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Stereochemical Studies of Monoterpene Compounds. III.[1] Stereochemistry and Intramolecular Hydrogen Bonding of 1-Hydroxy-*p*-menth-3-en-2-one and Its Reduction Products[2]

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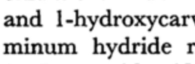
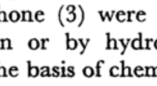
1-Hydroxy-*p*-menth-3-en-2-one (1) was prepared from α-terpinene by the *t*-butyl chromate oxidation. *trans*- and *cis*-*p*-Menth-3-ene-1,2-diols (4 and 5), 1-hydroxyisocarvomenthone (2), and 1-hydroxycarvomenthone (3) were also prepared from the compound 1 by lithium aluminum hydride reduction or by hydrogenation. The configurations of these compounds, 1—5, were identified on the basis of chemical evidence, and then the preferred conformation was determined by infrared spectroscopy on the basis of the conception of intramolecular hydrogen bonding. 1 and 2 were found to exist predominantly in the hydrogen-bonded conformations, 1a and 2a, respectively. With respect to 3, the existence of the conformational equilibrium, $3a \rightleftharpoons 3b$, was demonstrated by the presence of the free and bonded hydroxyl bands. Moreover, 4 and 5 were proved to take the preferred conformations of 4a and 5a respectively.

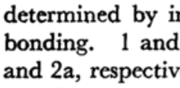
The conformational analysis of monoterpene cyclic diols[3] and monoterpene hydroxyketones[4] has been investigated in order to clarify the correlation between the formation of the intramolecular hydrogen bond and the conformation of the hydroxyl group in these compounds. α-Hydroxycyclohexanone derivatives can take the intramolecularly hydrogen-bonded forms, c and d, in addition to two interconvertible, unbonded chair-forms, a and b.



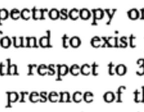
a



b



c



d

The conformer c contains intramolecular hydrogen bonding between the hydroxyl group and the lone-pair electrons on the carbonyl group (OH···O), whereas the hydroxyl group of the conformer d interacts with pi-electrons on the carbonyl group (OH···π). A characteristic hydroxyl-stretching absorption due to the OH···O-type hydrogen bond[4,5] gives a band at from 3480 to 3500 cm^{-1}. On the other hand, a band resulting from the OH···π interaction[5] appears at from 3600 to 3610 cm^{-1}. Hence, it is expected that the conformation of α-hydroxycyclohexanone derivatives may be determined on the basis of the conception of intramolecular hydrogen bonding. We wish to report here on the preparation of, and the correlation between the conformations and the intramolecular hydrogen bonding of, 1-hydroxy-*p*-menth-3-en-2-one (1), 1-hydroxyisocarvomenthone (2), 1-hydroxycarvomenthone (3), and *trans*- and *cis*-*p*-menth-3-ene-1, 2-diols (4 and 5).

Preparation and Configurations. 1-Hydroxy-*p*-menth-3-en-2-one (1) was prepared from α-terpinene by *t*-butyl chromate oxidation following a method previously reported.[6] The hydrogenation of 1 on palladium-charcoal gave a diastereoisomeric pair of ketols, 2 and 3, in the ratio of 2 to 1. In order to determine the configurations of 2 and 3, these ketols were further reduced with lithium aluminum hydride and then converted into *p*-menthane-1,2-diols, the configuration of which had already been established.[7] The ketol 2, was proved to be 1-hydroxyisocarvomenthone (2), since the reduction of 2 gave 1-hydroxyisocarvomenthol (6) and 1-hydroxyneoisocarvomenthol

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[1] Part II of this series: T. Suga, T. Shishibori and T. Matsuura, *J. Org. Chem.*, **32**, 965 (1967).

[2] Partly presented at the 16th and 17th Annual Meetings of the Chemical Society of Japan, Tokyo, April, 1963 and 1964.

