We have repeated the $Zn(BH_4)_2$ reduction of DL-**12** and obtained in low yield a mixture of products (TLC) from which only compound DL-**5** was identifiable. (Dr. Gensler has kindly pointed out that the $Zn(BH_4)_2$ used in his work had been prepared from $NaBH_4$ while ours was derived from $LiBH_4$.) Apparently reduction of complex ketones by mixed metal hydrides is erratic.

$NaBH_4$ in methanol had been used successfully[1] to reduce ketone **9** (2α,3α) to alcohol **8** (2α,3α,4α). Subsequently we have found that ketones **10** and **11** by the same reagent yield alcohols **1** and **3**, respectively, the reported products by $Zn(BH_4)_2$ reduction.[9]

(6) We are indebted to Drs. W. J. Gensler and A. von Wartburg for these reference samples.
(7) J. L. Hartwell and A. W. Schrecker, *Prog. Chem. Org. Nat. Prod.*, **15**, 83 (1958).
(8) E. Schreier, *Helv. Chim. Acta*, **47**, 1520 (1964).
(9) W. J. Gensler, F. Johnson, and A. D. Sloan, *J. Am. Chem. Soc.*, **82**, 6074 (1960).
(10) A. W. Schrecker and J. L. Hartwell, *J. Am. Chem. Soc.*, **76**, 752 (1954).
(11) The olefin α-apopodophyllotoxin (**15**, 2α), which would be the primary product of dehydration of **7** (or **8**), is unknown. Apparently it is unstable and is promptly isomerized to the β isomer [W. J. Gensler, Q. A. Ahmed, Z. Muljiani, and C. D. Gatsonis, *J. Am. Chem. Soc.*, **93**, 2515 (1970)]. Following the reaction by TLC failed to show a second olefinic product.
(12) Further confirmation was forthcoming when a sample of **7** provided by Dr. von Wartburg proved to be identical with our product by direct comparisons (IR, NMR). The Sandoz compound (unpublished) had been prepared in 1970 by Mr. Max Kuhn (private communication from Dr. von Wartburg).
(13) A. W. Schrecker and J. L. Hartwell, *J. Am. Chem. Soc.*, **75**, 5916 (1953).
(14) More detailed studies with this and the other diastereomers are in progress. The stability of the lactone ring of **8** is especially interesting in view of the previous observation[1] that it is the one stereoisomer which is cleaved to hydroxy acid under hydrogenolysis conditions (Pd/C).
(15) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. H. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).
(16) Drs. von Wartburg and E. Schreier in a private communication have confirmed that their manganese dioxide oxidations of DL-**6** to the ketone DL-**12** were "slow and incomplete".
(17) DL-Epiisopodophyllotoxin (DL-**6**) also dissolves poorly in these solvents; probably the poor yield in its oxidation can be attributed to the low solubility. DL-Isosikkomotoxin, which differs from DL-**12** only in having methoxy groups at C-6 and C-7 instead of the 6,7-methylenedioxy group, was oxidized to the corresponding ketone by MnO_2 in 60% yield.[5]
(18) Melting points were determined on an electrical hot stage and are uncorrected. Infrared spectra were obtained using a Perkin-Elmer Infracord 137; optical rotation measurements with a Carl Zeiss photoelectric precision polarimeter. Ultraviolet spectra were measured on a Beckman Acta T. M. III spectrometer. Mass spectra were obtained on a Finnegan 1015 GC–MS spectrometer. Nuclear magnetic resonance spectra were done on Varian A-60A, XL-100, or CFT-20 spectrometers, with tetramethylsilane as internal reference; chemical shifts are given on the τ scale.
(19) These signals are temporarily unassigned [see D. C. Ayres, J. A. Harris, P. N. Jenkins, and L. Phillips, *J. Chem. Soc.*, 1343 (1972)].
(20) E. Wiberg and W. Henle, *Z. Naturforsch.*, **76**, 579 (1952).
(21) Epimers **5** and **6** are well resolved by HPLC on a μ-Porasil (Waters Associates) column by methylene chloride–2-propanol (97:3) at a flow rate of 0.7 ml/min.
(22) Based on starting compound consumed.
(23) A. W. Schrecker and J. L. Hartwell, *J. Am. Chem. Soc.*, **74**, 5676 (1952).
(24) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

A Reinvestigation of the Reaction of α-Pinene with Hypochlorous Acid

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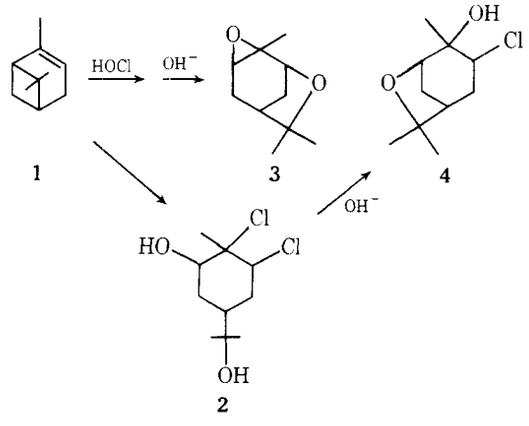
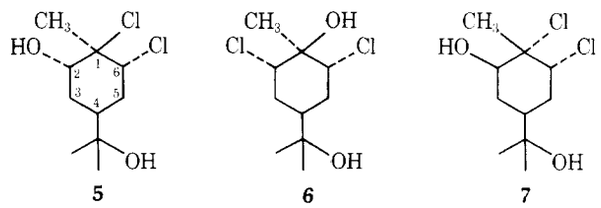
Treatment of α-pinene with hypochlorous acid yields three isomeric *p*-menthane dichlorohydrins **5**, **6**, and **7** in a ratio of 90:5:1, respectively. The structure and stereochemistry of these isomers were established by spectral and chemical means. Treatment of dichlorohydrin **5** with 1 equiv of potassium hydroxide at ambient temperature affords an epoxychlorohydrin **13**. Further reaction of **13** with another equivalent of base at ambient temperature yields a 60:40 mixture of (−)-pinol oxide (**3**) and pinol chlorohydrin (**4**). Epoxide **13** is selectively converted to (−)-pinol oxide (**3**) by reaction with potassium hydroxide at 100 °C or to pinol chlorohydrin (**4**) by reaction with water containing a trace of acid. Zinc and ethanol slowly converts pinol chlorohydrin (**4**) into (+)-pinol (**14**) which is epoxidized to (+)-pinol oxide (**3**), the enantiomer of (−)-pinol oxide (**3**) obtained by the action of alkali on **5**.

