BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 41 1170—1174 (1968)

Intramolecular Hydrogen Bonding in Monoterpene Alcohols Containing π-Electronic System[1]

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(Received July 26, 1967)

The nature of intramolecular hydrogen bonding in diastereoisomeric pairs of 10-nor-8-oxomenthols (VIII and IX) and 10-nor-8-oxocarvomenthols (X and XI) has been studied by infrared spectroscopy. It was found that 10-nor-8-oxoneomenthol (IX) contains the OH···O type intramolecular hydrogen bond, while 10-nor-8-oxomenthol (VIII) contains the OH···π interaction in addition to the OH···O hydrogen bond. 10-Nor-8-oxocarvomenthols (X and XI) were internally unbonded. In addition, the extent and the limitation of the intramolecular OH···π interaction has been investigated for the diastereoisomeric pairs of a series of *p*-menth-8-enols: *p*-menth-8-en-4-ols (I and II), isopulegols (III and IV), dihydrocarveols (V and VI), and *trans*-β-terpineol (VII). Thus, the hydroxyl group in α- or β-unsaturated alcohols I, II, III and IV was found to be internally bonded to the π-electrons on the double bond; the other isomers are internally unbonded.

The facts that intramolecular hydrogen bonding depends on the configuration and the conformation of compounds containing a hydroxyl group are of great potential utility for the structure elucidation and the conformational analysis.[2,3] The relationship between the configuration and the infrared spectral parameter has been studied extensively for the open chain and the cyclic compounds.[3] However, little data are available on intramolecular hydrogen bonding in cyclohexanol derivatives bearing the hydrogen accepting group, such as an isopropenyl, an acetyl, or a hydroxyisopropyl group. For the cyclohexanol derivatives having one of these groups, the rotational conformations of the group are possible in addition to the chair-chair interconversion of the ring. It is expected that the conformation of the group can be suggested from the examination of intramolecular hydrogen bonding.

In this paper, the spectral parameters relating to the intramolecular hydrogen bond between the hydroxyl and carbonyl groups in a diastereoisomeric pair of 10-nor-8-oxomenthols (VIII and IX) were compared with the ones of the OH···O hydrogen bond and the OH···π interaction in the diastereoisomeric pairs of isopulegols (III and IV) and *p*-menthane-3,8-diols (XII and XIII). In addition, the extent and the limitation of the intramolecular interaction between the hydroxyl group and the π-electrons has been investigated for the diastereoisomeric pairs of a series of *p*-menth-8-enols: *p*-menth-8-en-4-ols (I and II), isopulegols (III and IV), dihydrocarveols (V and VI) and *trans*-β-terpineol (VII).

Results and Discussion

In Figs. 1 and 2 are shown the actual O–H stretching absorption curves of the monoterpene alcohols (III, IV, VIII and IX). An unresolved band was divided by graphical separation,[4] assuming that the band is an overlapping of the symmetric bands. The data of the hydroxyl bands divided are summarized in Table 1.

***trans*- and *cis*-*p*-Menth-8-en-4-ols (I and II).** The spectra of I and II exhibited the principal band 3606 and 3604 cm^{-1} with a weak shoulder at 3622 and 3621 cm^{-1} respectively. In both I and II, the strong band at the low frequency side is attributed to the hydroxyl group which interacts with the π-electrons of the isopropenyl group, and the weak, high-frequency band corresponds to the unbonded tertiary hydroxyl band, which has been reported[5-7] to appear at 3613—3619 cm^{-1}. The separation by 16 and 17 cm^{-1} between the free and bonded hydroxyl bands in I and II, respectively, agrees with 15.4 cm^{-1} of allyl alcohol.[8,9] It is possible to say roughly

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[1] This paper forms Paper IV[2] in the Hiroshima University series on Stereochemical Studies of Monoterpene Compounds, and was presented at 20th Annual Meeting of the Chemical Society of Japan, Tokyo, April 1967.

[2] Paper III of this series: T. Suga, T. Shishibori and T. Matsuura, This Bulletin, **41**, 944 (1968).

[3] M. Tichý, "Advances in Organic Chemistry," Vol. 5, Interscience Publishers and John Wiley & Sons, Inc., New York, N. Y. (1965), p. 115.

[4] Examples of the graphical separation are shown in Figs. 1 and 2. N. Mori, S. Omura, N. Kobayashi and Y. Tsuzuki, This Bulletin, **38**, 2149 (1965).

[5] L. P. Kuhn, *J. Am. Chem. Soc.*, **74**, 2492 (1952).

