Stereochemical Studies of Monoterpene Compounds. XV.[1] A Conformational Study of Carvomenthone Derivatives by Means of Temperature-dependent Circular Dichroism[2]

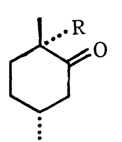
Takayuki SUGA and Satoru WATANABE

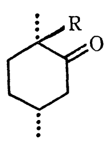
Department of Chemistry, Faculty of Science, Hiroshima University, Higashisenda-machi, Hiroshima

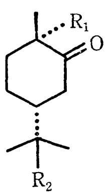
(Received August 5, 1971)

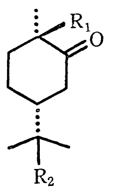
The conformations of (1*R* : 4*R*)-(−)-*p*-menth-8-en-2-one (**1**) and of diastereoisomeric pairs of (+)-1-hydroxy-*p*-menth-8-en-2-one, (**2**) and (**3**), (+)-1-hydroxy-*p*-menthan-2-one, (**6**) and (**7**), and (+)-1-hydroxy-8-bromo-*p*-menthan-2-one, (**10**) and (**11**), were examined by a combination of infrared spectra and temperature-dependent circular-dichroism (CD). Explanations are given mainly with regard to the epimeric pair, (**2**) and (**3**). It is demonstrated that α-hydroxyketone (**2**) exists in a conformational equilibrium among **2a**, **2b**, and **2c**. The **2a** conformer predominantly exists in a polar medium and at low temperatures, whereas the **2b** conformer is more stable than **2a** in a nonpolar medium. On the other hand, the epimer (**3**) exists preferentially in the **3a** conformation in both polar and nonpolar media and at low temperatures. The CD curves of compounds **6** and **7** exhibited the exactly same behavior as those in compounds (**2**) and (**3**) respectively. These results are interpreted in terms of the competition of the steric factor and the intramolecular hydrogen bonding.

Circular dichroism (CD) at different temperatures has been found to be very useful for investigating the conformational equilibrium in a flexible cyclohexanone structure.[3] α-Hydroxycyclohexanones provide interesting examples because, in addition to a possible conformational equilibrium, intramolecular hydrogen bonding between the hydroxyl and the carbonyl groups can be expected. Djerassi *et al.*[4] have recently demonstrated the conformational mobility in only (1*S* : 4*R*)-(+)-1-hydroxy-*p*-menthan-2-one (**6**), one of the C-1 epimers, on the basis of measurements of the variable temperature CD curves. This paper will deal with the conformational analyses of (1*R* : 4*R*)-(−)-*p*-menth-8-en-2-one (**1**) and the epimeric pairs of carvomenthone derivatives, (1*S* : 4*R*)- and (1*R* : 4*R*)-(+)-1-hydroxy-*p*-menth-8-en-2-ones (**2**) and (**3**), their acetates (**4**) and (**5**), (1*S* : 4*R*)- and (1*R* : 4*R*)-(+)-1-hydroxy-*p*-menthan-2-ones (**6**) and (**7**), their acetates (**8**) and (**9**), and (1*S* : 4*R*)- and (1*R* : 4R)-(+)-1-hydroxy-8-bromo-*p*-menthan-2-ones (**10**) and (**11**), all done by means of a combination of infrared spectra and temperature-dependent circular dichroism.





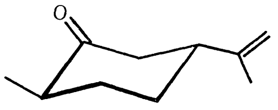




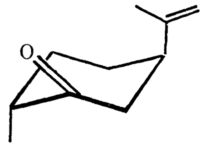
1: R=H
2: R=OH
4: R=OAc
3: R=OH
5: R=OAc
6: R_1=OH R_2=H
8: R_1=OAc R_2=H
10: R_1=OH R_2=Br
7: R_1=OH R_2=H
9: R_1=OAc R_2=H
11: R_1=OH R_2=Br

Results and Discussion

The CD curves of (1*R* : 4*R*)-(−)-*p*-menth-8-en-2-one (**1**) in MI and EPA exhibited a positive Cotton effect, and the rotational strength is almost temperature-independent over the range from 25 to −186°C. The menthenone (**1**) may exist in two interconvertible chair conformations, **1a**$\rightleftarrows$**1b**. According to the octant rule,[5] the **1a** conformer should exhibit a positive Cotton effect, and the **1b** conformer, negative one. Therefore, the positive conformer **1a** is more stable than **1b** in respect to the energetic and steric requirements.