α-Pinene (**1**) is known to react with 2 equiv of hypochlorous acid[2–4] to afford, among other products, an optically active dichlorohydrin **2**, mp 136–137 °C. The action of alkali on



dichlorohydrin **2** or on the crude mixture obtained from hypochlorous acid and α-pinene gave pinol oxide (**3**)[5] and optically active, mp 131–132 °C, and racemic, mp 104–105 °C, pinol chlorohydrin (**4**). Assignment of stereochemistry to these materials based on the evidence provided in the literature is not possible. Moreover, a number of the confusing observations made by Wagner[2] and Henderson[3] can be traced to their use of α-pinene which was of questionable optical purity[7] and contained β-pinene.

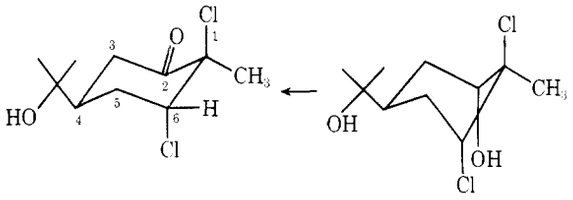
Our need for a sample of optically active pinol oxide (**3**) prompted us to reinvestigate the action of hypochlorous acid on (+)-α-pinene.[8] We observed that the procedure of Wagner[2] involving the addition of a sodium hypochlorite solution to acetic acid and α-pinene led to a complicated mixture of products. We then turned to the procedure of Henderson and Marsh[3] using a distilled solution of hypochlorous acid prepared from calcium hypochlorite and boric acid[10] and in this way obtained three isomeric *p*-menthane dichlorohydrins **5**, **6**, and **7** in a ratio of 90:5:1, respectively.



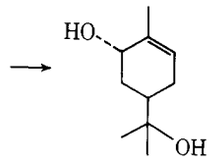
The major product **5** partially crystallized from the crude mixture. The remainder of the mixture was subjected to column chromatography affording additional quantities of pure **5** as well the two minor isomers **6** and **7**, both of which were still contaminated with **5**.

With pure dichlorohydrin **5** in hand an investigation of its structure and stereochemistry was undertaken. The most significant feature of its NMR spectrum was a methyl singlet at 1.76 ppm assigned to the methyl group at C-1 which must be attached to a carbon bearing a chlorine atom. The reaction of dichlorohydrin **5** with zinc and ethanol afforded *trans*-sobrerol (**8**),[11] which establishes a trans relationship between the C-2 hydroxyl group and the C-4 hydroxyisopropyl group in **5**.

Oxidation of **5** with Jones reagent gave the dichlorohydroxycarvone derivative **9**.[12] A triplet at 4.60 ppm with a



9 **5a**



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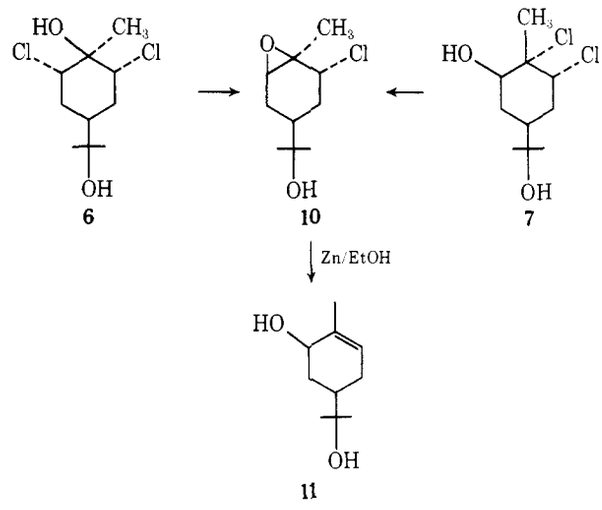
coupling constant of 2.5 Hz[13] suggested the presence of an equatorial proton at C-6. An equatorial methyl and axial chlorine at C-1 were demonstrated by a small upfield shift of the methyl signal at 1.75 ppm on changing from deuteriochloroform to benzene,[14] by an infrared carbonyl absorption at 5.80 μ which is essentially identical with the carbonyl absorption exhibited by carvomenthone (5.82 μ),[15] and by an ultraviolet maximum at 302 nm (ϵ 40) which is markedly shifted to higher wavelength[16] from the maximum at 286 nm shown by carvomenthone. Thus, the geometry of the two chlorines in **9** must be trans and the dichlorohydrin from which it is derived must have the structure, stereochemistry, and conformation depicted by **5a**.