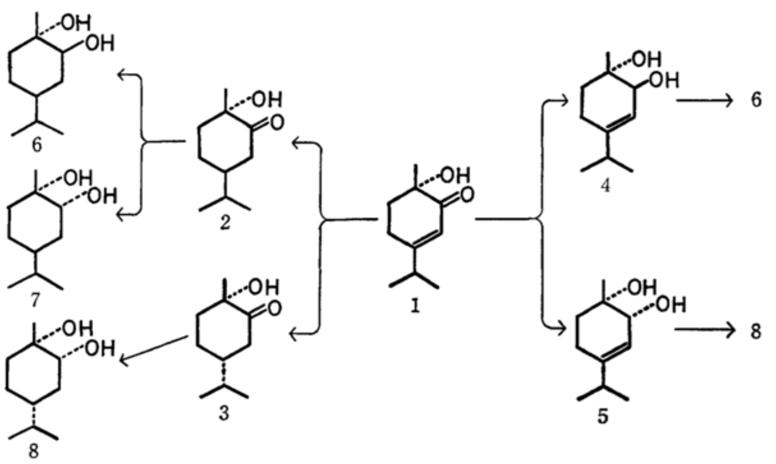
[3] T. Suga, T. Shishibori and T. Matsuura, This Bulletin, **37**, 310 (1964).

[4] T. Suga, T. Shishibori and T. Matsuura, *J. Org. Chem.*, **32**, 965 (1967).

[5] M. Ōki and H. Iwamura, Preprints for the 20th Annual Meeting of the Chemical Society of Japan, Part III (April, 1967), p. 128.

[6] T. Matsuura and T. Suga, *J. Org. Chem.*, **30**, 518 (1965).

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

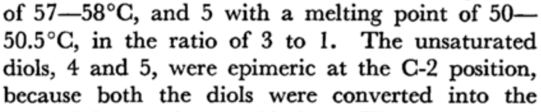


Scheme 1. The configurational assignment of 1-hydroxy-*p*-menth-3-en-2-one (1) and its reduction products.

(7). The reduction of 3 afforded 1-hydroxycarvomenthol (8), and so the ketol 3 must be 1-hydroxycarvomenthone (3).

The lithium aluminum hydride reduction of 1 gave the unsaturated diols 4, with a melting point of 57—58°C, and 5 with a melting point of 50—50.5°C, in the ratio of 3 to 1. The unsaturated diols, 4 and 5, were epimeric at the C-2 position, because both the diols were converted into the original ketone 1 on oxidation. The unsaturated diols 4 and 5 were further hydrogenated on palladium-charcoal in an attempt to assign the configuration of the hydroxyl groups; 4 gave a *trans*-diol, 1-hydroxyisocarvomenthol (6), and 5 yielded a *cis*-diol, 1-hydroxycarvomenthol (8). The unsaturated diols, 4 and 5, were thus proved to be *trans*- and *cis*-*p*-menth-3-ene-1,2-diols respectively.

Conformation and Intramolecular Hydrogen Bonding. As the configurations of the unsaturated hydroxyketone, 1, and its reduction products, 2, 3, 4 and 5, have been identified as above, the preferred conformation of these compounds was determined by considering a correlation between the hydroxyl-stretching absorption band and the distance of the intramolecular hydrogen bond.



1a 1b

1-Hydroxy-p-menth-3-en-2-one. 1-Hydroxy-*p*-menth-3-en-2-one (1) can exist in two interconvertible conformations 1a and 1b, in which the carbonyl group and the carbon atoms at C-1, C-3, C-4, and C-5 are co-planer, whereas only the carbon atom at C-6 is apart from the plane.