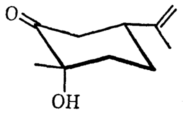


1a

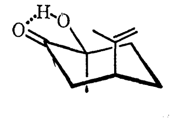


1b

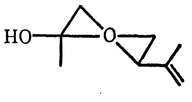
The CD curves of α-hydroxyketone (**2**) showed an inversion of the sign of the Cotton effect upon the change in the solvent polarity, as is shown in Fig. 1, in contrast with the corresponding dehydroxyketone (**1**). Such a phenomenon is interpreted in terms of the competition of the steric factor and the intramolecular hydrogen bonding. In the conformational equilibrium, **2a**$\rightleftarrows$**2b**, the intramolecularly hydrogen-nonbonded conformer **2a** should exhibit a positive Cotton effect, and the hydrogen-bonded conformer **2b** a negative one. In a nonpolar solvent, the stabili-



2a



2b



2c

---

[1] Paper XIV of this series: T. Suga, K. Imamura, and T. Shishibori, This Bulletin, **45**, 545 (1972).

[2] Presented at the 21st Annual Meeting of the Chemical Society of Japan, Osaka, April, 1968.

[3] "Optical Rotatory Dispersion and Cicular Dichroism in Organic Chemistry," ed. by G. Snatzke, Heyden & Ltd., London (1967), pp. 16, 335.

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

[5] W. Moffit, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *ibid.*, **83**, 4013 (1961).

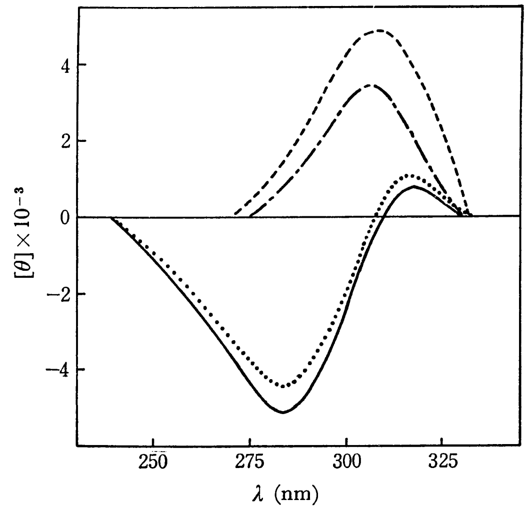


Fig. 1. CD curves of (1*S* : 4*R*)-(+)-1-hydroxy-*p*-menth-8-en-2-one (**2**) in selected solvents at +25°C: ······ in CCl_4, —— in isooctane, – – – in MeOH, and ---- in DMSO.

zation due to intramolecular hydrogen bonding overcomes the steric repulsion.[6] However, the stabilizing intramolecular hydrogen bond will be broken in a polar solvent, so that steric requirements mainly dominate the conformation of **2**. Therefore, the positively-rotating, nonbonded form, **2a**, is preferred in the polar solvents, and the negatively rotating, bonded form, **2b**, in the nonpolar solvents. The conformer populations were calculated[8] on the basis of the CD curves in selected solvents; the results are shown in Table 1.

TABLE 1. POPULATION OF **2b** IN SELECTED SOLVENTS

Solvent	$R_0^T\times10^{40}$ (C.G.S.)	Population of **2b** (%)
Isooctane	−3.82	78
CCl_4	−3.67	77
Dioxane	+2.91	13
MeOH	+2.85	13
DMSO	+4.33	0

