

A Stable Rearrangement Product of Humulene-4,5-epoxide

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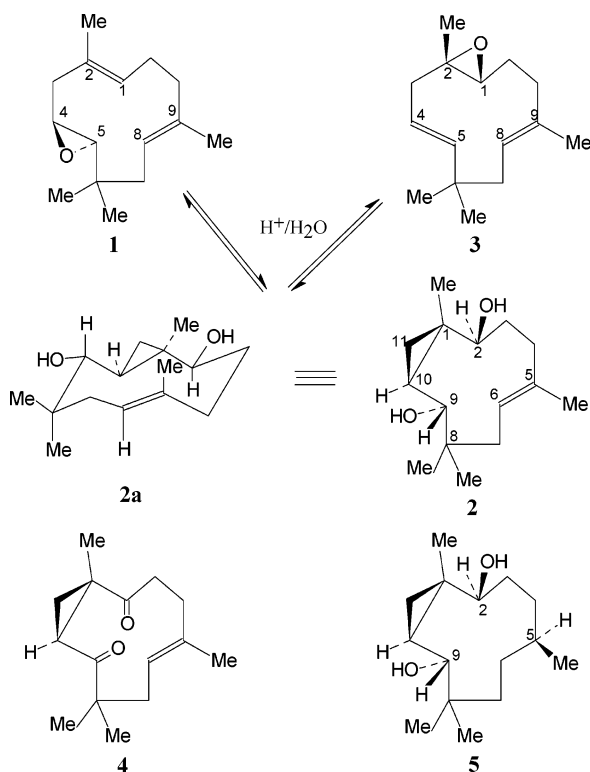
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Humulene-4,5-monoepoxide, **1**, may rearrange to the cyclopropyl diol **2** during chromatography over silica. The rearrangement can be reversed with acid.

The epoxides of humulene are naturally occurring and are of special concern to the brewing industry.¹ The interesting interconversion of epoxide **1** to epoxide **3**, proceeding through the cyclopropyl diol **2**, has already been observed.² Treatment of either epoxide **1** or **3** with refluxing acid (pH 4) gave in each case a mixture of more than 30 products, from which compound **2** was isolated, and, although its structure was later revised,³ its melting point has never been disclosed.

We now report that chromatography of epoxide **1** over silica affords diol **2**. Thus, diol **2** may appear as an artifact in the purification of epoxide **1** or **3**, and so this report also serves as a warning to workers in the field.



Epoxide **1**, synthesized from humulene through humulene triepoxide by the method of Roberts,⁴ was contaminated with various diepoxides and a triepoxide of humulene. Chromatography over silica gave elution of the compounds in the order of the number of oxygen atoms they contain. After triepoxide had been washed off, the column was cleaned with ether, whereupon product **2** eluted to form glistening crystals on the tip of the column. Subse-

quent chromatography of purified epoxide **1** also yielded diol **2**. Yields of diol **2** were variable, ranging up to 15%, depending upon the time the epoxide was in contact with the silica and upon the quantity of acid and water present.

The structure **2** was not immediately obvious. Elemental analysis was troublesome due to avid retention of water, but finally $C_{15}H_{26}O_2$, m/z 238, was obtained. From its polarity, both oxygen atoms in the compound were hydroxyl groups, yet the 1H NMR spectrum showed no protons geminal to hydroxyls downfield of δ 3.0, with only a single vinyl proton in this region, so these two hydroxyls were tentatively assumed to be tertiary. However the ^{13}C NMR spectrum provided two methine carbons (δ 82.5, 74.8) attached to oxygen, and since these values are too far downfield to be associated with an epoxide,⁵ they were assigned to secondary hydroxyls. High-field cyclopropyl protons were consistent with structure **2**, and H-2 (δ 2.78) and H-9 (δ 2.95) could be assigned on the basis of their coupling patterns.

The diol **2** cleanly oxidized to a diketone **4**, which showed no infrared hydroxyl absorption but which gave bands at 1680 and 1675 cm^{-1} , consistent with the presence of two carbonyls both adjacent to a cyclopropane moiety.⁶ The diol **2** could also be hydrogenated to a mixture of diastereomers, from which a single isomer, the saturated diol **5**, was isolated following extensive recrystallization. Compound **5** retained the protons H-2 (δ 2.75) and H-9 (δ 3.18) at high-field, and so it is the cyclopropane ring in these compounds which contributes to the upfield shift, rather than the double bonds.

Acetylation of diol **2** gave a diacetate showing the expected downfield shift of the protons geminal to the acetate group at δ 4.23 (H-2) and 5.65 (H-9). The diacetate gave a consistent melting point and provided NMR spectra similar to those reported⁷ for a diacetate obtained from epoxide **1** on treatment with BF_3/Ac_2O and for which an X-ray structure is available to establish the configuration, which also follows from mechanistic considerations.