The hydroxyl group of 1 is pseudo-equatorial in the conformer 1a and pseudo-axial in the conformer 1b. An examination of a Dreiding model[8] showed that the distance between the hydroxyl and carbonyl groups (OH···O) is *ca.* 2.1 Å in the conformer 1a and *ca.* 2.9 Å in the conformer 1b. Hence, an OH···O-type intramolecular hydrogen bonding can be expected in 1a, while the OH···π interaction is preferable in 1b. The infrared spectrum of the hydroxyl-stretching region of 1 showed a concentration-independent band at 3517 cm^{-1} (ε 82), which can be attributed to the OH···O-type bonded hydroxyl group. In addition to this principal band, a weak hydroxyl band, probably due to the OH···π interaction, was observed at 3603 cm^{-1} (ε 12) in a dilute solution. This weak band disappeared in a concentrated solution, and a new broad band resulting from the intermolecular hydrogen bond appeared at *ca.* 3400 cm^{-1}. These facts imply that, in a dilute solution, the unsaturated hydroxyketone 1 exists in the conformational equilibrium mixture 1a$\rightleftarrows$1b, in which the conformer 1a is preferred, and that, in a concentrated solution, the hydroxyl and carbonyl groups of the conformer 1b interact intermolecularly with other molecules.

1-Hydroxyisocarvomenthone and 1-Hydroxycarvomenthone. 1-Hydroxyisocarvomenthone (2) and 1-hydroxycarvomenthone (3) may take two interconvertible chair-forms (2a and 2b, and 3a and 3b, respectively). In the conformers 2a and 3b, with an equatorial hydroxyl group, OH···O intramolecular hydrogen bonding between the hydroxyl and carbonyl groups is possible, since the OH···O distance is estimated by means of the Dreiding model[8] to be *ca.* 2.1 Å. On the other hand, such bonding is considered to be difficult in the conformers 2b and 3a, because of the longer OH···O

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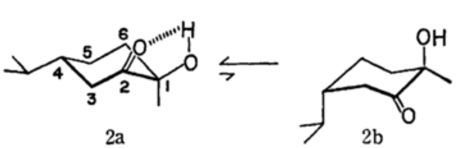
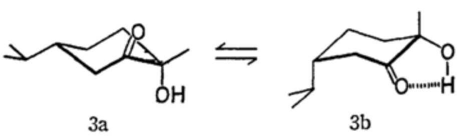
[8] "Dreiding Stereomodels," W. Büchi Manufacture of Glass Apparatus Flawil, Switzerland. The OH···O distance was estimated by using this model.

distance of *ca.* 3.2 Å and the unfavorable direction of the orbital of the lone-pair electrons on the carbonyl oxygen atom, making it difficult to form a OH···O-type hydrogen bond.

The infrared spectra of compound 2 revealed only a concentration-independent band at 3504 cm^{-1} (ε 100) due to the OH···O-type intramolecular hydrogen bond. This implies that the preferred conformation of 2 is the conformer 2a with an equatorial hydroxyl group, while that of the conformer 2b with a free axial hydroxyl group is not present or, if so, exists in a population so low as to make it impossible to observe its spectral band.



2a 2b



3a 3b

On the other hand, compound 3 showed two peaks, at 3610 (ε 53) and 3502 cm^{-1} (ε 74), in a 0.005 M carbon tetrachloride solution. The former is attributed to the free hydroxyl group, and the latter, to the OH···O-type hydrogen bond. Upon an increase in the concentration of the solution, the frequency of the band due to intramolecular hydrogen bonding did not show any shift, whereas the strength of a newly-appeared band at *ca.* 3450 cm^{-1} resulting from an intermolecularly-hydrogen-bonded hydroxyl group, increased, in contrast to the decrease in the free hydroxyl band, which finally disappeared in the neat sample. These facts indicate that the conformational equilibrium 3a⇄3b exists in a dilute solution, and also that the free hydroxyl groups of the conformer 3a interact with each other in a concentrated solution.