The inability to cleanly separate dichlorohydrins **6** and **7** from **5** prevented a direct determination of their structure and stereochemistry. However, inspection of the NMR spectrum of an 80:20 mixture of **6** and **5** revealed a sharp singlet at 1.50 ppm assigned to a CH_3CO group at C-1 and a clean quartet at 4.37 ppm which was the only downfield signal attributed to **6**. The symmetric nature of the latter signal suggested a symmetric structure for **6** and if this were indeed the case, then **6** must be optically inactive. There was no way to ascertain this fact directly because the mixture showed low optical rotation values presumedly attributed to the presence of **5**. This matter was resolved by treating the mixture of **6** and **5** with potassium carbonate in aqueous methanol, which led to an easily separated mixture of epoxychlorohydrin **10** and pinol oxide (**3**) and pinol chlorohydrin (**4**) which are derived from dichlorohydrin **5** (see below). Epoxide **10** proved to be optically inactive and requires that its precursor be dichlorohydrin **6**.[17] Treatment of epoxide **10** with zinc and aqueous ethanol afforded *dl-cis*-sobrerol (**11**),[11] which further established the geometric relationship of the functional groups in **10** and **6**.

The problems encountered with the separation of **7** from **5** were much the same experienced with **6**. When treated with potassium carbonate in aqueous methanol the mixture of **7** and **5** yielded the same three products, **3**, **4**, and **10**, obtained from the mixture of **6** and **5**. In this instance, however, the epoxychlorohydrin **10** proved to be optically active requiring its precursor to be formulated as structure **7**.

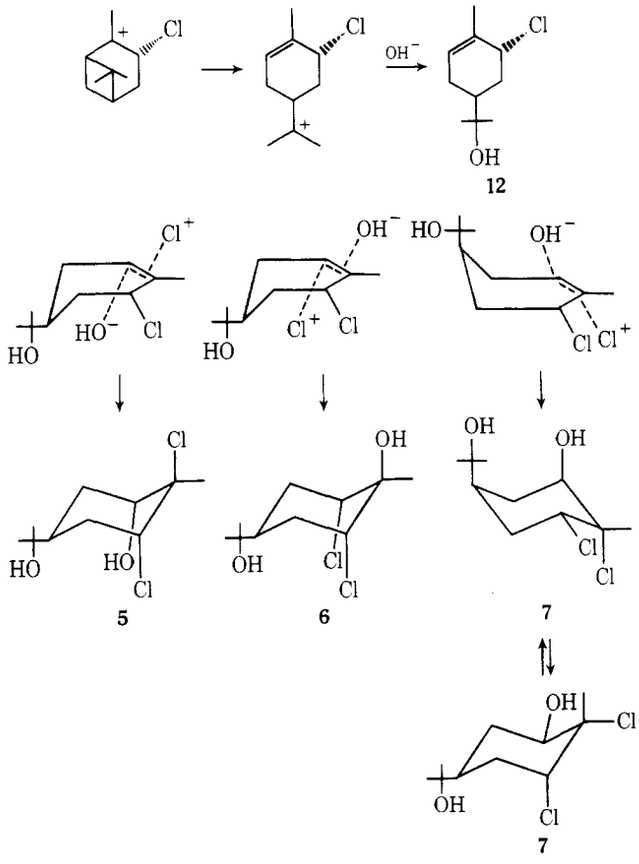
It may be noted that the three dichlorohydrins **5**, **6**, and **7**



6 **10** **7**

11

have the same stereochemistry at C-6 suggesting that they are formed from a common intermediate which is generated by initial attack of chloronium ion from the least hindered side at the C-2 position of α-pinene (**1**). Ring opening and capture of hydroxide ion would convert intermediate **1a** into the unsaturated chlorohydrin **12**.[18] Anti-diaxial addition of the second hypochlorous acid molecule to **12** is apparently initiated to the greatest extent by a chloronium ion approaching from the least hindered side of the carbon–carbon double bond, i.e., trans to the chlorine at C-6, to form dichlorohydrin **5**. The predominant formation of this seemingly anti-Markownikoff product[20] may also be a consequence of the inductive effect of the chlorine at C-6 since it is known that addition of hypochlorous acid to allyl chloride gives predominantly 2,3-dichloro-1-propanol.[22] Formation of the minor isomers **6** and **7** is a consequence of chlorine attack on **12** from the more hindered side with overall anti-diaxial addition leading to **6**. The very small amount of **7** may result from



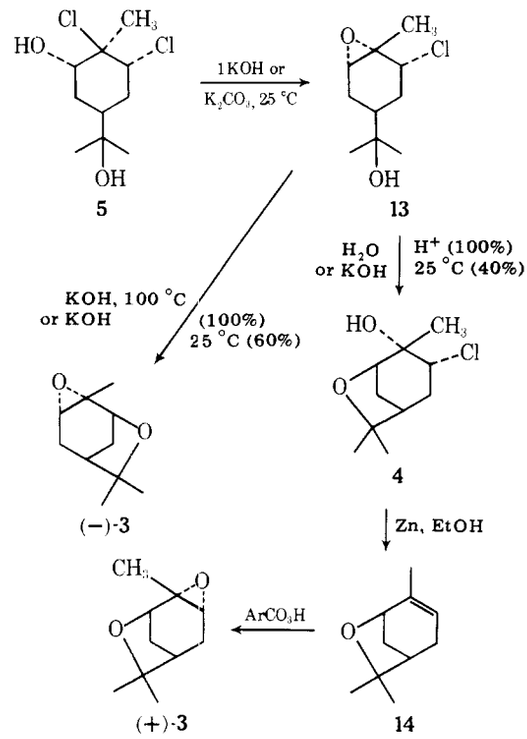
12

5 **6** **7**

7

diaxial addition to a less stable conformation of **12** or some other obscure mechanism.

