H_3, s), 3.70 (C-3 CH_3O or C-4 CH_3O, s), 3.83 (C-3 CH_3O or C-4 CH_3O, s), 6.77 (C-1 H, C-2 H, q, $J_{1,2}$ = 8 cps, center peaks separated by 4 cps).

Registry No.—**1**, 3570-10-3; **2a**, 7635-63-4; **6a**, 7635-64-5; **8a**, 7635-65-6; **2b**, 7635-66-7; **3a**, 7635-67-8; **6b**, 7756-52-7; **8b**, 7635-68-9; **8c**, 7635-69-0; **7b**, 7635-70-3; **8d**, 7635-71-4; **8e**, 7635-72-5; **9a**, 7635-73-6; **10a**, 7635-74-7; **10b**, 7635-75-8; **9b**, 7635-76-9; **11b**, 7635-77-0; **7c**, 7635-78-1; **11c**, 7635-79-2; **11a**, 7635-80-5.

Acknowledgment.—We wish to thank Dr. James Kerwin for his advice and encouragement throughout the course of this work and Dr. Joseph Weinstock for suggesting the preparation of the methanesulfonate ester for nmr studies. We also thank members of the Analytical and Physical Chemistry Section, Smith Kline and French Laboratories for elemental analyses and determination of optical rotations and ultraviolet and nmr spectra.

Stereochemical Studies of Monoterpene Compounds. II.[1] The Conformation of 4-Hydroxymenthones[2]

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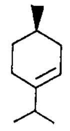
Received July 13, 1966

A diastereoisomeric pair of 4-hydroxymenthones was prepared from (+)-*p*-menth-3-ene by oxidation. The configuration of these isomers was assigned as (1*R*:4*R*)-(−)-4-hydroxymenthone (**3**) and (1*R*:4*S*)-(+)-4-hydroxyisomenthone (**6**) by chemical evidences. The conformation of hydroxy ketones **3** and **6** was examined by a combination of ultraviolet, infrared, and nuclear magnetic resonance spectra, optical rotatory dispersion, and circular dichroism measurements. α-Hydroxymenthone (**3**) exhibited the inversion in the sign of the Cotton effect upon changing solvent; this phenomenon was interpreted as indicating the existence of the conformational equilibrium **3a** ⇄ **3b**. On the other hand, another isomer (**6**) did not show such an inversion of the sign of the Cotton effect, taking preferentially conformation **6a**.

Optical rotatory dispersion[3,4] (ORD) and circular dichroism[4,5] (CD) have been found useful in studying the conformation of optically active, flexible substituted cyclohexanones, because of the peculiar sensitivity of this method to subtle conformational alteration. α-Hydroxycyclohexanones represent an interesting example of such mobility, since intramolecular hydrogen bonding can be expected together with a possible chair–chair conformer equilibrium. Djerassi, *et al.*, have recently demonstrated the conformational mobility in (+)-1-hydroxycarvomenthone on the basis of the optical rotatory dispersion[6] and the variable-temperature circular dichroism.[7] We wish to report here on the preparation of and the assignment of the conformation to a diastereoisomeric pair of 4-hydroxymenthones, (1*R*:4*R*)-(−)-4-hydroxymenthone (**3**) and (1*R*:4*S*)-(+)-4-hydroxyisomenthone (**6**).



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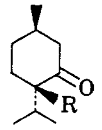
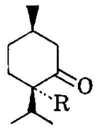
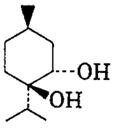


3, R = OH
5, R = OAc
12, R = H



6, R = OH
10, R = OAc
13, R = H



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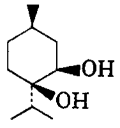

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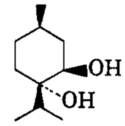

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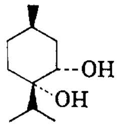

9

Preparation and Configuration.—(−)-α-Hydroxy ketone **3** was synthesized by the *t*-butyl chromate oxidation of (+)-*trans*-4-hydroxyneomenthol (**2**), which was derived from (+)-*p*-menth-3-ene (**1**) by the performic acid oxidation. On the other hand, (+)-α-hydroxy ketone **6** was prepared from **1** by the potassium permanganate oxidation. Both **3** and **6** yielded the same derivative, (−)-*p*-menth-3-en-5-one 2,4-dinitrophenylhydrazone, when treated with a hot ethanol–sulfuric acid solution of 2,4-dinitrophenylhydrazine. However, on treatment with a cold, dilute hydrochloric acid solution of the reagent, each of **3** and **6** yielded the corresponding 2,4-dinitrophenylhydrazone derivatives. These facts and some of physical properties shown in Table I indicate **3** and **6** to be a diastereoisomeric pair.

Table I

Physical Properties of 4-Hydroxymenthones

Compd	$\lambda_{max}^{isooctane}$	ϵ	$\nu_{C=O}^{CCl_4}$,[a] cm⁻¹	$\delta_{CH_3 \text{ to C-1}}^{CCl_4}$, ppm	$[\alpha]^{25}D$ (neat), deg	Mp of 2,4-DNPH,[b] °C
3	279	35.3	1711	0.96	−32.50	102.5–103
6	276	75.3	1712	1.04	+72.46	123–124

[a] Ketols **3** and **6** showed distinctive differences in the fingerprint region of the infrared spectra. [b] 2,4-DNPH = 2,4-dinitrophenylhydrazone.

