Tetrahedron Vol 32, pp. 1621 to 1626 Pergamon Press 1976. Printed in Great Britain

AQUEOUS CHLORINATION OF α-TERPINEOL

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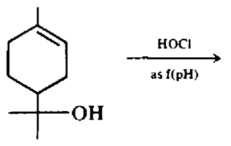
(*Recieved in USA* 5 *August* 1975; *Received in UK for publication* 20 *January* 1976)

Abstract—Of the multitude of products obtained upon the aqueous chlorination of α-terpineol (**1**), under both acidic and basic conditions, the major ones are the diequatorial *trans*, **4**, and diaxial *trans*, **5**, Markovnikov adducts of hypochlorous acid to the olefinic center. With the exclusion of small amounts of dichloride formation, the remainder of the products appear to be derived from **4** and **5** by hydrolysis or elimination sequences. The product distribution exhibits an expected pH dependence that is useful in the structural assignments.

INTRODUCTION

Historically, some of the oldest known addition studies dealt with electrophilic additions of halogens to monocyclic terpenes.[1] Not surprisingly, the reactions were somewhat restricted to conditions that produced manageable results (i.e. bromine, in a non-polar solvent, normally preferred over chlorine as the halogenating agent). Furthermore, aqueous halogenations, especially aqueous chlorinations, often produced prohibitively complex mixtures and were unsuitable for any product or mechanistic study. Yet aqueous chlorination studies of naturally abundant monocyclic terpenes would seem to demand an investigation from a more pragmatic viewpoint in that these products undoubtedly will be formed in the widespread use of chlorine in disinfection, wood bleaching, and related processes.[2a,b] The possibility of forming stable and toxic chlorinated derivatives would seem to make imperative a preliminary examination of the aqueous chlorination chemistry of a common monocyclic terpene.

With the above considerations in mind we decided to approach the question of product identification and interpretation in the aqueous chlorination of α-terpineol (*p*-menth-1-en-8-ol, **1**), an excellent example of an ubiquitous monocyclic terpene.[3a–d] An earlier investigation of the interaction of α-terpineol (**1**) with sodium hypochlorite gave an unidentified mixture of products and was inconclusive.[4a,b] We decided to reapproach this problem with the aid of preparative GLC and high pressure LC chromatography with the hope of characterizing the type of compounds formed in a typical aqueous chlorination of a naturally occurring monocyclic terpene. A mechanistic interpretation, and a pH profile of the product distribution, would seem invaluable to those concerned with accounting for the accumulation and origin of potentially hazardous chlorinated species in natural waters.[5a,b,c]



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RESULTS

The aqueous chlorination of α-terpineol (**1**) was examined over a pH range of about 2–10, the lower pH corresponding closely to a saturated chlorine solution and the higher pH to a sodium hypochlorite solution. The product distribution, as might be expected, will be a function of pH as one changes the percent hypochlorous acid in the following equilibrium.[2,6]

$$Cl_2 + H_2O \rightleftharpoons ClOH + HCl.$$

To aid in the presentation in the Discussion, the various products formed are listed in Table 1 according to chlorine content as dichloro, monochloro, and non-chlorine containing compounds. A special effort was made to detect and identify every observable compound as relative yields have less significance when one is concerned with accumulation and toxicity. In the present analysis we were able to reproducibly detect (LC and GLC) products in the half-percent range. Identification and separation procedures are given in Experimental.

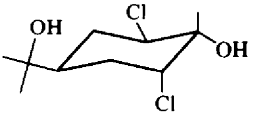
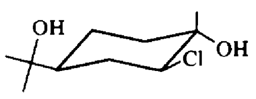
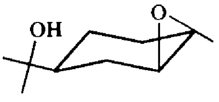
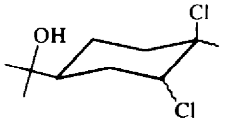
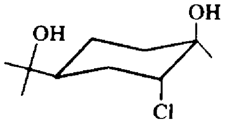
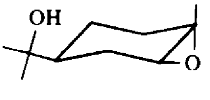
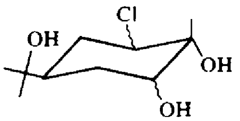
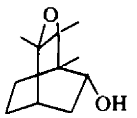
The distribution of these products as a function of pH is given in Table 2. The distribution was similar in the pH range 2–6 and one set of values is listed for pH 2.2. Likewise the results above a pH of 7.9 were similar and one set of values for pH 10 is given. The results are very reproducible for a given set of experimental conditions and the percentages represent all observable products. These percentages agree, roughly, with actual isolated yields and it appears that all compounds that are present to the extent of 0.5% or greater were detectable by analytical high pressure LC.