An investigation of the action of bases on dichlorohydrin **5** revealed that several products are formed depending on reaction conditions. Treatment of **5** with 2 equiv of potassium hydroxide in water at reflux gave a high yield of pinol oxide (**3**) containing a trace of pinol chlorohydrin (**4**). When the same reaction was conducted at ambient temperature a 60:40 mixture of **3** and **4** was obtained. With 1 equiv of base at ambient temperature the epoxychlorohydrin **13** was the only

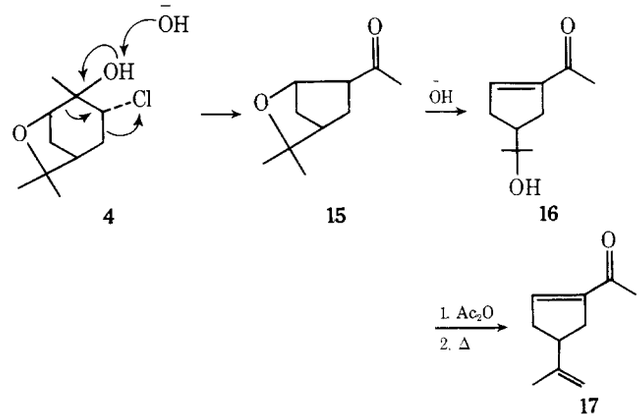


product. Epoxychlorohydrin **13** is the precursor for both **3** and **4** since it is converted to pinol oxide **3** in high yield when treated with 1 equiv of base at reflux and gives a 60:40 mixture of **3** and **4** when the reaction is conducted at ambient temperature. When **13** was kept in water containing a trace of acid it was quantitatively transformed into pinol chlorohydrin (**4**).[23]

The structure of pinol chlorohydrin (**4**) was demonstrated by an NMR methyl singlet at 1.36 ppm which indicates the compound is a tertiary alcohol. The large coupling constant exhibited by the quartet at 4.32 ppm suggests that the C-3 proton is axial and the chlorine equatorial. The cis relationship of the chlorohydrin is in accord with the observation that **4** is recovered unchanged after exposure to base at ambient temperature.[2,5] Prolonged heating of **4** with zinc and ethanol gave (+)-pinol (**14**) which on epoxidation with *m*-chloroperbenzoic acid afforded (+)-pinol oxide (**3**), $[\alpha]_D$ +32.24°, the enantiomer of (−)-pinol oxide (**3**), $[\alpha]_D$ −32.06°, obtained by the action of base on dichlorohydrin **5**.

It is instructive to note that the pinol skeletons of **3** and **4** are enantiomeric. This is expected if the action of base on epoxychlorohydrin **13** proceeds by way of an intramolecular alkoxide displacement of epoxy oxygen or chloride. Since the conversion of **13** can be controlled to yield either **3** or **4** and since **13** is readily prepared from (+)-α-pinene, (+)-α-pinene becomes a convenient starting material for the synthesis of both pure enantionmers of pinol oxide (**3**).

One final reaction of pinol chlorohydrin (**4**) is worthy of comment. Treatment of **4** with aqueous potassium hydroxide at reflux afforded the acetylcyclopentene derivative **16** whose structure was confirmed by acetylation and pyrolysis to 1-



acetyl-4-isopropenylcyclopentene (**17**).[24] A quasi-benzylic acid type of rearrangement[25] of **4** would yield **15** which then undergoes a base-initiated elimination to afford the acetylcyclopentene **16**.

Experimental Section

All boiling and melting points are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Infracord, Model 137-B. NMR spectra were recorded with Varian Associates A-60A and Perkin-Elmer R-32 instruments and are reported in parts per million from tetramethylsilane as an internal standard. Optical rotations were measured with a Zeiss polarimeter. Mass spectra were determined on a Hitachi RMU-6D instrument by the Purdue University Spectral Service. Ultraviolet spectra were recorded on a Cary Model 15 instrument. Microanalyses were performed by Dr. C. S. Yeh and associates.

Reaction of (+)-(1*R*,5*R*)-α-Pinene with Hypochlorous Acid. To 5 ml (0.31 mol) of (+)-α-pinene was added dropwise with vigorous stirring (30 min) 850 ml (0.028 mol) of 0.033 M hypochlorous acid solution.[10] The mixture was extracted with 25 ml of pentane. The pentane solution was dried (Na_2SO_4) and evaporated to leave 2.72 g of pure α-pinene. The aqueous phase was saturated with sodium chloride and extracted with ether. The ether solution was dried (Na_2SO_4) and the ether removed to leave 2.67 g of a viscous light yellow oil which gradually deposited crystals on standing. The mixture was diluted with carbon tetrachloride and the solid separated by filtration. Extensive column chromatography of the carbon tetrachloride solution on silica gel using ether–pentane as eluent gave additional quantities of the pure major product **5** and fractions rich in two minor components **6** and **7** which could not be freed entirely from the major product. The proportion of **5**, **6**, and **7** (90:5:1) was estimated by examining the NMR spectra of the crude product and various chromatography fractions.