On reduction with lithium aluminum hydride, **3** gave (+)-*trans*-4-hydroxyneomenthol (**2**)[1] and (+)-*cis*-4-hydroxymenthol (**4**),[8] and **6** yielded a glycol (**7**) (mp 93–94°) and (−)-*trans*-4-hydroxyneoisomenthol (**8**).[8] Because the absolute configuration of the diols **2**, **4**, and **8** has already been established, hydroxy ketones **3** and **6** were proved to be (1*R*:4*R*)-(−)-4-hydroxymenthone and (1*R*:4*S*)-(+)-hydroxyisomen-

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[1] Paper I of this series: T. Suga, T. Shishibori, and T. Matsuura, *Bull. Chem. Soc. Japan*, **37**, 310 (1964).

[2] Presented at the 18th Annual Meeting of the Chemical Society of Japan, Osaka, April 1965.

[3] C. Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p 102.

[4] P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1965.

[5] K. M. Wellman, E. Bunnenberg, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 1870 (1963).

[6] C. Djerassi, R. Records, B. Bach, *Chem. Ind.* (London), 258 (1961).

[7] K. M. Wellman, W. S. Briggs, and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 73 (1965).

[8] W. Tagaki and T. Mitsui, *J. Org. Chem.*, **25**, 1476 (1960).

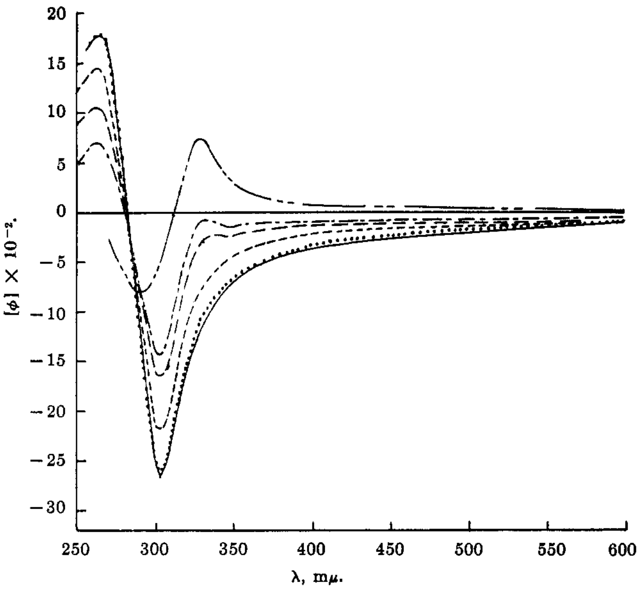


Figure 1.—Optical rotatory dispersion curves of (−)-4-hydroxymenthone (**3**): — - - — - -, in $(CH_3)_2SO$; — - — -, in CH_3OH; — — —, in dioxane; - - - -, in CH_3CN; ······, in CCl_4; and ———, in isooctane.

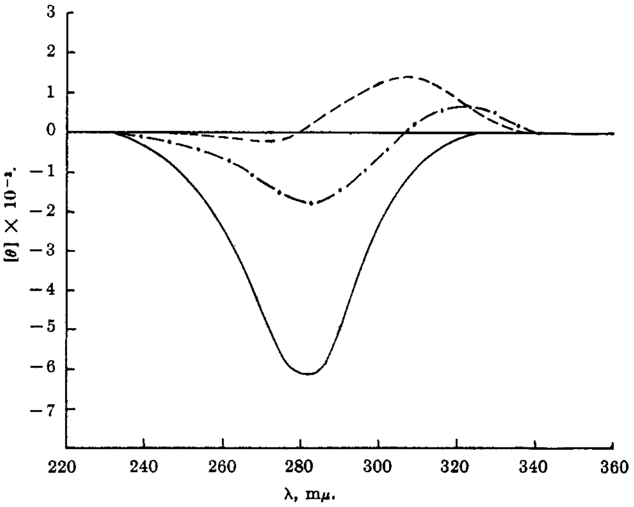
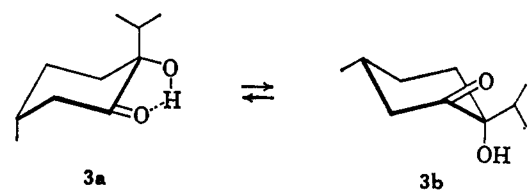


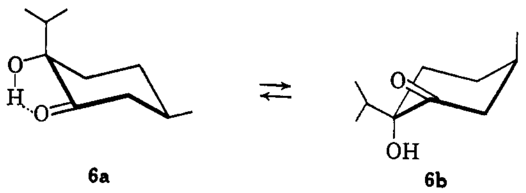
Figure 2.—Circular dichroism curves of (−)-4-hydroxymenthone (**3**) at room temperature: - - - -, in $(CH_3)_2SO$; -·-·-·, in CH_3OH; and ———, in isooctane.

thone, respectively. The reduction of 4-hydroxyisomenthone (**6**) with lithium aluminum hydride should produce a pair of *cis* and *trans* glycols as in the case of **3**. Since (−)-*trans*-4-hydroxyneoisomenthol (**8**) resulting from the reduction of **6** is one of the expected pair, it is highly probable to assign the glycol **7**[9] as (+)-*cis*-4-hydroxyisomenthol (**9**).