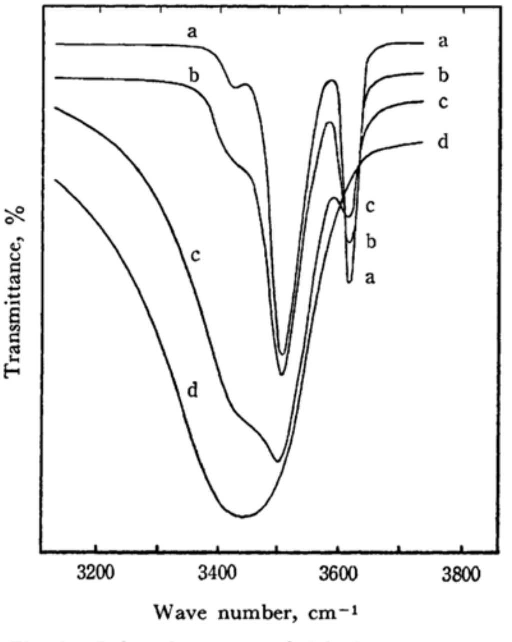


Fig. 1. Infrared spectra of 1-hydroxycarvomenthone (3) in a carbon tetrachloride solution of various concentration: a, 0.005 M; b, 0.05 M; c, 0.5 M; d, neat.

The difference in the conformational preference in the equilibrium mixture of the ketols 2 and 3 may be explained as follows. The difference in conformational free energy between the non-hydrogen-bonded form of the conformer 2a and the conformer 2b is expected to be of the value of *ca.* −1.1 kcal/mol.[9] In addition, the stabilization due to intramolecular hydrogen bonding between the hydroxyl and carbonyl groups in 2a can contribute to the conformational preference of the conformer 2a. Thus, the ketol 2 is thought to exist predominantly in the conformation 2a.

On the other hand, the difference in conformational free energy between the conformer 3a and the non-hydrogen-bonded form of the conformer 3b is expected to be of the value of *ca.* −3.1 kcal/mol.[9] If the stabilization due to intramolecular hydrogen bonding in 3b is sufficient to overcome the instabilization due to the steric repulsion among the 1,3-diaxial atoms and groups, the conformer 3b would be present. However, the stabilization due to intramolecular hydrogen bonding is expected to be of the value of $-\Delta G=1$ kcal/mol at room temperature, since the OH···O-type intramolecular hydrogen bond, forming a five-membered ring, results in a decrease in entropy ($-\Delta S=3.5$ e. u.), plus an enthalpy of the hydrogen bond ($-\Delta H=$ 2 kcal/mol).[12] Therefore, the 3a conformer with a free hydroxyl group, seems to exist preferentially in the conformational equilibrium 3a⇄3b.

trans- and cis-p-Menth-3-ene-1,2-diols. *trans-p-*Menth-3-ene-1,2-diol (4) may take three interconvertible half-chair forms, 4a—4c. Since the OH···O distances[8] are *ca.* 2.2 Å in 4b and 4c and *ca.* 4.0 Å in 4a, the intramolecular hydrogen bond is possible in 4b and 4c, which have equatorial

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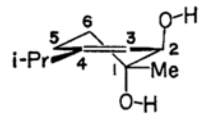
9) Estimated approximately by adding the corresponding values for a hydroxyl, a methyl, and an isopropyl groups, since such summation has been verified to be approximately correct in some cases.[10] The differences in free energy between the equatorial and axial forms of the hydroxyl, methyl and isopropyl groups are −0.7, −1.7 and −2.1 kcal/mol[11] respectively.

10) E. L. Eliel, N. L. Allinger, S. T. Angyal and G. A. Morrison, "Conformational Analysis," John Wiley & Sons, Inc., New York, N. Y. (1965), p. 58.

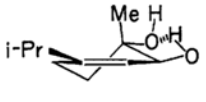
11) Ref. 10, p. 44.

12) L. P. Kuhn and R. A. Wires, *J. Am. Chem. Soc.*, **86**, 2161 (1964); C. Duculot, *Compt. rend.*, **241**, 1925 (1955).

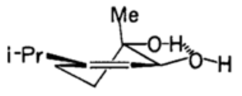
and quasi-equatorial hydroxyl groups, but such a bond is impossible in the conformer 4a, which has axial and quasi-axial hydroxyl groups. The infrared spectrum of 4 in a dilute carbon tetrachloride solution exhibited only a band at 3616 cm^{-1} due to the free hydroxyl group. *trans*-diol 4 was thus found to exist predominantly in the conformation 4a.