DISCUSSION

The chlorine addition reactions, whether starting with chlorine gas (for highly acidic reactions) or sodium hypochlorite solutions, were run with about two equivalents of available chlorine. This quantity is essentially the minimal quantity necessary to insure the complete reaction of α-terpineol (**1**). Reactions with a larger excess of chlorine, and reaction times beyond the disappearance of α-terpineol (**1**), lead to only a very small and slow increase in the chlorine content of the chlorinated mixture, presumably via a free radical substitution and/or a dehydration and addition sequence. As suggested by this, the product distribution was quite insensitive to small changes in reaction conditions.

An examination of the major products formed at a pH of 2.2 and 10 revealed a self-consistent pattern. The major product under the acidic conditions was assigned to the *trans*-diaxial adduct **5** of hypochlorous acid. The configu-

Table 1. Products formed in the aqueous chlorination of α-terpineol (1)[a]

Dichloro Derivatives[b]	Monochloro Derivatives[b]	Non-chlorinated[b] Products
 β-2,α-6-dichloro-*cis* *p*-menthane-1,8-diol (2)[c]	 α-2-chloro-*cis*-*p*-menthane-1,8-diol (4)[c]	 *p*-menthane-α-1,2-epoxy-8-ol (7)[c]
 1,2-dichloro-*p*-menthane-8-ols (3)[c]	 β-2-chloro-*trans*-*p*-menthane-1,8-diol (5)[c]	 *p*-menthane-β-1,2-epoxy-8-ol (8)[c]
	 6-chloro-*cis*-*p*-menthane-1,2,8-triol (6)[c]	 2-*endo*-cineolylol (9)[c]

[a] Not all of the products are formed at any given pH; see product distribution as function of pH in Table 2.

[b] Chlorine content established by mass spectral analysis and microanalysis.

[c] Acceptable names based on alternate *p*-menthane nomenclature are, for 4, 1,8-dihydroxy-neoisocarvomenthyl chloride; for 5, 1,8-dihydroxyneocarvomenthyl chloride; for 7, *trans*-*p*-methane-1,2-epoxy-8-ol; for 8, *cis*-*p*-menthane-1,2-epoxy-8-ol.[7]

Table 2. pH dependency of product formation in the reactions of hypochlorous acid with α-terpineol (1)[a,b]

Compound[c]	Percentages at pH 2.2	Percentages at pH 10
1	0	0
2	9	0
3	2	0
4	29	42
5	53	0
6	4	19
7	1	39
8	1	0
9	1	0

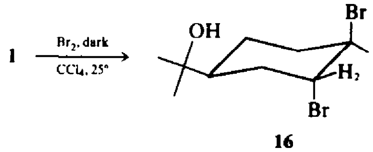
[a] A LC analysis on a Corasil column of the ether extracts.

[b] The data are reproducible for a given set of experimental conditions and are believed to be accurate to ±1%. The percentages were obtained by integration of results on LC column and are not corrected for molar responses.

[c] Toxicity: With the exception of 3, the compounds formed have a toxicity to *Daphnia magna*, LC_{50}(48 hr), similar to or even less than that of α-terpineol (120 ppm). The dichlorides 3 are on order of magnitude more toxic at about 15 ppm (unpublished results of this laboratory).

ration at C_2 is readily established by PMR, $\delta H_2 = 4.09$, $J_{2e,3e} = J_{2e,3a} = 3.9$ Hz, but the assignment at C_1 is based on mechanistic grounds and conversion into the corresponding epoxide 7.