Conformational Analysis.—(1*R*:4*R*)-(−)-4-Hydroxymenthone (**3**) and (1*R*:4*S*)-(+)-4-hydroxyisomenthone (**6**) can exist in two interconvertible chair conformations (**3a** and **3b**, and **6a** and **6b**, respectively). According to the octant rule,[10] conformers **3b** and **6a** should exhibit a positive and conformers **3a** and **6b** a negative Cotton effect.



3a **3b**



6a **6b**

As shown in Figure 1, the ORD curves of **3** exhibit the trough of a negative Cotton effect at 302 mμ in isooctane and in carbon tetrachloride, but the first extremum of a positive Cotton effect at 328 mμ in dimethyl sulfoxide. This extremum is also observed on the strong negative Cotton effect curves in both methanol and dioxane. These phenomena observed in the ORD curves are compatible with the results of the CD measurements in the selected solvents as shown in Figure 2. Such an inversion of the sign of the Cotton effect upon changing solvent can be ascribed to conformational alteration; hydroxy ketone **3** would exist preferentially in conformation **3a** with the equatorial hydroxyl group in the nonpolar solvents, whereas this preferred conformation would be changed to **3b** with the axial hydroxyl in the polar medium. This is also supported by the fact that the first extremum (peak) of the ORD curves in dimethyl sulfoxide was shifted by 26 mμ toward a longer wavelength as compared with the extremum (trough) of the curve in isooctane. Such a wavelength shift has already been shown by Djerassi, *et al.*, in cases of (+)-1-hydroxycarvomenthone[6] and the steroidal α-hydroxy ketones.[11] The orientation of the hydroxyl group as mentioned above was moreover emphasized by a bathochromic shift of 17 mμ of the carbonyl $n \rightarrow \pi^*$ band, in the ultraviolet spectrum of **3**, upon changing the solvent from the nonpolar to the polar ones, as shown previously for α-hydroxy ketones.[6,11,12]

The infrared spectrum of **3** in carbon tetrachloride showed only a concentration-independent band at 3495 cm^{-1} owing to an intramolecularly hydrogen-bonded hydroxyl function. This band is shifted down by 130 cm^{-1} from a free hydroxyl band of *p*-menthan-4-ol (**11**), the carbonyl-free parent alcohol of **3**. The nmr spectrum of **3** exhibited only a small shift (0.51 ppm) of the hydroxyl proton signal on dilution with carbon tetrachloride, in contrast to **11** which caused a pronounced high-field shift (2.25 ppm) of the hydroxyl proton signal on dilution. The former phenomenon has been already shown with respect to *ortho*-substituted phenols[13] capable of forming the intramolecular hydrogen bond. On the other hand, the infrared spectrum of **3** in dimethyl sulfoxide solution exhibited a broad band at 3330 cm^{-1} attributed to the formation of the intermolecular hydrogen bond between the hydroxyl group and the solvent. These results sup-

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[9] *p*-Menthane-3,4-diol (**7**) showing this melting point has not yet been reported. The exact structural confirmation could not be advanced on account of a small amount of the crystals obtained. We are now investigating the exact configurational assignment.

[10] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961).

[11] Chapter 8 in ref 3.

[12] R. C. Cookson and S. H. Dandegaonker, *J. Chem. Soc.*, 352 (1955); G. Baumgartner and C. Tamm, *Helv. Chim. Acta*, **38**, 441 (1955).

[13] J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 400.

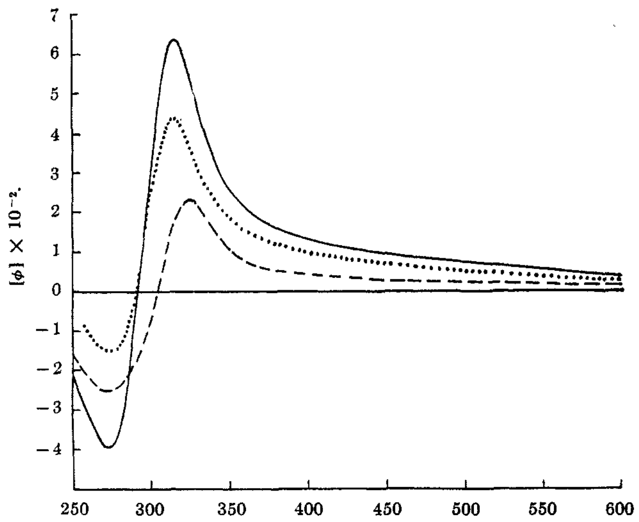


Figure 3.—Optical rotatory dispersion curves of (+)-4-acetoxymenthone (5): ———, in CH$_3$OH; ······, in (CH$_3$)$_2$SO; and – – – –, in isooctane.