The predominant existence of the **2b** conformer in a nonpolar solvent, carbon tetrachloride, was further proved by a study of the infrared spectrum, which exhibited two bands, at 3612 (ε 29) and 3512 cm^{-1} (ε 41) (Fig. 2), resulting from a free hydroxyl group and an intramolecularly interacted hydroxyl group[9] between the hydroxyl group and the lone-pair electrons of the carbonyl group. The influence of hydrogen bonding on the conformer population is further supported by the following two facts: (a) The CD curves of its acetate (**4**), in which the intramolecular hydrogen bond is inherently absent, exhibited only a positive Cotton effect, regardless of the solvent polarity, because of the loss of the stabilizing energy by hydrogen bonding. (b) The hydrobrominated compound **10** showed CD curves similar to those of the acetate (**4**) in both the polar and nonpolar solvents, because the positively-rotating, nonbonded conformer is stabilized by the anchoring effect[10] of the bulky 2-bromisopropyl group. This is supported by the infrared spectrum, in which the intensity of the free hydroxyl band of the hydrobrominated compound (**10**) at 3606 (ε 87) cm^{-1} increased greatly at the expense of the bonded peak at 3503 (ε 12) cm^{-1} (Fig.2), in contrast with the case of the parent compound (**2**).

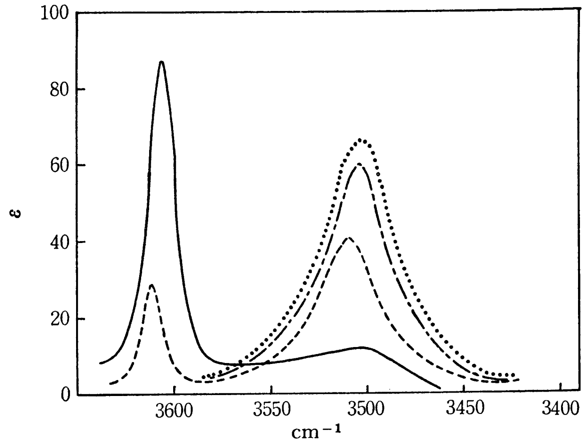


Fig. 2. IR spectra of α-hydroxyketones in carbon tetrachloride at +25°C: ---- for compounds **2**, – – – for **3**, —— for **10**, and ······ for **11**.

The variable-temperature CD curves of the compound (**2**) in the MI solvent exhibited a double-humped Cotton effect which strikingly implies the temperature dependence of its conformation (Fig. 3). Such a double-humped Cotton effect arising from the n-π^* transition may be explained in terms of the solvational and/or the conformational equilibria. But, the blue-shifted band presumably due to an equilibrium between the solvated and nonsolvated species has been said[11,12] not to show any increase in apparent rotational strength at lower temperatures. Therefore, the double hump observed on the Cotton effect curves has been interpreted as being due to only the conformational equilibria involving the competition of the steric factor and the intramolecular hydrogen bonding. At 25°C, the intramolecularly-hydrogen-bonded form (**2b**) with the negative Cotton effect is preferred. However, the stabilizing intramolecular hydrogen bond will be broken as the tempera-

---

[6] Assuming ΔG of the methyl, hydroxyl, and isopropyl groups to be 1.7, 0.7, and 2.0 kcal/mol,[7] respectively, a free energy difference ($-\Delta G$) for equilibria, **2a**—**2b** and **3a**—**3b**, on the basis of steric factor shows that conformers **2a** and **3b** would be energetically favored by *ca.* 1.0 and 3.0 kcal/mol. However, the **2a** conformer would be less favored and **3a** futher favored by an estimation of the hydrogen bond energy (2—5 kcal/mol). A clear-cut distinction between relative energies of **2a** and **2b** would be diffificult.

[7] N.L. Allinger and E. L. Eliel, "Topics in Stereochemistry, Vol. 1," Interscience publishers, New York (1968), p. 199.

[8] A. Moscowitz, K. Wellman, and C. Djerassi, *J. Amer. Chem. Soc.*, **85**, 3515 (1963).

[9] L. Joris, P. R. Schleyer, and R. Gleiter, *ibid.*, **90**, 327 (1968).

[10] S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955); N. L. Allinger and J. Allinger, *ibid.*, **80**, 5476 (1958).

[11] K. M. Wellman, P. H. A. Laur, W. S. Briggs, A. Moscowitz, and C. Djerassi, *ibid.*, **87**, 66 (1965).

