220.1827), and 238.1926 for compounds **6** and **7** corresponding to the composition  $C_{15}H_{26}O_2$  (238.1933).

The  $^1H$ -nmr and ms data are summarized below for **6**.  $^1H$ -Nmr spectra were recorded at 400 MHz in  $CD_3OD$ ,  $CDCl_3$ , or  $DMSO-d_6$  as solvents. Chemical shifts (ppm) are reported relative to TMS. The proton coupling constants were determined from phase-sensitive COSY nmr spectra.  $^{13}C$ -nmr spectra were recorded at 100 MHz.

4,11,11-TRIMETHYL-8-METHYLENE-BICYCLO[7.2.0]UNDECANE-4,5-DIOL (**6**).— $^1H$  nmr (400 MHz,  $CDCl_3$ )  $\delta$  0.97 (3H, s,  $CH_3$ -13), 1.00 (3H, s,  $CH_3$ -12), 1.14 (3H, s,  $CH_3$ -14), 1.34 (1H, dddd,  $J=19.5$  (2b), 8.9 (3a), 7.1 (1) and 3.5 (3b) Hz, H-2a), 1.55 (1H, dd,  $J=15.2$  (3b) and 8.9 (2a)

Hz, H-3a), 1.57 (1H, dddd,  $J=17.7$  (6b), 8.9 (7a), 5.6 (5) and 4.2 (7b) Hz, H-6a), 1.58 (1H, dd,  $J=17.7$  (10b) and 6.0 (9) Hz, H-10a), 1.65 (1H, dd,  $J=8.9$  (9) and 7.1 (2a) Hz, H-1), 1.65 (1H, dd,  $J=19.5$  (2a) and 9.6 (3b) Hz, H-2b), 1.73 (1H, dddd,  $J=17.7$  (6a), 9.6 (7b), 5.6 (5), and 4.2 (7a) Hz, H-6b), 1.73 (1H, dd,  $J=17.7$  (10a) and 7.1 (9) Hz, H-10b), 1.92 (1H, ddd,  $J=15.2$  (3a), 9.6 (2b), and 3.5 (2a) Hz, H-3b), 2.06 (1H, ddd,  $J=15.9$  (7b), 8.9 (6a), and 4.2 (6b) Hz, H-7a), 2.21 (1H, br s, -OH), 2.36 (1H, ddd,  $J=8.9$  (1), 7.1 (10-b), and 6.0 (10a) Hz, H-9), 2.43 (1H, ddd,  $J=15.9$  (7a), 9.6 (6b), and 4.2 (6a) Hz, H-7b), 3.59 (1H, d,  $J=5.6$  (6ab) Hz, H-5), 4.92 (1H, s, H-15a), 4.93 (1H, s, H-15b), coupling constant  $J < 2$  Hz: H-15/H-10b, H-5/H-14, H-3a/H-14, H-13/H-10b.  $^{13}C$  nmr (100 MHz,  $CDCl_3$ )  $\delta$  56.97,  $CH$  (C-1), 23.22,  $CH_2$  (C-2), 40.76,  $CH_2$  (C-3), 75.07, C (C-4), 73.37,  $CH$  (C-5), 32.61,  $CH_2$  (C-6), 34.71,  $CH_2$  (C-7), 152.00, C (C-8), 42.33,  $CH$  (C-9), 36.11,  $CH_2$  (C-10), 34.09, C (C-11), 30.05,  $CH_3$  (C-12), 22.06,  $CH_3$  (C-13), 21.47,  $CH_3$  (C-14), 110.45,  $CH_2$  (C-15). Eims  $m/z$  238 ( $M^+$ , 12), 220 ( $M^+ - H_2O$ , 2), 192 (3), 180 (11), 179 (100), 164 (4), 163 (4), 161 (6), 133 (5), 127 (17), 124 (6), 123 (45), 121 (12), 111 (6), 110 (5), 109 (29), 108 (7), 107 (14), 105 (6), 98 (5), 97 (8), 96 (10), 95 (25), 93 (15), 91 (7), 85 (8), 83 (16), 82 (10), 81 (37), 79 (14), 77 (6), 71 (6), 70 (6), 69 (35), 68 (5), 67 (21), 57 (10), 56 (7), 55 (47), 53 (12). Cims, isobutane  $m/z$  238 ( $M^+$ , 4), 237 (19), 222 (15), 221 ( $MH^+ - H_2O$ , 100), 220 ( $MH^+ - H_2O$ , 3), 219 (14), 203 (15). Eims, silylated  $m/z$  382 ( $M - 2H^+ + 2(CH_3)_3Si^+$ , 1), 292 (6), 223 (14), 198 (20), 197 (24), 183 (18), 176 (18), 147  $\{[(CH_3)_2SiOSi(CH_3)_3]^+, 34\}$ , 143 (47), 133 (11), 131 (10), 130 (21), 117 (18), 93 (13), 75 (22), 73 (100), 69 (16). Ft-ir (neat)  $\nu$  max 3403, 2953, 2930, 2863, 1638, 1462, 1441, 1381, 1285, 1121, 1053, 1013, 993, 945, 924, 885  $cm^{-1}$ .

**SUPPLEMENTARY MATERIAL AVAILABLE.**—Mass spectral data,  $^1H$ - and  $^{13}C$ -nmr spectra and gc graphs of compounds **1–7** (22 pages), are available from the senior author.

#### ACKNOWLEDGMENTS

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