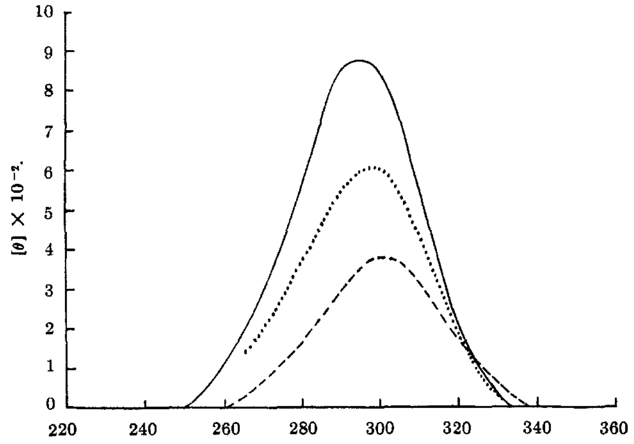


Figure 4.—Circular dichroism curves of (+)-4-acetoxymenthone (5) at room temperature: ———, in CH$_3$OH; ······, in (CH$_3$)$_2$SO; and – – – –, in isooctane.

port the idea that conformer **3a** is preferential in the nonpolar solvent, whereas conformer **3b** is preferential in dimethyl sulfoxide.

The ORD curves of (+)-4-acetoxymenthone (**5**), the acetylated compound of **3**, exhibited only a positive Cotton effect (Figure 3) both in nonpolar and polar solvents, but the amplitude diminished upon changing a solvent from dimethyl sulfoxide to isooctane. Recently, on the basis of the CD measurements, Djerassi, *et al.*,[14] have shown some examples where the amplitude of the ORD curves in the conformational equilibrium system, as in (−)-menthone (**12**) (**12a** $\rightleftarrows$ **12b**),[15] is a resultant of two oppositely rotating Cotton effects. The room-temperature CD curves (Figure 4) of **5**, in which the C-4 hydrogen of **12** is replaced by the acetoxy group, are solvent dependent in the manner similar to the ORD curves, but the curves did not exhibit the negative band expected for the conformer with the axially oriented alkyl substituents. Accordingly, this implies that **5** exists predominantly as conformation

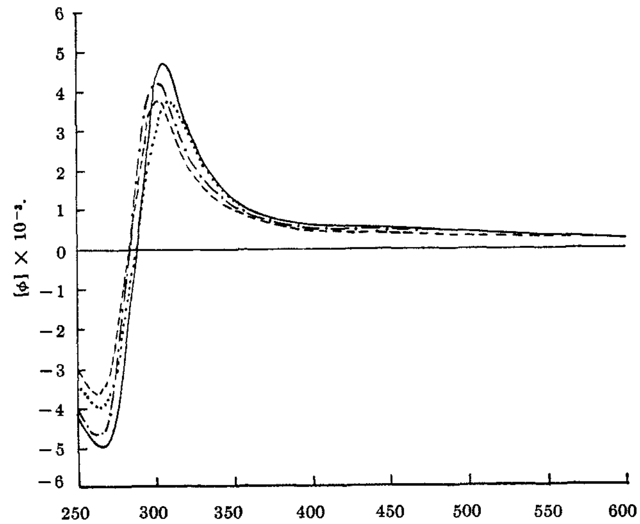
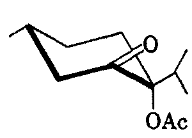
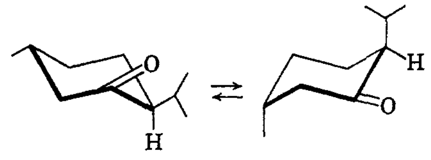


Figure 5.—Optical rotatory dispersion curves of (+)-4-hydroxyisomenthone (6): ———, in dioxane; –·–·–, in CH$_3$OH; – – – –, in isooctane; and ······, in (CH$_3$)$_2$SO.

5a in both nonpolar and polar solvents. The cause of the changes of the amplitude of the ORD curves and of the molecular ellipticity of the CD curves is not made clear. However, the solvational equilibrium seems to be concerned in this phenomenon, as indicated by Djerassi, *et al.*,[14] for **12**.



5a



12a **12b**

Concerning the parent hydroxy ketone (**3**), the population of **3a** will increase in the nonpolar solvents because the destabilizing electrostatic interaction between the carbonyl and the axial hydroxyl groups in **3b** is replaced by the formation of an intramolecular hydrogen bonding in **3a**. On the other hand, methanol and dimethyl sulfoxide are solvents which would be expected to form an intermolecular hydrogen bond to the carbonyl and/or the hydroxyl group, and the population of **3a** decreases concomitantly in the polar solvent, since the stabilizing intramolecular hydrogen bond between the carbonyl and the equatorial hydroxyl groups will be broken. Thus, the conformational equilibrium of hydroxy ketone **3** in various solvents appears to be determined to a large extent by the interaction of the hydroxyl group with its surroundings.