Pure (1*R*,2*S*,4*S*,6*R*)-1-*cis*-6-dichloro-*trans*-*p*-menthane-*cis*-2,8-diol (**5**) was obtained by recrystallization from carbon tetrachloride and showed mp 134–135 °C; $[\alpha]^{26}_D$ −15.05° (*c* 3.76, $CHCl_3$); IR ($CHCl_3$) 2.80 and 2.90 μ; NMR ($CDCl_3$) 1.21 [s, 6,$(CH_3)_2C$], 1.76 (s, 3, CH_3CCl), 1.8–2.4 (m, 5), 2.66 (2, –OH), 4.02 (m, 1, –CHO), and 4.46 ppm (m, 1, –CHCl); mass spectrum *m/e* (rel intensity) 225 (1), 207 (3), 187 (3), 93 (18), 59 (100), 43 (35), 41 (13), and 39 (7).

Conversion of Dichlorohydrin 5 to *trans*-Sobrerol (8) with Zinc and Ethanol. A mixture of 863 mg (0.036 mol) of **5**, 2.5 g (0.038 g-atom) of acid-washed zinc dust, 20 ml of 95% ethanol, and 5 ml of water was refluxed for 18 h. The mixture was cooled, diluted with 50 ml of water, saturated with sodium chloride, and extracted with ether. The ether solution was dried (Na_2SO_4) and evaporated to give 536 mg of white solid. Recrystallization from ethyl acetate gave pure *trans*-sobrerol (**8**): mp 148–149 °C (lit.[11] mp 148–149 °C); NMR ($CDCl_3$) 1.20 [s, 6, $(CH_3)_2C$–], 1.3–2.3 (m, 7), 1.79 (s, 3, $CH_3C{=}C$–), 4.04 (m, 1, CHO) and 5.5 ppm (m, CH=C–); mass spectrum *m/e* (rel intensity) 170 (2), 152 (28), 137 (25), 110 (12), 109 (85), 108 (14), 95 (21), 94 (18), 93 (16), 81 (19), 79 (50), 71 (12), 69 (17), 59 (100), 55 (21), 43 (77), 41 (37), and 39 (21).

(1*R*,4*S*,6*R*)-1-*cis*-6-Dichloro-8-hydroxy-*trans*-*p*-menthan-2-one (9). Approximately 1 ml of Jones reagent was added to a vigorously stirred solution of 400 mg (0.0017 mol) of **5** in 25 ml of acetone at 0 °C. Isopropyl alcohol was added to destroy the excess oxidant and ether was added. The salts were removed and washed with ether. The ether solution was washed with water and dried ($MgSO_4$) and the ether was removed to yield 356 mg of an oil. Pure **9** obtained by TLC could not be induced to crystallize and showed $[\alpha]^{25}_D$ +39.56° (*c* 3.20,

$CHCl_3$); IR 2.95 and 5.80 μ; NMR ($CDCl_3$) 1.25 [s, 6, $(CH_3)_2C$–], 1.75 (s, 3, CH_3CCl), 2.0–3.1 (m, 6), and 4.60 ppm (t, 1, J = 2.5 Hz, –CHCl); NMR (C_6H_6) 1.00 [s, 6, $(CH_3)_2C$–], 1.72 (s, 3, CH_3CCl), and 4.29 ppm (t, 1, –CHCl); mass spectrum m/e (rel intensity) 238 (1), 223 (3), 145 (9), 109 (31), 59 (84), 43 (100), 41 (21), and 39 (14).

Anal. Calcd for $C_{10}H_{16}Cl_2O_2$: C, 50.21; H, 6.69; Cl, 29.71. Found: C, 50.50; H, 6.91; Cl, 29.63.

Reaction of a Mixture of 5 and 6 with Potassium Carbonate. A solution of 2 g of a 2:1 mixture of **5** and **6** and 3 g of potassium carbonate in 20 ml of methanol and 10 ml of water was refluxed for 4 h. The solution was taken up in ether which was then washed with water and dried (Na_2SO_4). Removal of the solvent left 1.4 g of a brown oil. Column chromatography of the oil on silica gel using ether–pentane as an eluent gave 570 mg of pinol oxide (**3**), 90 mg of pinol chlorohydrin (**4**), and 448 mg of *cis*-6-chloro-1,2-epoxy-*trans*-*p*-methan-8-ol (**10**): $[\alpha]^{29}D$ 0° (*c* 6.40, $CHCl_3$); IR 2.93, 3.43, 6.70, 6.94, 7.25, 7.32, 7.66, 7.82, 7.97, 8.10, 8.24, 8.75, 8.95, 9.16, 9.45, 9.81, 10.20, 10.42, 10.61, 10.76, 10.88, 11.34, 11.82, 12.20, 13.13, and 14.1–14.5 μ; NMR ($CDCl_3$) 1.15 [s, 6, $(CH_3)_2C$–], 1.47 (s, 3, CH_3CO), 1.7–2.3 (m, 5), 3.14 (d, 1, CHO–), and 4.43 ppm (t, 1, –CHCl); mass spectrum m/e (rel intensity) 204 (1), 151 (5), 111 (10), 109 (15), 107 (13), 105 (16), 95 (10), 93 (34), 84 (12), 81 (10), 71 (17), 69 (12), 67 (10), 59 (100), 55 (11), 53 (11), 43 (98), 41 (29), and 39 (22).

When the reaction of the mixture of **5** and **6** with potassium carbonate was conducted at ambient temperature the NMR spectrum of the crude product indicated a mixture of epoxide **10** and epoxide **13**.