[12] T. Shishibori, T. Suga, S. Watanabe, and T. Matsuura, This Bulletin, **42**, 3284 (1969).

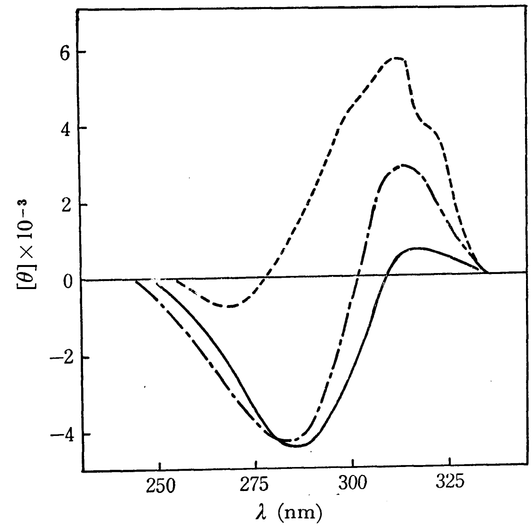


Fig. 3. CD curves of (1*S* : 4*R*)-(+)-1-hydroxy-*p*-menth-8-en-2-one (**2**) in MI: —— at +25°C, – – – at −74°C, and ---- at −186°C.

ture is lowered[4] so the steric requirements mainly dominate the **2a** conformer. The CD curves of **2** in EPA, incontrast with those in MI, showed only a positive Cotton effect with an increase in the apparent rotational strength as the temperature was lowered. This implies that the nonbonded conformer (**2a**) is also energetically preferred in EPA.

On the other hand, the CD curves of **2** in decalin (Fig. 4) exhibited an increase in the rotational strength in the short-wavelength band upon a change in the temperature from −74 to +25°C, and then a decrease from +25 to +150°C. These observations are not consistent with the simple equilibrium, **2a**⇌**2b**. At higher temperatures, the bonded form (**2b**) will diminish with an increase in the amounts of the nonbonded form (**2a**) and/or of the positively-rotating, twist form (**2c**), as has been suggested previously.[4]

Compound **3**, an epimer of **2**, may exist in two such interconvertible chair conformations as the positively-rotating, hydrogen-bonded conformer (**3a**) and the negatively-rotating, nonbonded one (**3b**).

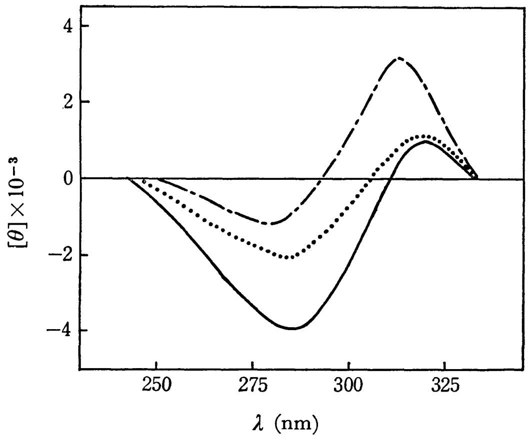
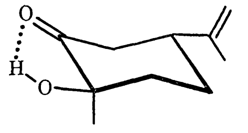
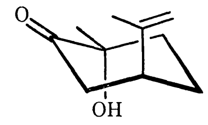


Fig. 4. CD curves of (1*R* : 4*R*)-(+)-1-hydroxy-*p*-menth-8-en-2-one (**2**) in decalin: – – – at −74°C, —— at +25°C, and ······ at +150°C.



3a



3b

The compound (**3**) showed only a positive Cotton effect curve with a rotational strength which is almost independent of the solvent polarity. The CD curves of its acetate, **5**, and the hydrobrominated compound, **11**, also showed a solvent-independent, positive Cotton effect at 25°C. Consequently, the **3a** conformer, with an equatorial isopropenyl group, is predominant regardless of the presence of an intramolecular hydrogen bond. The conformer homogeneity of **3** in the nonpolar solvent was ascertained on the basis of infrared spectrum measurements. The spectrum (Fig. 2) in carbon tetrachloride exhibited only a band at 3508 cm^{-1} (ε 61) resulting from an intramolecular hydrogen bond[9] between the hydroxyl group and the lone-pair electrons on the carbonyl oxygen. The two compounds, (**7**) and (**11**), related to the compound (**3**) also exhibited only a similar band assigned to the intramolecular hydrogen bonding (Fig. 2).