The ORD curves (Figure 5) of (+)-4-hydroxyisomenthone (**6**) in the various solvents exhibited a positive Cotton effect with the nearly equal amplitude without such an inversion of sign as observed with **3**, and also the room-temperature CD curves (Figure 6) showed only a solvent-independent, single, positive maximum in the 290-mμ region. Moreover, the ultraviolet spectrum did not show such a solvent-dependent wavelength shift as was observed with **3**. However, the infrared and the nmr spectra exhibited the same situations as in those of **3**, and indicated that in carbon tetrachloride an intramolecular hydrogen bond existed between the carbonyl and the hydroxyl groups, whereas

(14) K. M. Wellman, P. H. A. Laur, W. S. Briggs, A. Moscowitz, and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 66 (1965).

(15) G. Ohloff, J. Osiechi, and C. Djerassi, *Chem. Ber.*, **95**, 1400 (1962).

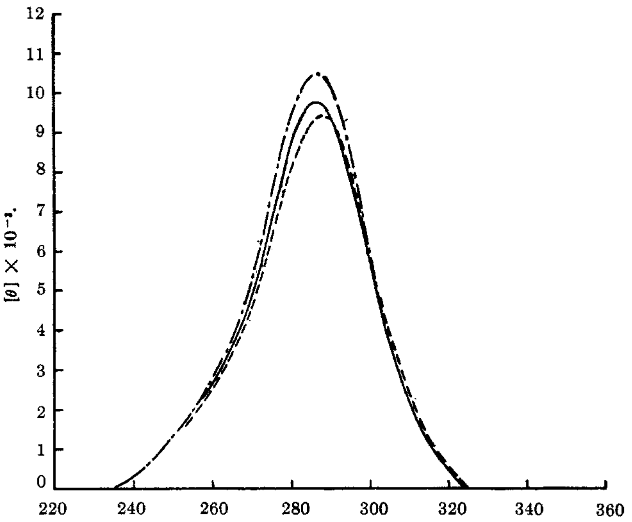


Figure 6.—Circular dichroism curves of (+)-4-hydroxyisomenthone (6) at room temperature: — — — —, in CH_3OH; – – – –, in $(CH_3)_2SO$; and ———, in isooctane.

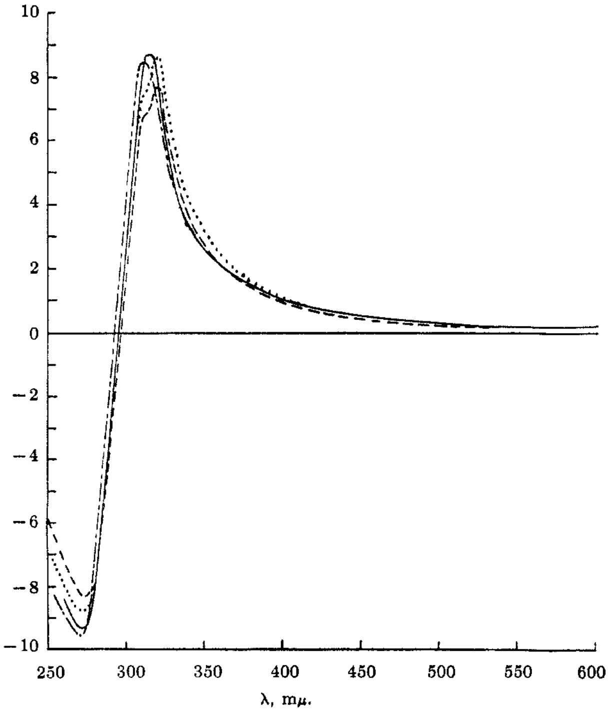
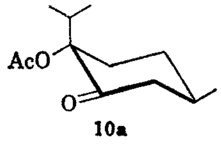
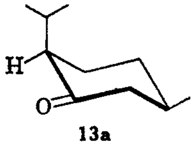


Figure 7.—Optical rotatory dispersion curves of (+)-4-acetoxyisomenthone (10): ———, in $(CH_3)_2SO$; — — — —, in CH_3OH – – – –, in isooctane; and ······, in CCl_4.

in dimethyl sulfoxide an intermolecular hydrogen bond was formed between the hydroxyl function and the solvent. The ORD curve (Figure 7) of the acetylated compound of **6**, (+)-4-acetoxyisomenthone (**10**), exhibited also only a positive Cotton effect with the solvent-independent amplitude in both nonpolar and polar solvents, and **10** was expected to be present in the conformation **10a**, in agreement with the recent conclusions[14,15] that the acetoxy or hydroxyl-free ketone of **6**, (+)-isomenthone (**13**), exists predominantly in conformation **13a** by the conformational analysis on the basis of the ORD and the CD spectra. As to (+)-4-hydroxyisomenthone (**6**), therefore, conformer **6a** seems to be energetically more favorable than **6b**, even if the stabilizing intramolecular hydrogen bond between the carbonyl and the hydroxyl groups is not formed.



10a



13a

Experimental Section

The ORD and the ultraviolet spectra were measured at room temperature with a Japan Spectroscopic Co. Ltd. (Tokyo) automatically recording spectropolarimeter, Model ORD/UV-5, using the normally programmed slit width, and the CD curves were also obtained by the same spectropolarimeter equipped with the circular dichroism attachment. Measurements were carried out using a cell 10 or 20 mm long and *c* 0.3 to 0.4. The infrared spectra in the hydroxyl stretching region were recorded in 0.1 to 0.003 *M* carbon tetrachloride solution at 25° by a Hilger H-800 double-beam spectrophotometer equipped with a calcium fluoride prism. The nmr spectra were determined with a Varian Associates, A-60, high-resolution spectrometer using tetramethylsilane as an internal standard (δ = 0 ppm). Vapor phase chromatographic analyses were made using a Shimadzu (Kyoto) GC-1A gas chromatograph with a thermal conductor-type detector and 4 mm × 3 m column packed with 5% Thermol-1 on quartz (150–200 mesh).