The reversible nature of the reaction **2** to **1** became apparent when the proximity of the two hydroxyl groups in diol **2** was explored through attempted acetone formation. Diol **2** is stable in refluxing acetone, but the addition of a trace of *p*-toluenesulfonic acid converted the diol at room temperature within 2 h into epoxide **1** in more than 90% yield. Both hydroxyl groups in conformer **2a** of compound **2** are pseudoequatorial, both suitably placed antiperiplanar to the C10–C1 bond of the cyclopropyl ring to permit facile conversion into epoxide **1** after protonation of the C2 hydroxyl.

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Experimental Section

General Experimental Procedures. ^1H (220 Mz) and ^{13}C NMR (25.1 Mz) spectra were recorded in CDCl_3 solution. ^{13}C multiplicities were assigned by off-resonance decoupling.

Diol 2. Humulene-4,5-monoepoxide **1** was prepared from humulene triepoxide by the Stirling⁴ method. The oil showed (analytical TLC, petroleum/EtOAc, 9:1) predominantly monoepoxide **1** (R_f 0.49), with minor amounts of humulene (R_f 0.68), humulene-1,2-monoepoxide (R_f 0.39), humulene diepoxides (R_f ~0.24), and unreacted humulene triepoxide (R_f 0.06). In this relatively nonpolar analytical system, compound **2** has R_f 0.0. Column chromatography (petroleum/diethyl ether, 49:1) afforded the monoepoxide **1**. Further elution with increasing amounts of ether afforded the di- and triepoxides. Elution with ether then afforded compound **2** (typically 7–15%), which crystallized at the column tip. [1*RS*,2*RS*,5*E*,9*SR*,10*RS*]-1,5,8,8-Tetramethylbicyclo[8.1.0]undec-5-ene-2,9-diol, **2**, as the racemate, had mp 109–111 °C (ether/petroleum). The compound retained water tenaciously (*anal.* for a sample dried overnight over P_2O_5 and high vacuum: C 75.4%, H 11.3%, calcd for $\text{C}_{15}\text{H}_{26}\text{O}_2$, C 75.6%, H 11.0%). IR (Nujol) ν_{max} 3320 s, 1660 w, 1095, 1022, 925 cm^{-1} ; ^1H NMR δ 5.26 (br dd, H-6), 2.95 (d, H-9), 2.78 (dd, H-2), 2.12 (dd, H-7a), 1.87 (dd, H-7b), 1.6–2.2 (4H, m, H-3 and H-4), 1.63 (s, C5-Me), 1.09 (ddd, H-10), 0.95, 0.95, 1.05 (three 3H s, Me), 0.56 (dd, H-11a), 0.36 (dd, H-11b); with $J_{2,3a} = 3$, $J_{2,3b} = 10$, $J_{6,7a} = 4$, $J_{6,7b} = 11$, $J_{7a,7b} = -14$, $J_{9,10} = 7$, $J_{10,11a} = 6$, $J_{10,11b} = 10$, $J_{11a,11b} = -4.5$ Hz. Decoupling at δ 1.63 converted the δ 5.26 system into a sharp dd, $J = 11$ and 4 Hz. Irradiation at δ 1.8 converted the δ 2.78 system into a broad singlet. Irradiation at δ 2.0 converted the δ 5.26 system into a broad doublet, $J = 11$ Hz. ^{13}C NMR δ 132.6 (C-5), 124.9 (C-6), 82.5 (C-2), 74.8 (C-9), 40.2 and 38.4 (C-4 & C-7), 39.8 (C-8), 31.8 (C-3), 31.2 (C-10), 30.2 (Me), 28.3 (C-1), 18.5 (Me), 17.8 (C-11), 16.4 (Me), 13.7 (Me). These ^{13}C values are all within 0.2 ppm of those listed³ for a compound obtained (no mp reported) by hydrolysis of a diacetate, and they agree well (except for one peak, δ 23.2 rather than 31.8 for C-3, believed to be a typographical error) with data² for a compound (no mp reported) isolated as one of more than 30 products from aqueous acid treatment of humulene monoepoxide **1** or **3**. EIMS m/z 238 (M, 2%), 220 (M – H_2O , 2), 205 (M – H_2O – Me, 2), 202 (M – $2\text{H}_2\text{O}$, 3), 192 (2), 191 (2), 187 (4), 178 (35), 138 (30), 135 (25), 125 (35), 121 (20), 111 (100), 109 (45).

Compound **2** was also obtained in similar yield during the chromatographic purification of monoepoxide **1**.