Support for the *diaxial* pathway for the *trans* addition comes from a look at the bromination of this system. Bromine, presumably via a bromonium ion intermediate,[8] is known to yield *trans diaxial* and *diequatorial* dibromides in related 3- and 4-substituted cyclohexenes, the ratios dependent on the size and position of the alkyl substituent.[9a,b] The addition of bromine to 1 was originally investigated[10] before the turn of the century, but it is easy to show now by PMR that the major dibromide, formed almost exclusively, has an *axial* bromine at C_2, $\delta H_2 = 4.77$, $J_{2e,3a} = J_{2e,3e} = 2.5$ Hz. This suggests that the dibromide 16 is *diaxial* in agreement with an *anti* stereospecific process[11] that has been observed frequently in related reactions.[9,12-15] Likewise the Markovnikov addition of hypochlorous acid to 1 to produce 5 can also be interpreted in terms of an *anti* opening of the intermediate β-chloronium ion 10 by water. The *axial* attack of water, via a prechair transition state, produces the *diaxial* product 5. The selectivity observed, and the similarity to the bromination reaction, seem to make some sort of chloronium ion intermediate more plausible than an intermediate with an open carbonium ion at C_1.[16a-d]



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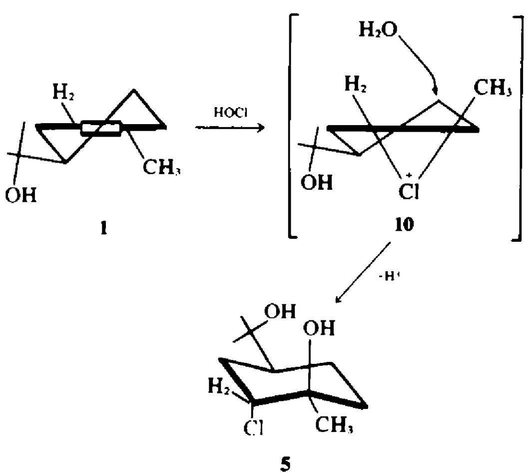
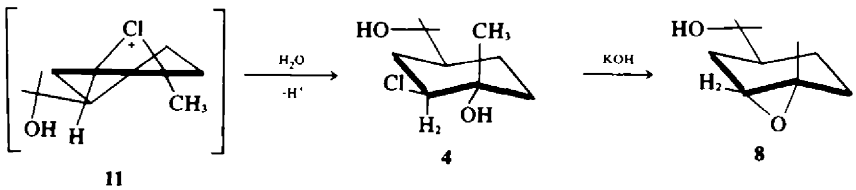
In agreement with the *diaxial* assignment for 5 is the observation that 5 is not observed at pH 10, but instead the corresponding α-epoxide 7 becomes a major product. The *diaxial* chlorohydrin 5 would be expected to lose hydrogen chloride readily under basic conditions.[17,18a,b,c] The isolated chlorohydrin 5 in fact readily collapses to 7 when placed under pH 10 conditions. In the PMR spectrum of 7 the signal for H_2 occurs as a doublet $\delta = 2.96$,



with $J_{2,3e}$ = 4.5 Hz. This is almost identical to an analogous epoxide in the limonene system reported by Tadwalker *et al.*[19]

The slight distortion of the chair 6-membered ring by the epoxide ring produces dihedral angles between H_2 and H_{3a} and between H_2 and H_{3e} that are compatible with the observed couplings of 0 and 4.5 Hz, respectively.[18a,b,c,20,21]

The double bond of α-terpineol (**1**) is conformationally biased but remote steric effects, such as the substituted isopropyl group at C_4, would not be expected to have a significant directive effect.[9,12] It is thus not surprising that another major product in both the acidic and basic additions is the one derived from Markovnikov addition to the α chloronium ion **11**, derived from initial complexation to the α side of the π system. A *trans* addition, probably by *diaxial* opening of the appropriate conformer of **11**, ultimately leads to the formation of the *diequatorial* chlorohydrin **4**. A *diequatorial* chlorohydrin is not expected to collapse as readily as **5** to the corresponding epoxide, but the isolated chlorohydrin **4** can be converted to the β-epoxide **8** under typical reaction conditions for epoxide formation from *trans* diequatorial chlorohydrins.[22a,b] The signal for H_2 in **8** appears as a slightly broadened singlet, δ 3.01, again in agreement with the small coupling values expected from a slight distortion and similar to the analogous limonene system.[19,23]