Materials.—All solvents, except as mentioned below, for spectrometric measurements were Spectro Grade or guaranteed reagent. Commercially available dimethyl sulfoxide was distilled just before use, after being dried by refluxing over fused potassium hydroxide and then calcium hydride. (+)-*p*-Menth-3-ene (**1**, bp 168–169°, n^{25}D 1.4485, $d^{25}{}_4$ 0.8080, $[\alpha]^{25}$D +114.88°) was prepared from methyl (−)-menthylxanthate (mp 40.5–41°), derived from (−)-menthol ($[\alpha]^{25}$D −49.72°, offered by Takasago Perfumery Co., Ltd.), by the pyrolysis following the method reported.[16] According to the racemization procedure[17] with *p*-toluenesulfonic acid, the hydrocarbon was shown to be a mixture of (+)-*p*-menth-3-ene (72%) and (+)-*p*-menth-2-ene (28%). However, the isolation of pure *p*-menth-3-ene was so difficult that the hydrocarbon mixture was employed as the sample, without further purification.

(1*R*:4*R*)-(−)-**4-Hydroxymenthone** (**3**).—Following the preceding paper of this series,[1] (+)-*trans*-4-hydroxyneomenthol [**2**, mp 76.5–77°, $[\alpha]^{25}$D +27.5 (*c* 1, methanol), mono-3,5-dinitrobenzoate mp 150–151°, $[\alpha]^{25}$D +36.8° (*c* 1, chloroform)], was prepared from **1** by the performic acid oxidation. The 3,4-diol (**2**, 20 g) in 100 ml of benzene was oxidized at 30° for 4 hr with a benzene solution of *t*-butyl chromate prepared[18] from 11.7 g of chromium trioxide, 23.3 g of *t*-butyl alcohol, and 150 ml of benzene, and then the whole reaction mixture was treated in the same manner as described previously.[18,19] Distillation of 19.8 g of a neutral product obtained gave 11.9 g of a distillate boiling at 100–125° (13 mm), and 7.4 g of the unchanged diol as a residue. Further purification of the distillate by chromatography on a silica gel column with a mixture of *n*-hexane and ethyl acetate gave 10.6 g of α-hydroxy ketone **3** having bp 87–88° (6 mm); n^{25}D 1.4605; $d^{25}{}_4$ 0.9805; $[\alpha]^{25}$D −32.50° (neat); $\lambda_{max}^{isooctane}$ 279 mμ (ϵ 35.3), $\lambda_{max}^{CCl_4}$ 281 mμ (ϵ 38.4), $\lambda_{max}^{dioxane}$ 284 mμ (ϵ 34.1), λ_{max}^{MeOH} 284 mμ (ϵ 35.1), $\lambda_{max}^{(CH_3)_2SO}$ 294 mμ (ϵ 31.5); $\nu_{max}^{liquid\ film}$ 3488, 1154 (OH), 1711 (C=O), 1433 cm^{-1} (CH_2CO). The nmr spectrum of the neat sample exhibited the isopropyl group proton signal as a pair of doublets centered at δ 0.66 and 0.96 (*J* = 6.5 cps). The latter doublet overlapped completely that of the C-1 methyl group proton signal. The hydroxyl proton signal appeared at δ 3.76 in the neat sample and at 3.25 in 2.5% carbon tetrachloride solution. The ORD and CD curves are illustrated by Figures 1 and 2, respectively. Vapor phase and chromatostrip[20] chro-

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[16] L. Tschugaeff, *Ber.*, **32**, 3332 (1899); W. Hückel, W. Tappe, and G. Legutke, *Ann.*, **543**, 194 (1940).

[17] J. P. Wibaut, H. C. Beyerman, and H. B. Van Leeuwen, *Rec. Trav. Chim.*, **71**, 1032 (1952).

[18] R. V. Oppenauer and H. Oberrauch, *Anales Asoc. Quim. Arg.*, **37**, 246 (1949).

[19] T. Suga, K. Kihara, and T. Matsuura, *Bull. Chem. Soc. Japan*, **38**, 893 (1965); T. Suga and T. Matsuura, *ibid.*, **38**, 1503 (1965).

[20] J. G. Kirchner, J. M. Miller, and G. J. Keller, *Anal. Chem.*, **23**, 420 (1951); J. M. Miller and J. G. Kirchner, *ibid.*, **25**, 1107 (1953).

matographic analyses indicated this hydroxy ketone to be homogeneous.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.44; H, 10.70.

The 2,4-dinitrophenylhydrazone [mp 102.5–103°, λ_{max}^{EtOH} 360 mμ (ε 22,400)] corresponding to the original hydroxy ketone was obtained when it was treated with a 2 *N* hydrochloric acid solution of 2,4-dinitrophenylhydrazine at room temperature.