The temperature-dependent CD curves of **3** in MI and EPA over the range from 25 to −186°C showed only a positive Cotton effect with a slightly increase in the rotational strength as the temperature was lowered. This implies that the positively-rotating, chair conformer (**3a**) is most stable from the steric and energetic[6] points of view. The compound (**3**) in decalin revealed a decrease in the rotational strength of its positive CD curves at both higher and lower temperatures. This indicates that the hydrogen-bonded conformer (**3a**) would diminish with an increase in the population of the nonbonded conformer when taken out of room temperature.

The saturated compounds **6**, **7**, **8**, exhibited the same phenomena in their CD curves as those in the cases of the corresponding unsaturated compounds, (**2**), (**3**), (**4**), and (**5**) respectively. All the CD data of the saturated compounds are presented in the Experimental section.

Experimental

Measurements. The CD curves were obtained by means of a Japan Spectroscopic Co., Ltd., automatically-recording spectropolarimeter, Model ORD/UV-5, equipped with a circular dichroism attachment, using a variable temperature CD cell designed and constructed by one of the present authors. The EPA solvent is composed of ether-isopentane-ethanol in the ratio of 5 : 5 : 2 by volume. The MI solvent is composed of methylcyclohexane-isopentane in the ratio of 1 : 3 by volume.

The infrared spectra in the hydroxyl-stretching region were measured with a Perkin-Elmer Model 621 Grating Infrared spectrometer at 25°C. A sodium chloride absorption cell (10 mm long) was used; the concentration of the solution was 0.005 mol/*l*.

The NMR, mass, IR, and UV spectra, although not shown below, supported exactly the structure of the compounds on which the CD curves were measured. Only the methods of preparation of the compounds and the data on the CD curves are given below.

(1R : 4R)-(−)-p-menth-8-en-2-one (***1***). The Jones' oxidation of (+)-neodihydrocarveol[13] produced (1*R* : 4*R*)-(−)-*p*-menth-8-en-2-one (**1**): n_D^{25} 1.4650; $[\alpha]_D^{25}$ −200° (MeOH, *c* 0.08); CD (max) in MI (*c* 0.134): $[\theta]_{295}^{+25^\circ}$ +3251, $[\theta]_{300}^{+25^\circ}$ +2955, $[\theta]_{304}^{-186^\circ}$ +3944, $[\theta]_{299}^{-186^\circ}$ +3944, $[\theta]_{309}^{-186^\circ}$ +3199, in EPA (*c* 0.084): $[\theta]_{293}^{+25^\circ}$ +3182, $[\theta]_{290}^{-186^\circ}$ +3206, $[\theta]_{299}^{-186^\circ}$ +2829, $[\theta]_{309}^{-186^\circ}$ +1886.

(1S : 4R)-(+)-1-hydroxy-p-menth-8-en-2-one (***2***) *and (1R : 4R)-(+)-1-hydroxy-p-menth-8-en-2-one* (***3***). These compounds were the same as those prepared in the previous paper,[14] to which the physical properties are referred. Their acetates, (**4**) and (**5**) were prepared by the acetylation of **2** and **3** respectively with acetic anhydride in the presence of *p*-toluenesulfonic acid.

The compound (***2***): CD (max) in EPA (*c* 0.0589): $[\theta]_{307}^{+25^\circ}$ +4329, $[\theta]_{307}^{-74^\circ}$ +5101, $[\theta]_{300}^{-186^\circ}$ +6515.

The compound (***3***): CD (max) in MeOH (*c* 0.1684): $[\theta]_{290}^{+25^\circ}$ +10269, in DMSO (*c* 0.1332): $[\theta]_{294}^{+25^\circ}$ +8992, in isooctane (*c* 0.1684): $[\theta]_{286}^{+25^\circ}$ +11195, in decalin (*c* 0.0611): $[\theta]_{285}^{-74^\circ}$ +10307, $[\theta]_{285}^{+25^\circ}$ +9168, $[\theta]_{289}^{+150^\circ}$ +7248, in EPA (*c* 0.0652): $[\theta]_{286}^{+25^\circ}$ +8843, $[\theta]_{290}^{-74^\circ}$ +8898, $[\theta]_{290}^{-182^\circ}$ +10856.