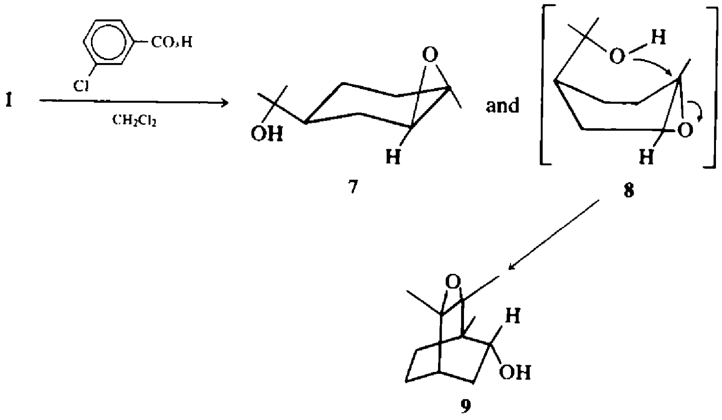
It seemed reasonable to confirm the epoxide structures **7** and **8**, and hence the chlorohydrins **5** and **4**, by direct epoxidation of α-terpineol (**1**). The two major products in the *m*-chloroperoxybenzoic acid epoxidation of **1** are, in fact, ethers that can be separated by preparative GLC in roughly equal amounts. One of these corresponds exactly to the α-epoxide **7**, but the other ether was identified by a spectral and chromatographic comparison with the reported 2-*endo*-cineolylol (**9**).[24,25]

The bicyclic ether **9** presumably is formed from the β-epoxide **8** by an intramolecular attack (boat conformation) on the epoxide ring. Similar results have been noted by Cocker in the closely related sobrenol system.[26] Not surprisingly the 2-cineolylol ether **9** is observed, along with **8**, as a minor product in the hypochlorous acid addition to **1** under acidic conditions (note Table 2). The conversion of **8** to **9** under acidic conditions was independently verified for an isolated sample of **8**.

The major products in the aqueous chlorination of **1** thus can be interpreted in terms of *trans* Markovnikov electrophilic additions, one *diaxial* and one *diequatorial*. These observations are in agreement with known steric effects,[9] torsional effects,[12] and with other addition reactions to cyclohexene systems.[27,28a,b] The minor products in this reaction are also significant if one is concerned with accumulation, and therefore an interpretation of their formation, even if less exacting, also seems desirable. The proposed structures and postulated origin of the remaining products, while not as rigorous as for the major chlorohydrins **4** and **5**, produce a reasonably self-consistent pattern which may be of some predictive value in related terpenes.[29]

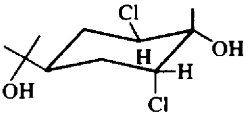
Certain of these products are trivial in that they are simply derived from the *trans* chlorohydrins **4** and **5**. Thus the epoxides **8** and **7** are related to the corresponding chlorohydrins and the bicyclic ether **9** likewise appears to be a secondary product from the rearrangement of the β-epoxide **8**.

The mixture of the dichlorides **3** is related to the



chlorohydrins in that it is presumably a mixture of the *trans* adducts of chlorine addition to **1**.[30] This mixture was confirmed by a spectral and chromatographic comparison of the chlorine adducts of α-terpineol (**1**) when the addition was carried out in carbon tetrachloride in the dark.[31]

The product **2** is interesting in that it is both a diol and a dichloride. PMR studies suggested **2** to be a di-t-diol with the methyl and isopropyl side chains intact. Two downfield signals in the PMR spectrum were attributed to H_{2e}, $\delta = 4.10$ and H_{6a}, $\delta = 4.58$, and structure **2** is suggested for this minor product. Its formation helps to account for the gradual increase in chlorine content with time in the presence of excess hypochlorous acid.[32–34]