Anal. Calcd for $C_{16}H_{22}N_4O_5$: N, 15.99. Found: N, 15.73.

On the other hand, the 2,4-dinitrophenylhydrazone melting at 147.5–148.5° was produced on treating **3** with a hot ethanol–sulfuric acid solution of 2,4-dinitrophenylhydrazine.[21] The dinitrophenylhydrazone showed $[\alpha]^{25}D$ −190.8° (*c* 0.1886, methanol) when the optical rotation was measured by the ORD spectropolarimeter. The mixture melting point was 144–144.5° on admixture with (±)-*p*-menth-3-en-5-one 2,4-dinitrophenylhydrazone (mp 145–146°). The infrared spectrum of our dinitrophenylhydrazone was superimposed completely on that of the racemic dinitrophenylhydrazone.

Reduction of 3 with Lithium Aluminum Hydride.—To 0.33 g of lithium aluminum hydride in 25 ml of dry ether was added dropwise a solution of 2.0 g of **3** in 16 ml of dry ether, and the mixture was refluxed for 8 hr, and then allowed to stand overnight. This treatment afforded 2.0 g of a crude diol, which was frationated into two eluates by column chromatography on silica gel with a mixture of isopropyl ether and ethyl acetate. The first eluate (0.70 g) was (+)-*trans*-4-hydroxyneomenthol (**2**), mp and mmp 76.5–77°.

The second eluate gave 0.41 g of a crystalline mass, which showed mp 80–81°, $[\alpha]^{20}D$ +13.1° (*c* 1, methanol), and the infrared absorption bands at 3628 (free OH) and 3584 cm^{-1} (intramolecularly hydrogen-bonded OH), and produced the mono-3,5-dinitrobenzoate melting at 124–125°. *Anal.* Found: N, 7.73.

Anal. Calcd for $C_{10}H_{22}O_2$: C, 69.72; H, 11.70. Found: C, 69.44; H, 11.77.

The infrared spectrum of the crystalline diol was superimposed completely on that of (+)-*cis*-4-hydroxymenthol (**4**) reported,[8] and also the physical properties are identical with those reported for **4**:[8,22] mp 80–81°; $[\alpha]^{20}D$ + 13°(*c* 1, methanol); $\nu_{max}^{CCl_4}$ 3627, 3581 cm^{-1}; mono-3,5-dinitrobenzoate mp 124–125°.

(+)-4-Acetoxymenthone (**5**).—A mixture of 1.0 g of **3**, 0.5 g of *p*-toluenesulfonic acid, and 20 ml of acetic anhydride stood overnight at room temperature. This treatment gave 1.1 g of the acetylated compound: bp 102–103° (2.5 mm); $n^{25}D$ 1.4573; $[\alpha]^{25}D$ +24.40° (*c* 0.4, methanol); $\lambda_{max}^{isooctane}$ 287 mμ (ε 38.9), $\lambda_{max}^{CCl_4}$ 289 mμ (ε 34.5), λ_{max}^{MeOH} 285 mμ (ε 46.3), $\lambda_{max}^{(CH_3)_2SO}$ 288 mμ (ε 45.9); $\nu_{max}^{liquid\ film}$ 1739, 1246 (acetate), 1724 cm^{-1} (carbonyl). Figures 4 and 5 show the ORD and the CD spectra, respectively.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.74; H, 9.25.

(1*R*:4*S*)-(+)-4-Hydroxyisomenthone (**6**).—To the solution of 69 g of **1** in 875 g of 80% aqueous acetone, 120 g of the powdered potassium permanganate was added in small portions during a period of 10 hr with stirring at −10°, and the mixture was maintained under the same conditions for further 3 hr, and then allowed to stand overnight. This treatment, after the reaction mixture was treated as usual, afforded 36.5 g of an oily product. The distillation of the product gave the unchanged hydrocarbon (22% yield), an α-hydroxy ketone (50%), and **4** [28%, mp 80–81°, $[\alpha]^{22}D$ +12.5° (*c* 2, methanol), mono-3,5-dinitrobenzoate mp 125–126°].

Further purification of the hydroxy ketone by chromatography on a silica gel column with a mixture of *n*-hexane and ethyl acetate gave 8.4 g of α-hydroxy ketone **6**: bp 86–88° (6 mm); $n^{25}D$ 1.4592; $d^{25}{}_4$ 0.9751; $[\alpha]^{25}D$ +72.46° (neat); $\lambda_{max}^{isooctane}$ 281 mμ (ε 45.0), $\lambda_{max}^{CCl_4}$ 281 mμ (ε 51.9), $\lambda_{max}^{dioxane}$ 282 mμ (ε 47.8), λ_{max}^{MeOH} 282 mμ (ε 49.7), $\lambda_{max}^{(CH_3)_2SO}$ 284 mμ (ε 46.7);] $\nu_{max}^{liquid\ film}$ 3489, 1161 (OH), 1712 (C═O), 1433 cm^{-1} (CH_2CO). The ORD and the CD curves are shown in Figures 5 and 6, respectively. The nmr spectrum of the neat sample showed a doublet at δ 1.04 (*J* = 6.5 cps, methyl at C-1), and a pair of doublets at 0.65 and 0.96 (*J* = 6.5 cps, isopropyl). The hydroxyl proton signal was observed at δ 3.68 (singlet) in the neat sample, and at 3.45 (singlet) in 2.5% carbon tetrachloride solution. This hydroxy ketone was shown to be pure by vapor phase and chromatostrip chromatographic analyses.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.57; H, 10.59.