The acetate (***4***): bp 55—56°C/30 mmHg; n_D^{25} 1.4688; $[\alpha]_D^{25}$ +4.81° (MeOH, *c* 0.1454); CD (max) in MeOH (*c* 0.1454); $[\theta]_{288}^{+25^\circ}$ +2931, in DMSO (*c* 0.142): $[\theta]_{294}^{+25^\circ}$ +2945, in isooctane (*c* 0.1644): $[\theta]_{292}^{+25^\circ}$ +3021.

The acetate (***5***): bp 75—80°C/8 mmHg; $[\alpha]_D^{25}$ +61.58° (MeOH, *c* 0.1624); CD (max) in MeOH (*c* 0.1624): $[\theta]_{290}^{+25^\circ}$ +6817, in DMSO (*c* 0.149): $[\theta]_{293}^{+25^\circ}$ +6656, in isooctane (*c* 0.1648): $[\theta]_{294}^{+25^\circ}$ +6534.

(1S : 4R)-(+)-1-hydroxy-p-methan-2-one (***6***) *and (1R : 4R)-(+)-1-hydroxy-p-menthan-2-one* (***7***). The reduction of the menthenones (**2**), (**3**), and (**5**) in methanol on 10%-palladium charcoal gave the corresponding saturated comcompounds, (**6**), (**7**), and (**9**).

The compound (***6***): n_D^{25} 1.4621; $[\alpha]_D^{25}$ +23.47° (MeOH, *c* 0.1704); CD (max) in MeOH (*c* 0.1704): $[\theta]_{272}^{+25^\circ}$ −922, $[\theta]_{306}^{+25^\circ}$ 1910, in DMSO (*c* 0.1692): $[\theta]_{308}^{+25^\circ}$ +2255, in dioxane (*c* 0.172): $[\theta]_{276}^{+25^\circ}$ −1566, $[\theta]_{310}^{+25^\circ}$ +1827, in CCl_4 (*c* 0.151): $[\theta]_{282}^{+25^\circ}$ −5201, $[\theta]_{316}^{+25^\circ}$ +594, in isooctane (*c* 0.1686): $[\theta]_{280}^{+25^\circ}$ −4881, $[\theta]_{307}^{+25^\circ}$ +133, in decalin (*c* 0.156): $[\theta]_{282}^{-74^\circ}$ −1827, $[\theta]_{310}^{-74^\circ}$ +2166, $[\theta]_{282}^{+25^\circ}$ −4819, $[\theta]_{318}^{+25^\circ}$ +360, $[\theta]_{282}^{+72^\circ}$ −4161, $[\theta]_{318}^{+72^\circ}$ +371, $[\theta]_{284}^{+150^\circ}$ −2089, $[\theta]_{318}^{+150^\circ}$ +402, in MI (*c* 0.144): $[\theta]_{282}^{+25^\circ}$ −5688, $[\theta]_{316}^{+25^\circ}$ +312, $[\theta]_{274}^{-74^\circ}$ −3072, $[\theta]_{306}^{-74^\circ}$ +2513, $[\theta]_{305}^{-192^\circ}$ +4758, in EPA (*c* 0.143): $[\theta]_{275}^{+25^\circ}$ −1726, $[\theta]_{308}^{+25^\circ}$ +3138, $[\theta]_{307}^{-192^\circ}$ +4696, $[\theta]_{318}^{-192^\circ}$ +3882, (*c* 0.172 at −74°) $[\theta]_{270}^{-74^\circ}$ +683, $[\theta]_{307}^{-74^\circ}$ +2904.