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In the PMR spectrum of **6** a non-resolvable two-proton multiplet is observed at $\delta = 3.92$, $W_{1/2} = 10$ Hz, and the methyl and isopropyl side chains are intact. Of the three discernible OH groups, one can be shown to be secondary by the observation of a vicinal splitting through oxygen when dry acetone-d_6 was used as the solvent. The other two OH groups apparently are tertiary. The low solubility of **6** precluded a satisfactory shift reagent separation of the multiplet at $\delta = 3.92$, but it is assumed to arise from a proton on a carbon bearing a chlorine and the proton α to the secondary OH group. The latter can be confirmed by the observation that the addition of heavy water to the acetone-d_6 sample sharpens this signal by removing the vicinal coupling to the hydroxyl proton.[35]

It seems reasonable that the formation of **6** is related to one of the other products. In fact the hydrolysis of **2** to **6** occurs, as can be independently verified, under either basic or acidic conditions, and could possibly account for the formation of **6** with the present reaction conditions. However, intermediates corresponding to OH participation could not be detected, even though related intermediates have been observed in analogous systems,[36] and the assignment of configuration at C_2 and C_6 is not possible.

CONCLUSIONS

It appears that the major products formed in the aqueous chlorination of α-terpineol (**1**) can be accounted for by two *trans* Markovnikov adducts of the elements of hypochlorous acid. The pH profile of this reaction and the formation of other minor products can be related to the major *trans* adducts by secondary reactions that appear to follow the expected steric, torsional, and electronic demands of the menthane derivatives. These results will be useful not only in cataloging toxicity information but hopefully will provide a mechanistic basis for a study of related chlorinated terpenoids. A useful extension of work of this kind would be to determine the stability of the chlorinated terpenes in an aqueous environment and to examine their potential to bioaccumulate.

EXPERIMENTAL

Analytical. pH Measurements were recorded by a Corning Scientific Instruments Model 7 pH meter. Analytical vapor phase chromatography was performed on a Tracor Model 550 (FID detector), while preparative work was carried out on a Varian Autoprep Model A-700 (TC detector). M.ps were determined with a Thomas Hoover capillary m.p. apparatus and are uncorrected. Elemental analysis were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York. NMR spectra were obtained with a Varian Associates Model A-60D Spectrometer using tetramethylsilane as an internal reference. Mass spectra were obtained on a Varian CH5 instrument and infrared on a Beckman IR 33. The liquid chromatographic monitoring of samples was performed on 1/8 × 2′ Corasil II columns that were mounted in a Waters Associates ALC 202 (differential refractive index detector). Product resolution was accomplished in two solvent systems and their separations are summarized in Table 3.

Reagents. The α-terpineol (**1**) used was obtained from Eastman Organic Chemicals and was purified by fractional distillation at reduced pressure. Sodium hypochlorite, 5%, was obtained from the J. T. Baker Chemical Co.

Preparative chlorination of α-terpineol (**1**). For the preparative formation of the product mixture, a high concentration chlorination of **1** was carried out by passing Cl gas through a stirred mixture of α-terpineol (6 g) in 3 l water until the yellow color of Cl persisted. The excess Cl was allowed to escape by stirring overnight. The product mixture was removed by a continuous ether extraction and, after drying over $MgSO_4$, the removal of the solvent left 6 g of an oily residue. The product distribution, as determined by analytical LC (see Table 3), was similar to the controlled reactions used in the product distributions given in Table 2. Separation was accomplished by column chromatography on silica gel with an initial benzene elution with subsequent ether/benzene elutions, increasing the ether/benzene ratio until pure ether was the eluent. The separation was monitored by analytical LC.

β-2, *α-6-Dichloro*-cis-p-*menthane*-1, *8-diol* (**2**). The column chromatography fraction corresponding to **2** was purified by recrystallization from chloroform, m.p. 138–139°; NMR (acetone-d_6), δ 1.18 (s, 6, CH_3), δ 1.80 (s, 3, CH_3), δ 2.95 (s, 1, OH), δ 4.10 (s, 1, OH), δ 4.10 (m, 1, H_2, $w_{1/2} \sim 11$ Hz) and δ 4.58 (m, 1, H_2, $W_{1/2} \sim 9$ Hz). The mass spectral and IR characteristics are consistent with the dichlorodiol **2**. (Found: C, 49.76; H, 7.56. Calc. for $C_{10}H_{18}OCl_2$: C, 49.80; H, 7.52%).