4a

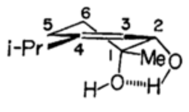


4b

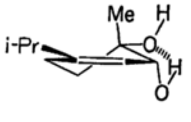


4c

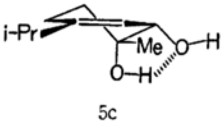
cis-p-Menth-3-ene-1,2-diol (5) may take four interconvertible, internally-bonded half-chair forms, 5a—5d. Since each of the OH···O distances in 5a—5d is estimated to be 2.2 Å,⁸⁾ the intramolecular hydrogen bond is possible in all the conformers. The infrared spectrum of 5 showed two bands, at 3617 and 3578 cm^{-1}. The former was attributed to a free tertiary hydroxyl group, since the characteristic frequencies¹³⁾ for the unbonded tertiary hydroxyl group have been reported to be 3613—3619 cm^{-1}. The 3578-cm^{-1} band was assigned to an intramolecularly hydrogen-bonded hydroxyl group. Thus, *cis*-diol 5 would exist in the conformer 5a or 5b, in which the less basic secondary hydroxyl group is bonded to the oxygen atom of the more basic tertiary hydroxyl. However, the conformational preference in the equilibrium 5a$\rightleftarrows$5b can not be determined only on the basis of the $\Delta\nu$ in the infrared spectrum, because of the equality of the OH···O distances in 5a and 5b.



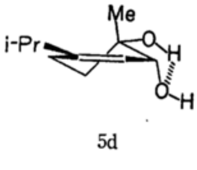
5a



5b



5c



5d

The NMR spectra of the unsaturated diols 4 and 5 afforded further evidence for the conformational assignment described above. The carbinol proton on the C-2 position of the compounds 5 and 4 exhibited signals at δ 3.77 (doublet, J=3.4 cps, half-band width $W_{1/2}$=8 cps) and at δ 4.05 (broad singlet, $W_{1/2}$=6 cps) respectively, in a deuterochloroform solution. In general, the axial carbinol proton resonates at a higher magnetic field than does the equatorial carbinol proton, and the former has the wider half-band width than the latter.¹⁴⁾ According to this general rule, the carbinol proton on the C-2 position of the compound 4 is equatorial, and that of the compound 5 takes an axial conformation. Thus, it can be deduced that the unsaturated diol 4 exists predominantly in the conformation 4a. This result further supports the assignment resulting from the infrared spectrum measurement. Concerning the unsaturated diol 5, on the other hand, it was found that the conformation 5a seems to be preferential in such a conformational equilibrium, 5a$\rightleftarrows$5b, as is deduced from the infrared spectral data.

Experimental

1-Hydroxy-*p*-menth-3-en-2-one (1). The compound used in the present work was the same as that prepared from α-terpinene by *t*-butyl chromate oxidation in a previous paper⁶⁾; it showed the follwoing properties: bp 99—100°C, n_D^{25} 1.4928, d_4^{25} 1.0074; ν_{max}^{neat} 3479, 1147 (OH), 3044, 1627, 878 (>C=CH–) 1430 (CH_2C=C); λ_{max}^{EtOH} 236 and 318 mμ (ε 13270 and 80); 2, 4-dinitrophenylhydrazone, mp 208—209°C, $\lambda_{max}^{CHCl_3}$ 392 mμ (ε 26000); phenylurethane, mp 132—132.5°C. The hydroxyl-stretching absorption frequencies in cm^{-1} (and the concentrationsin mol/*l*) were as follows: 3603, 3517 (0.005), 3603, 3517 (0.010), 3602, 3517, (0.05), 3602, 3515 (0.10), 3602, 3514 (0.25), 3601, 3510, (0.50), 3600, 3508 (1.0), 3480 (neat).