The compound (***7***): n_D^{25} 1.4593; $[\alpha]_D^{25}$ +97.23° (MeOH) *c* 0.1736); CD (max) in MeOH (*c* 0.1736): $[\theta]_{286}^{+25^\circ}$ +2036, in DMSO (*c* 0.064): $[\theta]_{288}^{+25^\circ}$ +7188, in dioxane (*c* 0.076): $[\theta]_{284}^{+25^\circ}$ +9399, in CCl_4 (*c* 0.092): $[\theta]_{282}^{+25^\circ}$ +9634, in isoocatne (*c* 0.0651): $[\theta]_{283}^{+25^\circ}$ +9472, in decalin (*c* 0.06): $[\theta]_{282}^{-74^\circ}$ +8270, $[\theta]_{282}^{+25^\circ}$ +8041, $[\theta]_{282}^{+72^\circ}$ +7341, $[\theta]_{284}^{+150^\circ}$ +5431, in MI (*c* 0.06): $[\theta]_{282}^{+25^\circ}$ +8840, $[\theta]_{284}^{-74^\circ}$ +9596, (*c* 0.056, at −192°) $[\theta]_{286}^{-192^\circ}$ +8828, in EPA (*c* 0.0524): $[\theta]_{284}^{+25^\circ}$ +10706, $[\theta]_{288}^{-74^\circ}$ +11403, $[\theta]_{291}^{-192^\circ}$ +12815, $[\theta]_{298}^{-192^\circ}$ +12132.

The acetate (***9***): n_D^{25} 1.4590; $[\alpha]_D^{25}$ +7.44°; CD (max) in MeOH (*c* 0.121): $[\theta]_{287}^{+25^\circ}$ +7516, in dioxane (*c* 0.12): $[\theta]_{291}^{+25^\circ}$ +7269, in isooctane (*c* 0.1176): $[\theta]_{290}^{+25^\circ}$ +6008.

The acetate (***8***): (1*S* : 2*S* : 4*R*)-1,2-Dihydroxy-*p*-menthane, prepared from the corresponding dihydroxy-*p*-menth-8-ene by hydrogenation, was converted into the hydroxyketone **6** by oxidation with chromic acid-pyridine complex. Then, the hydroxyketone was acetylated in the same manner as above to produce the acetoxyketone, **8**: n_D^{25} 1.4555; $[\alpha]_D^{25}$ +35.47° (MeOH, *c* 0.296); CD (max) in MeOH (*c* 0.296): $[\theta]_{286}^{+25^\circ}$ +1654, in dioxane (*c* 0.353): $[\theta]_{287}^{+25^\circ}$ +753, in isooctane (*c* 0.345): $[\theta]_{290}^{+25^\circ}$ +710.

(1S : 4R)-(+)-1-Hydroxy-8-bromo-p-menthan-2-one (***10***). A benzene solution of the hydroxyketone **2** was treated with a hydrobromic acid-acetic acid solution. After the reaction mixture was then poured into ice water, it was worked up as usual to yield the hydrobrominated compound (**10**) as white crystals: mp 65.5—66.0°C; $[\alpha]_D^{25}$ +63.4° (MeOH, *c* 0.122); CD (max) in MeOH (*c* 0.122): $[\theta]_{304}^{+23^\circ}$ +2825, in CCl_4 (*c* 0.092): $[\theta]_{311}^{+23^\circ}$ +2591.

(1R : 4R)-(+)-1-Hydroxy-8-bromo-p-menthan-2-one (***11***). The treatment of the hydroxyketone **3** in a manner similar to that above gave a hydrobrominated derivative (**11**): mp 61.5°C; $[\alpha]_D^{25}$ +64.4° (MeOH, *c* 0.114); CD (max) in MeOH (*c* 0.114): $[\theta]_{290}^{+23^\circ}$ +5254, in CCl_4 (*c* 0.091): $[\theta]_{286}^{+23^\circ}$ +6227.

The authors wish to thank the Takasago Perfumery Co. for its gift of limonene and Mr. Kiyoshi Imamura of our laboratory for his helpful assistance in the preparation of the hydrobrominated compounds.

---

13) T. Shishibori, This Bulletin, **41**, 1170 (1968).

14) T. Suga, T. Shishibori, S. Watanabe, and T. Matsuura, *J. Sci. Hiroshima Univ., Ser. A*-11, **32**, p. 331—335 (1968).