Table 3. Liquid chromatographic separations

Polar solvent system:[a]	99% $CHCl_3$, 1% CH_3OH	Non-polar solvent system:[b]	50% $C_6H_{14}/CHCl_3$
Compound	Elution time (min)	compound	Elution time (min)
2	1.25	**3**	2.0
4	1.75	**1**	2.5
5	2.25	**7**	5
6	6.5	**9**	6
		8	7

[a] Corasil II column, 0.5 ml/min.
[b] Corasil II column, 2.0 ml/min.

1,2-*Dichloro*-p-*menthane*-8-*ols* (**3**). The mixture of dichlorides[24] corresponding to **3** was obtained independently by dissolving α-terpineol (0.31 g 0.001 mol) in 14 ml CCl_4 containing Cl_2 (0.071 g, 0.001 mol). The solvent was removed after 0.5 hr and the crude product was subjected to column chromatography conditions corresponding to those applied to the products obtained from the aqueous chlorination. The resulting dichlorides had the expected mass spectral, IR and NMR characteristics and they corresponded to those for the product isolated from the aqueous preparative reaction.

α-2-*Chloro*-cis-p-*menthane*-1, 8-*diol* (**4**). As can be seen from Table 2, a basic heterogeneous chlorination of **1** corresponds to the best conditions for obtaining the *diequatorial* chlorohydrin **4**. In the preparative formation of **4**, α-terpineol 10 g (0.065 mol), was mixed with 0.5 l water. The mixture was stirred vigorously and 150 ml of a 5% NaOCl aq was added. The pH was brought to about a pH 8 by the dropwise addition of conc. HCl. Stirring was continued for 2 hr and then a soln of Na_2SO_3 was added to destroy excess Cl_2. The aqueous mixture was extracted with ether in a continuous extraction apparatus. The combined ether extracts were dried over $MgSO_4$ and the ether removed under reduced pressure yielding 10 g of a yellow oil. Crystals formed upon standing and they were recrystallized from a 3:1 soln of chloroform:hexane; m.p. 118.5–119.5°, NMR ($DCCl_3$), δ 1.20 (s, 6, CH_3), δ 1.30 (s, 3, CH_3), δ 4.00 (dd, 1, H_2, $J_{2,3a}$ = 11.0 Hz and $J_{2,3e}$ = 4.5 Hz). The mass and IR spectra were in agreement with the monochloro diol structure. (Found: C, 58.13; H, 9.25; Cl, 17.31. Calc. for $C_{10}H_{19}O_2Cl$: C, 58.11; H, 9.26; Cl, 17.15%).

β-2-*Chloro*-trans-p-*menthane*-1,8-*diol* (**5**). The peak corresponding to **5** in the preparative acidic aqueous chlorination of **1** was purified by recrystallization from chloroform, m.p. 93–94°; NMR (acetone-d_6), δ 1.12 (s, 6, CH_3), δ 1.28 (s, 3, CH_3), δ 2.96 (m, 1, OH): δ 2.95 (s, 1, OH): δ 4.09 (m, 1, H_2); mass and IR spectra confirmatory. (Found: C, 57.95; H, 9.08, Cl, 16.86. Calc. for $C_{10}H_{19}O_2Cl$: C, 58.10; H, 9.26; Cl 17.15%).

6-*Chloro*-cis-p-*menthane*-1, 2, 8-*triol* (**6**). This product can be isolated from either the acidic or basic aqueous chlorination. Purification was accomplished by recrystallization from acetone, m.p. 146–147°; NMR (acetone-d_6); δ 1.16 (s, δ, CH_3), δ 1.77 (s, 3, CH_3), δ 3.10 (m, 2, OH), δ 3.92 (m, 2, H_2 & H_6), δ 4.55 (d, 1, OH, J = 8 Hz); mass and IR spectra confirmatory. This triol can also be prepared by the hydrolysis of the dichloro diol **2**. Thus when **2** was dissolved in 1 M HCl and stirred at 25° for 48 hr, and worked up by ether extraction, the crystalline product obtained was identical in physical and spectral properties as well as m.m.p., with **6**. (Found: C, 53.93; H, 8.75; Cl, 15.81. Calc. for $C_{10}H_{19}O_3Cl$: C, 53.95; H, 8.60; Cl, 15.92%).