Catalytic Hydrogenation of 1. The unsaturated α-hydroxyketone 1 (2.84 g) in ethyl alcohol was hydrogenated in the presence of palladium-charcoal under an atmospheric pressure. The uptake of hydrogen amounted to 1.1 mol, and 1 was converted into a mixture of saturated hydroxyketones. The mixture was fractionated into two eluates by column chromatography on 200 g of silica gel with a mixture of *n*-hexane and ethyl acetate.

The first eluate (1.24 g) was 1-hydroxyisocarvomenthone (2): n_D^{25} 1.4627, d_4^{25} 0.9765; ν_{max}^{liq} 3494 (OH), 1712 (C=O), 1431 (CH_2CO), 1383, 1361 cm^{-1} (isopropyl). The hydroxyl-stretching absorption frequencies in cm^{-1} (and the molar concentration in a carbon tetrachloride solution) were as follows: 3504 (0.005), 3503 (0.050), 3502 (0.50), 3494 (neat).

The second eluate (0.92 g) was 1-hydroxycarvomenthone (3): n_D^{25} 1.4658, d_4^{25} 0.9852; ν_{max}^{liq} 3442 (OH), 1709 (C=O), 1425 (CH_2CO), 1384, 1360 (isopropyl). The IR spectra of 3 in the hydroxyl-stretching region

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13) L. P. Kuhn, *J. Am. Chem. Soc.*, **74**, 2492 (1952); A. R. H. Cole, G. T. A. Müller, D. W. Thornton and R. L. S. Willix, *J. Chem. Soc.*, **1959**, 1218; A. R. H. Cole, P. R. Jefferies and G. T. A. Müller, *ibid.*, **1959**, 1222.

14) R. U. Lemieux, R. K. Kulling, H. J. Bernstein and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

are shown in Fig. 1; the ν_{OH} values in cm^{-1} (and the concentrations in mol/l) were as follows: 3610, 3502 (0.005), 3610, 3502 (0.050), 3608, 3494 (0.50), 3441 (neat).

Reduction of 2 with Lithium Aluminum Hydride. To 0.14 g of lithium aluminum hydride in 10 ml of dry ether, there was added, drop by drop, over a 1 hr period, a solution of 0.81 g of 2 in 5 ml of dry ether; the mixture was refluxed for 5 hr and then allowed to stand overnight. The reaction mixture, after it had been treated as usual, afforded 0.80 g of a mixture of diols, which was fractionated into two eluates by column chromatography on silica gel with a mixture of *n*-hexane and ethyl acetate. The initial eluate (0.29 g) was 1-hydroxyneoisocarvomenthol (7): mp 72—72.5°C (lit.7) 72.5°C); ν_{OH} in a 0.0035 M carbon tetrachloride solution, 3619, 3581 cm^{-1} (lit.15) 3618, 3580 cm^{-1}). The second eluate (0.39 g) was 1-hydroxyisocarvomenthol (6): mp 51—52°C (lit.7) 53°C); ν_{OH} in a 0.0032 M carbon tetrachloride solution, 3617, 3597 cm^{-1} (lit.15) 3618, 3597 cm^{-1}).

Reduction of 3 with Lithium Aluminum Hydride. Hydroxyketone 3 (0.77 g) in 5 ml of dry ether was reduced with 0.14 g of lithium aluminum hydride suspended in 10 ml of dry ether in the same manner as was 2. The purification of the crude product by chromatography on a silica gel column gave 0.55 g of 1-hydroxycarvomenthol (8): mono-3,5-dinitrobenzoate, mp 116—117°C (lit.7) 117°C); ν_{OH} in a 0.0032 M carbon tetrachloride solution, 3628, 3588 cm^{-1} (lit.15) 3628, 3586 cm^{-1}).

Reduction of 1 with Lithium Aluminum Hydride. To 0.35 g of lithium aluminum hydride in 15 ml of dry ether, there was added, drop by drop, a solution of 2.00 g of 1 in 4 ml of dry ether; the mixture was stirred for 8 hr at room temperature, and then allowed to stand overnight. This treatment gave 2.00 g of a mixture of unsaturated diols. The mixture was fractionated into two eluates by column chromatography on 100 g of silica gel with a mixture of isopropyl ether and ethyl acetate. The initial eluate (0.38 g) was the unsaturated diol 5, and the final eluate (1.23 g) was the unsaturated diol 4.