Conversion of Epoxide 10 to (±)-*cis*-Sobrerol with Zinc and Ethanol. A mixture of 223 mg (0.0011 mol) of epoxide **10**, 0.5 g (0.0076 g-atom) of acid-washed zinc, 26 ml of ethanol, and 5 ml of water was kept at reflux for 70 h. Saturated ammonium chloride solution (15 ml) was added and the resulting solution was saturated with sodium chloride. The solution was extracted with ether, and the ether was dried (Na_2SO_4) and removed to yield 148 mg of a light yellow oil which slowly crystallized. The solid was washed with ether to give 82 mg of (±)-*cis*-sobrerol (**11**): mp 103–104 °C (lit.[11] mp 105–106 °C); NMR ($CDCl_3$) 1.18 [s, 6, $(CH_3)_2C$–], 1.3–2.5 (m, 7), 1.75 (s, 3, $CH_3C{=}C$–), 4.12 (m, 1, –CHO), and 5.47 ppm (m, 1, –CH=C–); mass spectrum m/e (rel intensity) 170 (1), 152 (24), 137 (34), 109 (69), 95 (22), 94 (78), 93 (38), 91 (15), 79 (68), 77 (17), 69 (21), 59 (100), 55 (22), 43 (74), 41 (30), and 39 (17).

Reaction of a Mixture of 5 and 7 with Potassium Carbonate. A solution of 350 mg (0.0015 mol) of a 55:45 mixture of **7** and **5**, 0.5 g (0.0036 mol) of potassium carbonate, 25 ml of methanol, and 3 ml of water was kept at reflux for 2.5 h. Workup in the usual manner gave 286 mg of a brown oil. Preparative TLC of this oil afforded 46 mg of pinol oxide (**3**), 11 mg of pinol chlorohydrin (**4**), and 133 mg of (1*R*,2*R*,4*S*,6*R*)-*cis*-6-chloro-1,2-epoxy-*trans*-*p*-menthan-8-ol (**10**). An analytical sample of (+)-**10** was obtained by recrystallization from ethyl acetate and showed mp 46–47 °C, $[\alpha]^{26}D$ +72.62° (*c* 2.40, $CHCl_3$), and IR and NMR spectra identical with those of (±)-**10** described above.

Anal. Calcd for $C_{10}H_{17}ClO_2$: C, 58.68; H, 8.31; Cl, 17.36. Found: C, 58.50; H, 8.34; Cl, 17.50.

Reaction of Dichlorohydrin 5 with Excess Potassium Hydroxide at 100 °C. A mixture of 14 g (0.058 mol) of **5**, 40 ml (0.142 mol) of 20% potassium hydroxide, and 100 ml of water was heated to reflux for 1 h. The mixture was extracted with ether, and the ether was dried (Na_2SO_4) and evaporated to leave 9.1 g of brown oil whose NMR spectrum indicated it to be pinol oxide (**3**) containing a small amount of pinol chlorohydrin (**4**). Two distillations in vacuo afforded 6.8 g of pure (−)-pinol oxide (**3**): $[\alpha]^{27}D$ −32.06 (*c* 4.32, $CHCl_3$); NMR ($CDCl_3$) 1.18 and 1.28 [s, 6, $(CH_3)_2C$–], 1.36 (s, 3, CH_3CO–), 1.7–2.2 (m, 5), 2.87 (d, –$\overline{CH–O–C}$–), and 4.17 ppm 1, (d, 1, –CHO).

Reaction of Excess Potassium Hydroxide with Dichlorohydrin 5 at Ambient Temperature. A mixture of 1.2 g (50 mmol) of **5**, 5 ml (178 mmol) of 20% potassium hydroxide, and 10 ml of water was stirred at ambient temperature for 16 h. The mixture was extracted with ether, and the ether was then dried and removed to yield 810 mg of a light brown oil. NMR analysis revealed the presence of 60% of pinol oxide (**3**) and 40% of pinol chlorohydrin (**4**). Upon standing the oil partially crystallized. The solid was separated and recrystallized from hexane to give 285 mg of pure **4**: mp 130–131 °C; NMR ($CDCl_3$) 1.19 and 1.29 [s, 6, $(CH_3)_2C$–], 1.7–2.5 (m, 6), 4.04 (d, 1, CHOC), and 4.32 ppm (q, 1, –CHCl), mass spectrum m/e (rel intensity) 204 (2), 168 (12), 140 (18), 125 (22), 109 (16), 107 (20), 98 (18), 97 (60), 83 (12), 82 (25), 81 (13), 71 (75), 70 (17), 69 (39), 67 (10), 55 (15), 43 (100), 41 (38), and 39 (22).