m-*Chloroperoxybenzoic acid epoxidation of* α-*terpineol* (**1**). The α-epoxide **7** and bicyclic ether **9** are best synthesized by direct epoxidation of **1**. In a 1 l. flask, fitted with a dropping funnel and a $CaCl_2$ filled drying tube, were placed 250 ml CH_2Cl_2 and 8 g of 85% (0.04 mol) *m*-chloroperbenzoic acid (Aldrich Chemical Co.). This soln was cooled in an ice-water bath and magnetically stirred while 5.5 g (0.035 mol) of **1**, in 100 ml CH_2Cl_2 was added over a 2 hr period. The soln was then allowed to warm to room temp. and 100 ml of a water soln of 2.8 g (0.056 eq) of Na_2CO_3 and 7.0 g (0.056 mol). of Na_2SO_3 was added dropwise over 10 min. The water soln, after stirring for 15 min, was weakly basic and gave a negative test with starch iodide paper.[17] The organic layer was separated and the aqueous soln was extracted with two 100 ml volumes ether. The combined organic extracts were dried over $MgSO_4$, filtered, and the solvent was removed at reduced pressure. A colorless oil, 5.6 g, was recovered. The two major components in this mixture were separated by vapor phase chromatography (10′ × 3/8″, 20% DEGS, 160°). The product with the shorter retention time (15 min) was a crystalline material that had the same physical and spectral properties and microanalysis as the recently reported 2-*endo*-cineolylol (**9**).[24] Oxidation to the corresponding ketone via a CrO_3–pyridine complex in CH_2Cl_2[38] and formation of the corresponding oxime gave a m.p. 138°, reported 139°.[39]

The product with the longer retention time (55 min) was an oil corresponding to **7**, b.p. 60° (0.2 mm); NMR (CCl_4), δ 1.08 (s, 6, CH_3), δ 1.25 (s, 3, CH_3), δ 2.96 (d, 1, H_2, $J_{2,3e}$ = 4.5 Hz). Mass and IR spectra confirmatory. (Found: C, 70.63; H, 10.43. Calc. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.60%).

p-*Menthane*-β-1,2-*epoxy*-8-*ol* (**8**). An analytical sample of **8** is most readily prepared by the treatment of **4** with base. In a 30 ml flask was placed 0.50 g (0.0025 mol) of **4** and 25 ml water. This mixture was cooled in an ice-water bath and magnetically stirred while 0.84 g (0.015 mol) KOH were added in small batches over a 6 hr period. The mixture was then allowed to warm to room temp. and the stirring was continued for another 3 hr. The aqueous mixture was extracted with four 25 ml volumes ether. The ether extracts were dried over $MgSO_4$, filtered, and the ether removed under reduced pressure. A short-path distillation produced 0.35 g of an oil, b.p. 55–60° (0.2 mm), NMR ($DCCl_3$); δ 1.15 (s, 6, CH_3), δ 1.13 (s, 3, CH_3), δ 3.06 (s, 1, H_2). Mass and IR spectra confirmatory. (Found: C, 70.48; H, 10.57. Calc. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66%).

Acknowledgements—We are indebted to the Environmental Protection Agency, Grant No. 18050 HIK, for support of this work. We further wish to thank Mr. Douglas Kuehl, National Water Quality Laboratory, Duluth, for his help in obtaining and interpreting the mass spectra. We also wish to thank Gerard Putz, John D. Nelson, Kathleen Mielke, and Robert J. Schmitt for their technical assistance.

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[35] The presence of a proton α to a OH group can be further verified by the observation that this proton, H_2, shifts upfield in acetone-d_6 and a trace of sodium deuteroxide owing to the sodium alkoxide contribution. Furthermore, H_6 is unaffected and the regeneration of **6** upon addition of acid is consistent with the expected reluctance of the alkoxide of **6** to collapse to an epoxide. An attempted conversion to the corresponding acetate was unsatisfactory.

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