The unsaturated diol 5 showed the following properties: mp 50—50.5°C; ν_{max}^{KBr} 3383, 1047, 1021 (OH), 3021 ($\rangle$C=CH–), 1667 (C=C), 1383, 1368 (isopropyl), 1428 cm^{-1} ($CH_2C{=}C$). The hydroxy-stretching absorption maximum in a 0.0032 M carbon tetrachloride solution appeared at 3619 and 3578 cm^{-1}. The NMR spectrum showed signals at δ 1.03 (doublet, J=6 cps, 6H, 9, 10-Me), δ 1.20 (singlet, 3H, 7-Me), δ 3.77 (doublet, J=3.4 cps, $W_{1/2}$=8 cps, 1H, C-2 H), and δ 5.40 (doublet, J=3.4 cps, 1H, C-3 H).

Found: C, 70.69; H, 10.77%. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66%.

The unsaturated diol 4 showed the following properties: mp 57—58°C; ν_{max}^{KBr} 3351, 1130, 1110 (OH), 3097, 1161, 845 ($\rangle$CH=CH–), 1379, 1362 (isopropyl), 1431 cm^{-1} ($CH_2C{=}C$). The hydroxyl-stretching absorption maximum in a 0.0032 M carbon tetrachloride solution appeared at 3616 cm^{-1}. The NMR spectrum showed the signals at δ 0.99 (doublet, J=6 cps, 6H, 9, 10-Me), δ 1.14 (singlet, 3H, 7-Me), δ 4.05 (broad singlet, $W_{1/2}$=6 cps, 1H, C-2 H), and δ 5.25 (broad singlet, 1H, C-3 H).

Found: C, 70.74; H, 10.92%. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66%.

On oxidation with *t*-butyl chromate for 2.5 days at room temperature, both 4 and 5 were converted into the original unsaturated ketol 1. This was confirmed by a comparison of the infrared spectra.

Catalytic Hydrogenation of the Unsaturated Diol 4. The unsaturated diol 4 in methyl alcohol was hydrogenated in the presence of prereduced palladium hydroxide on calcium carbonate under an atmospheric pressure. The uptake of hydrogen amounted to 0.97 mol, and 4 was converted into 1-hydroxyisocarvomenthol (6): mp 52—52.5°C (lit.7) 53°C); ν_{max}^{Nujol} 3322, 1069 cm^{-1} (OH); ν_{OH} in a 0.0043 M carbon tetrachloride solution, 3620 and 3602 cm^{-1} (lit.15) 3618, 3597 cm^{-1}); di-*p*-nitrobenzoate, mp 163—164°C (lit.7) mp 164°C).

Catalytic Hydrogenation of the Unsaturated Diol 5. The same treatment of 5 as has been described above afforded 1-hydroxycarvomenthol (8): mp 40—42.5°C; ν_{max}^{liq} 3368, 1035, 995 (OH), 1386, 1368 cm^{-1} (isopropyl); ν_{OH} in a 0.0043 M carbon tetrachloride solution, 3627 and 3588 cm^{-1} (lit.15) 3628, 3586 cm^{-1}); mono-3, 5-dinitrobenzoate, mp 116.5—117°C (lit.7) mp 117°C).

Measurement of the Infrared Spectra in the Hydroxyl-stretching Region. The infrared spectra were measured by a Hilger H-800 double-beam spectrophotometer under the following conditions: calcium fluoride prism; wave number accuracy at 3500 cm^{-1}: ±3 cm^{-1}; temperature, 25°C; solvent, spectro-grade carbon tetrachloride.

The authors wish to express their hearty thanks to Professor Shô Itô of Tohoku University for his NMR spectra measurements.

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15) A. R. H. Cole and P. R. Jefferies, *J. Chem. Soc.*, **1956**, 4391.