Reaction of 1 Equiv of Potassium Hydroxide with Dichlorohydrin 5 at Ambient Temperature. A mixture of 350 mg (14 mmol) of **5**, 0.5 ml (15 mmol) of 20% potassium hydroxide, and 20 ml of water was stirred at ambient temperature for 1 h. The usual workup gave 241 mg of a light yellow oil. TLC on silica gel using pentane–acetone–ethyl acetate gave 188 mg of pure (1*S*,2*S*,4*S*,6*R*)-*trans*-6-chloro-1,2-epoxy-*cis*-*p*-menthan-8-ol (**13**): $[\alpha]^{25}D$ +24.36° (*c* 2.34, $CHCl_3$); IR 2.93, 3.40, 6.91, 7.25, 7.82, 8.09, 8.27, 8.58, 8.75, 9.02, 9.25, 9.69, 9.90, 10.60, 11.39, 11.89, 12.21, 12.83, 13.60, and 14.20 μ; NMR ($CDCl_3$) 1.19 [s, 6, $(CH_3)_2C$–), 1.42 (s, 3, CH_3–$\overline{C–O–C}$), 3.30 (d, 1, –$\overline{CH–O–C}$), and 4.45 ppm (m, 1, –CHCl); mass spectrum m/e (rel intensity) 204 (1), 125 (13), 111 (10), 109 (16), 107 (15), 105 (10), 97 (14), 95 (11), 93 (15), 81 (12), 71 (21), 69 (20), 67 (10), 59 (79), 55 (13), 43 (100), 41 (28), and 39 (18).

Reactions of Epoxychlorohydrin 13. A. Potassium Hydroxide at Reflux. When a mixture of 70 mg of **13** was heated at reflux for 4.5 h with 0.2 ml of 20% potassium hydroxide and 10 ml of water there was obtained 49 mg of an oil whose NMR spectrum indicated that it was relatively pure pinol oxide (**3**).

B. Potassium Hydroxide at Ambient Temperature. A mixture of 240 mg of **13**, 0.4 ml of 20% potassium hydroxide, and 10 ml of water was stirred at ambient temperature for 16 h. The usual workup gave 189 mg of an oil whose NMR indicated the presence of 60% of pinol oxide (**3**) and 40% of pinol chlorohydrin (**4**).

C. Water and Catalytic Amount of Acid. A mixture of 197 mg of **13** was stirred with 10 ml of water containing 3 drops of 20% sulfuric acid at ambient temperature for 18 h. The usual workup gave 181 mg of white solid. Recrystallization from hexane afforded pure (−)-pinol chlorohydrin (**4**), mp 130–131 °C, $[\alpha]^{26}D$ −134.86° (*c* 1.4, $CHCl_3$).

When a 140-mg sample of **13** was stirred with water for 18 h, there was obtained 122 mg of **4**. When another sample of **16** was stirred with freshly distilled and degassed water under a nitrogen atmosphere, the sample of **13** was recovered unchanged.

(1*R*,5*R*)-(+)-Pinol (14). A mixture of 5.65 g (0.0276 mol) of (−)-pinol chlorohydrin (**4**), 5 g (0.0765 g-atom) of acid-washed zinc, 200 ml of ethanol, and 50 ml of water was heated at reflux for 16 days. Approximately 10 ml of ethanol was added each day to compensate for evaporative loss. After 2% hydrochloric acid was added the mixture was extracted with pentane. The pentane extracts were washed with 5% sodium bicarbonate solution and dried (Na_2SO_4), and the pentane was removed to leave 3.9 g of a colorless oil. The NMR spectrum of the oil revealed the presence of pinol contaminated with approximately 33% of pinol chlorohydrin (**4**). The pinol chlorohydrin (**4**) slowly crystallized from the oil and after 5 days the liquid portion was removed by a pipet and the solid washed with pentane. The combined liquid and pentane washings were distilled to afford 1.08 g of pure (+)-pinol (**14**), bp 25–29 °C (0.2 mm), $[\alpha]^{25}D$ +80.7° (*c* 3.0, $CHCl_3$).

(1*S*,3*R*,4*S*,5*R*)-*trans*-Pinol Oxide (3). A solution of 0.5 g of (+)-pinol (**14**) and 1 g of *m*-chloroperbenzoic acid in 40 ml of methylene chloride was stirred at ambient temperature for 48 h. The solution was taken up in ether and washed with saturated sodium bisulfite solution, 5% sodium bicarbonate solution, and water. The solution was dried (Na_2SO_4) and distilled to yield 456 mg of (+)-pinol oxide (**3**), bp 34–35 °C (0.3 mm), $[\alpha]^{26}D$ +32.24° (*c* 4.68, $CHCl_3$).

Reaction of Pinol Chlorohydrin (4) with Potassium Hydroxide. A mixture of 428 mg (21 mmol) of **4**, 1 ml (30 mmol) of 20% potassium hydroxide, and 10 ml of water was heated at reflux for 2 h. The mixture was extracted with ether, the ether fractions were dried (Na_2SO_4), and the ether was removed to give 276 mg of yellow oil. Preparative TLC of the oil on silica gel using pentane–ether–ethyl acetate yielded 152 mg of (4*S*)-1-acetyl-4-(1-hydroxy-1-methylethyl)cyclopentene (**16**): $[\alpha]^{26}D$ −13.8° (*c* 1.0, $CHCl_3$); IR 2.92, 5.87, 6.03, and 6.17 μ; NMR ($CDCl_3$) 1.19 [s, 6, $(CH_3)_2C$–], 1.5–2.2 (m, 2), 2.30 (s, 3, CH_3CO–), 2.45–2.80 (m, 4), and 6.68 ppm (m, 1, –CH=C–); mass spectrum m/e (rel intensity) 168 (2), 153 (6), 150 (15), 135 (14), 110 (40), 109 (16), 107 (12), 95 (23), 93 (12), 69 (12), 67 (33), 66 (14), 59 (45), 43 (100), 41 (16), and 39 (15).