The diacetate of compound **2** (Ac_2O /pyridine, 4 h, quantitative yield) gave chunky crystals, mp 144 °C (ether/petroleum) (lit.⁷ 140–142 °C) (*anal.* C 70.7%, H 9.5%, calcd for $\text{C}_{15}\text{H}_{30}\text{O}_4$ C 70.8%, H 9.4%). IR (Nujol) ν_{max} no OH, 1725 s br, 1240 s br, 1035, 1018, 950 cm^{-1} ; ^1H NMR δ 5.45 (br d, H-6), 4.65 (d, H-9), 4.23 (dd, H-2), 2.36 (dd, H-7a), 2.08 and 2.08 (two acetate Me), 1.93 (dd, H-7b), 2.3–1.7 (4H, m, H-3 and H-4), 1.74 (s, C9-Me), 1.22 (ddd, H-10), 1.20, 1.14, 0.95 (three s, Me), 0.70 (dd, H-11a), 0.14 (dd, H11b); with $J_{2,3a} = 3$, $J_{2,3b} = 10$, $J_{6,7a} = \text{small}$, $J_{6,7b} = 11$, $J_{7a,7b} = -15$, $J_{9,10} = 8$, $J_{10,11a} = 6$, $J_{10,11b} = 10$, $J_{11a,11b} = -5$ Hz, similar to the literature values.⁷

Diketone 4. Diol **2** (130 mg) was oxidized (5 h, RT) with pyridinium chlorochromate in CH_2Cl_2 containing NaOAc as buffer.⁸ The oily product (134 mg) partly crystallized overnight. Elution from a short silica column (petroleum/diethyl ether, 9:1) gave [1*RS*,5*E*,10*RS*]-1,5,8,8-tetramethylbicyclo[8.1.0]-undec-5-ene-2,9-dione, **4**, mp 75–76 °C (petroleum) (*anal.* C

76.9%, H 9.7%, calcd for $\text{C}_{15}\text{H}_{22}\text{O}_2$, C 76.9%, H 9.5%). IR (Nujol) ν_{max} no OH, 1680, 1675, 1105, 1090, 1075, 975, 930 cm^{-1} ; ^1H NMR δ 5.52 (br dd, H-6), 3.27 (X region of an ABCX system, H-3a), 2.4 (m, H-3b and H-7a), 2.5–2.1 (m, two H-4), 2.26 (obscured, H-7b), 2.20 (dd, H-10), 1.98 (dd, H-11a), 1.75 (s, C5-Me), 1.35 (dd, H-11b), 1.40, 1.26, 1.16 (three s, Me); with $J_{6,7a} = \text{small}$, $J_{6,7b} = 10$, $J_{10,11a} = 7$, $J_{10,11b} = 9$, $J_{11a,11b} = -3$ Hz. EIMS m/z 234 (M, 7%), 219 (M – Me, 5), 206 (M – CO, 2), 191 (M – Me – CO, 3), 151 (35), 124 (32), 123 (35), 109 (100), 95 (67).

Diol 5. Diol **2** (103 mg) in EtOH was hydrogenated (5 h, atmospheric pressure and room temperature) over Pd/C. Numerous recrystallizations (petroleum/diethyl ether) and careful drying gave [1*RS*,2*RS*,5*RS*,9*SR*,10*RS*]-1,5,8,8-tetramethylbicyclo[8.1.0]undecane-2,9-diol, **5** (78 mg). The C-5 configuration is uncertain, but follows if it is assumed that the conformation depicted in **2a** hydrogenates from the external face. Compound **5** as the racemate had mp 81–83 °C (ether/petroleum) (*anal.* C 75.2%, H 12.0%, calcd for $\text{C}_{15}\text{H}_{28}\text{O}_2$, C 75.0%, H 11.7%). IR (Nujol) ν_{max} 3310 s, no C=C, 1030, 935 cm^{-1} ; ^1H NMR δ 3.18 (d, $J = 7$ Hz, H-9), 2.75 (X region of an ABX system, H-2), 1.15, 1.08, 0.92 (three s, Me; obscuring H-10), 0.90 (d, Me), 0.7–0.3 (m, two H-11). This spectrum showed a small impurity doublet ($J = 7$ Hz) at δ 3.35, which may be H-9 of a conformer or of the C-5 configurational isomer. EIMS m/z 248 (M, 6%), 222 (M – H_2O , 7), 141 (37), 123 (35), 109 (27), 95 (100), with a metastable at 107.3 (141 – H_2O → 123).

Acid Treatment of Diol 2. Diol **2** was unchanged by boiling in acetone. Diol **2** dissolved in anhydrous acetone with a crystal of *p*-toluenesulfonic acid at room temperature had completely reacted overnight to give a one-spot oil (R_f 0.73 in EtOAc, compared with compound **2**, R_f 0.29). Subsequent runs showed that starting material was completely gone after 2 h. Normal workup followed by elution off a short column provided humulene 4,5-epoxide, **1** (yield >90%), with characteristic odor, identical retention times (silica and AgNO_3 impregnated plates), and superimposable spectra (^1H NMR, IR, MS) to authentic epoxide **1**. The analytical methodology available did not allow the detection of very minor amounts of the alternative 1,2-epoxide of humulene, which could have been a byproduct of this reaction.^{2,3}

Compound **2** showed signs of decomposition after some time on an AgNO_3 impregnated plate, to give a spot with the same R_f as humulene 4,5-epoxide, **1**.

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References and Notes

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