The corresponding 2,4-dinitrophenylhydrazone [mp 123–124°, λ_{max}^{EtOH} 359 mμ (ε 22,900)] was obtained on treating **6** with a dilute hydrochloric acid solution of 2,4-dinitrophenylhydrazine in the manner similar to the case of **3**.

Anal. Calcd for $C_{16}H_{22}N_4O_5$: N, 15.99. Found: N, 15.94.

As in the case of **3**, treatment of hydroxy ketone **6** with an ethanol–sulfuric acid solution of 2,4-dinitrophenylhydrazine gave (−)-*p*-menth-3-en-5-one 2,4-dinitrophenylhydrazone having mp 147–148° and $[\alpha]^{25}D$ −187.5° (*c* 0.1680, methanol).

Reduction of 6 with Lithium Aluminum Hydride.—Hydroxy ketone **6** (1.0 g) in 5 ml of ether was reduced with 0.45 g of lithium aluminum hydride suspended in 10 ml of ether in the same manner as was **3**. A crude diol (0.90 g) which was produced was chromatographed on a silica gel column with a mixture of isopropyl ether and ethyl acetate.

The initial eluate afforded 0.15 g of a diol,[9] which melted at 93–94° after crystallizing from *n*-hexane, and showed $[\alpha]^{22}D$ +18.9° (*c* 0.5, methanol).

The second eluate gave 0.60 g of a crystalline mass melting at 76–77°. The mass showed $[\alpha]^{20}D$ −16.7° (*c* 2, methanol) and produced the mono-3,5-dinitrobenzoate melting at 150–151°. The melting point of the benzoate derivative was depressed to 125–140° on admixture with that of **2**.

Anal. Calcd for $C_{17}H_{22}N_2O_2$: N, 7.65. Found: N, 7.53.

The infrared spectrum of the crystalline mass was superimposed completely on that of (−)-*trans*-4-hydroxyisomenthol (**8**) as reported,[8] and also the physical properties were in agreement with those reported[8] for **8**: mp 75–76°, $[\alpha]^{20}D$ −6° (*c* 2, methanol), mono-3,5-dinitrobenzoate mp 143–144°.

(+)-4-Acetoxyisomenthone (**10**).—The treatment of **6** as in the case of **3** gave the acetylated compound: mp 76.5–77°; $[\alpha]^{25}D$ +127.1° (*c* 0.39, methanol); $\lambda_{max}^{isooctane}$ 292 mμ (ε 42.4), $\lambda_{max}^{CCl_4}$ 292 mμ (ε 47.6), λ_{max}^{MeOH} 289 mμ (ε 49.0), $\lambda_{max}^{(CH_3)_2SO}$ 292 mμ (ε 45.3); ν_{max}^{KBr} 1740, 1242 (acetate), 1728 cm^{-1} (carbonyl). Figure 7 shows the ORD curves of this compound in several solvents.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.07; H, 9.36.

(±)-*p*-Menthan-4-ol (**11**).—Following the method reported,[23] this compound was prepared from 4-methylcyclohexanone and isopropyl iodide by Grignard reaction. Purification of the crude product by chromatography on a silica gel column with a mixture of *n*-hexane and ethyl acetate gave the pure alcohol **11**: bp 96–97° (25 mm) [lit.[23] bp 97° (25 mm); $n^{25}D$ 1.4529; $\nu_{max}^{liquid\ film}$ 3346, 1039 cm^{-1}]. The homogeneity of the alcohol was checked by vapor phase and chromatostrip chromatographic analyses. The infrared spectrum in 0.25 *M* carbon tetrachloride solution exhibited two hydroxyl bands at 3625 and 3349 cm^{-1}. However, in the spectrum of 0.005 *M* solution, only the 3625-cm^{-1} sharp band owing to the free hydroxyl was observed. The nmr spectrum of the neat alcohol showed the hydroxyl proton signal at δ 4.87, while the signal was shifted to δ 2.62 in 2.5% carbon tetrachloride solution.

Registry No.—**3**, 7616-79-7; **6**, 7599-80-6; 2,4-dinitrophenylhydrazone of **3**, 7599-81-7; **2**, 7599-82-8; **5**, 7599-83-9; **10**, 7733-97-3; 2,4-dinitrophenylhydrazone of **6**, 7647-91-8; (±)-*p*-menth-3-en-5-one 2,4-dinitrophenylhydrazone, 7647-92-9; (−)-*p*-menth-3-en-5-one 2,4-dinitrophenylhydrazone, 7599-85-1; **8**, 7647-94-1.

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[21] P. R. Jefferies and B. Milligan, *J. Chem. Soc.*, 4384 (1956).

[22] P. R. Jefferies and B. Milligan, *ibid.*, 4391 (1956).

[23] W. H. Perkin, *ibid.*, 832 (1906).