A solution of 243 mg of **16** in 10 ml of acetic anhydride was heated at reflux for 5 h. The solution was poured into 100 ml of water and solid sodium bicarbonate was added until evolution of carbon dioxide ceased. The solution was extracted with ether. The ether solution was dried (Na_2SO_4) and evaporated to leave 278 mg of a clear oil whose NMR confirmed the formation of the acetate derivative of **16**. The acetate was injected into a gas chromatograph with the injector block at 400 °C (10% SE-30 column at 150 °C) and (4*S*)-1-acetyl-4-isopropenylcyclopentene (**17**) was collected and displayed IR and NMR spectra identical with those of an authentic sample.[24] The 2,4-dinitrophenylhydrazone derivative of **17** was recrystallized from ethanol as dark red plates and showed mp 180–181 °C (lit. mp 178–180 °C).

Registry No.—**1**, 7785-70-8; (−)-**3**, 56142-60-0; (+)-**3**, 56142-61-1;

4, 60661-94-1; 5, 60661-95-2; 6, 60661-96-3; 7, 60686-99-9; 8, 38235-58-4; 9, 60661-97-4; (+)-10, 60661-98-5; (±)-10, 60687-02-7; 11, 60687-00-5; 13, 60687-01-6; 14, 55822-06-5; 16, 60661-99-6; hypochlorous acid, 7790-92-3; zinc, 7440-66-6; ethanol, 64-17-5; potassium carbonate, 584-08-7; potassium hydroxide, 1310-58-3.

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Pinol Derivatives from Lithium Aluminum Hydride Reduction of Cineole Chlorohydrin

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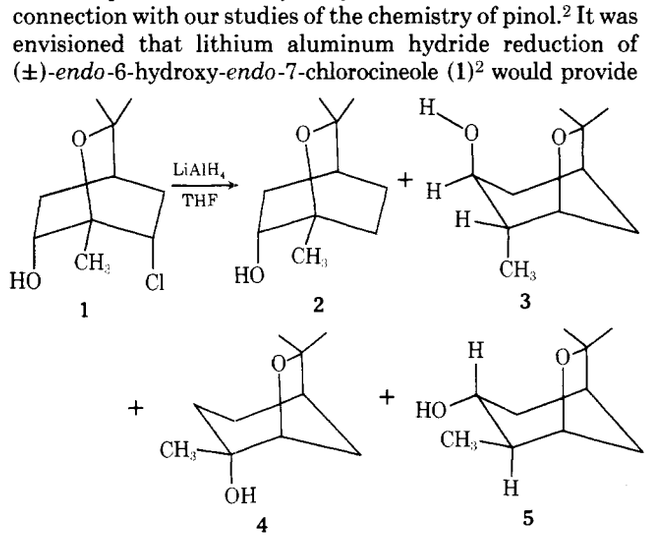
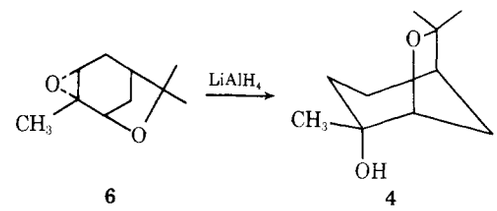
Lithium aluminum hydride reduction of (±)-*endo*-6-hydroxy-*endo*-7-chlorocineole (**1**) affords *cis*-3-hydroxy-*trans*-dihydropinol (**3**, 50%), *trans*-4-hydroxydihydropinol (**4**, 32%), *trans*-3-hydroxy-*cis*-dihydropinol (**5**, 11%), and *endo*-6-hydroxycineole (**2**, 5%). It is shown that treatment of chlorohydrin **1** with 1 equiv of hydride leads predominantly, via intermediate **14** followed by an oxygen and chlorine shift, to a pinol chlorohydrin derivative **17** which then loses chloride ion accompanied by a hydride shift to afford *trans*-dihydropinol-3-one (**12**). Ketone **12** is reduced from the least hindered side to give alcohol **3**. A competing process transforms intermediate **14** into pinol oxide (**6**) which is then reduced to alcohol **4**. Intermediate **14**, and possibly **17**, also affords small amounts of alcohol **5**.

A sample of *endo*-6-hydroxycineole (**2**) was desired in connection with our studies of the chemistry of pinol.[2] It was envisioned that lithium aluminum hydride reduction of (±)-*endo*-6-hydroxy-*endo*-7-chlorocineole (**1**)[2] would provide



a route for its preparation. However, vapor phase chromatographic analysis of the reduction product indicated the formation of a mixture comprised of four major components: *cis*-3-hydroxy-*trans*-dihydropinol (**3**, 50%), *trans*-4-hydroxydihydropinol (**4**, 32%),[3] *trans*-3-hydroxy-*cis*-dihydropinol (**5**, 11%), and *endo*-6-hydroxycineole (**2**, 5%). This publication is concerned with the evidence on which the assignment of these structures is based and the mechanism by which these compounds are formed.

The tertiary alcohol **4** was characterized by its NMR spectrum which showed, in part, methyl singlets at δ 1.23 and 1.37 ppm and a one-proton doublet at 3.82 ppm attributed to the bridgehead hydrogen of a pinol derivative. The structure of **4** was confirmed by comparison with an authentic sample prepared by lithium aluminum hydride reduction of (±)-pinol oxide (**6**).[4]



Complete characterization of **2** was not possible because of a lack of sufficient material. However, its infrared spectrum in solution showed hydroxyl absorption at 2.78 and 2.89 μ, while its CAT improved NMR spectrum displayed methyl singlets at 1.14, 1.27, and 1.34 ppm and a one-proton quartet ($W_{1/2}$ = 20 Hz) at 3.55 ppm whose chemical shift and multi-