[6] A. R. H. Cole, G. T. A. Müller, D. W. Thornton and R. L. S. Willix, *J. Chem. Soc.*, **1959**, 1218.

[7] A. R. H. Cole, P. R. Jefferies and G. T. A. Müller, *ibid.*, **1959**, 1222.

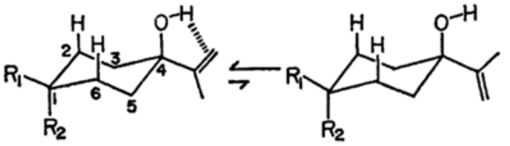
[8] M. Ōki and H. Iwamura, This Bulletin, **32**, 567 (1959).

[9] P. von R. Schleyer, D. S. Trifan and R. Bacskai, *J. Am. Chem. Soc.*, **80**, 6691 (1958).

TABLE 1. HYDROXYL STRETCHING ABSORPTIONS OF *p*-MENTH-8-ENOLS, 10-NOR-8-OXOMENTHOLS AND *p*-MENTHANE-3,8-DIOLS

Compound	ν_{OH}^{free} cm^{-1}	ε	ν_{OH}^{bonded} cm^{-1}	ε	$\varepsilon_b/\varepsilon_f$
trans-p-Menth-8-en-4-ol (I)	3622[a]	14	3606	68	4.9
cis-p-Menth-8-en-4-ol (II)	3621[a]	6	3604	74	12.3
Isopulegol (III)	3625[a]	10	3593[a] 3573	9 35	0.9 3.5
Neoisopulegol (IV)	3626	9	3575	43	4.8
Dihydrocarveol (V)	3630 3610[a]	50 25			
Neodihydrocarveol (VI)	3633	72			
trans-β-Terpineol (VII)	3617	58			
10-Nor-8-oxomenthol (VIII)	3625	20	3599 3535[a]	36 9	1.8 0.5
10-Nor-8-oxoneomenthol (IX)	3626	12	3537	46	3.8
10-Nor-8-oxocarvomenthol (X)	3630 3608	42 26			
10-Nor-8-oxoneocarvomenthol (XI)	3634	81			
cis-p-Menthane-3,8-diol (XII)	3622[a] 3615	62 66	3522	110	1.7
trans-p-Menthane-3,8-diol (XIII)	3614	61	3509	120	2.0

a: shoulder



Ia (R_1=Me, R_2=H)   Ib

IIa (R_1=H, R_2=Me)   IIb

that the $\varepsilon b/\varepsilon f$ value reflects the relative population of the bonded and free species,[8] where εb is the molecular extinction coefficient of the bonded hydroxyl and εf is that of the free hydroxyl group. The $\varepsilon b/\varepsilon f$ values were 4.9 for I and 12.3 for II. Comparison of these values with the value (1.8) of allyl alcohol[10] reveals that the population of such an internally hydrogen-bonded molecules as Ia and IIa is larger in *p*-menth-8-en-4-ols (I and II) than in allyl alcohol. The reason for this appears to be that the axial hydrogens on C-2 and C-6 in Ib and IIb may sterically repel the hydrogen of the tertiary hydroxyl group, forcing to direct it to the outer side of the cyclohexane ring, and towards the double bond of the isopropenyl group, as in Ia and IIa, whereas such repulsion is absent in allyl alcohol.

Isopulegol (III) and Neoisopulegol (IV). Neoisopulegol (IV) showed two distinct bands at 3626 and 3575 cm^{-1}. This carbinol may take the intramolecularly hydrogen bonded conformation IVa and unbonded one IVb. The former band is ascribed to a free hydroxyl group in IVb, because a free axial secondary hydroxyl frequency has been reported[5-7] to appear at 3627 to 3632 cm^{-1}. The latter is assigned to the band due to such a hydroxyl group interacted with the π-electrons as in IVa. On the other hand, isopulegol (III) showed an unresolved band, which was divided into three by graphical separation as shown in Fig. 1. The peak at 3625 cm^{-1} may be attributed to the free equatorial secondary hydroxyl group, a peak of which is said[5-7] to appear at 3623 to 3630 cm^{-1}. The peak at 3578 cm^{-1} indicates the presence of the OH···π interaction. The third band, which appeared at 3593 cm^{-1} seems to be due to either a hydrogen bonded hydroxyl or a conformational heterogeneity about the C–OH bond. Menthol corresponding to the saturated compound of III showed an unsymmetric band at 3626 and 3608 cm^{-1} owing to the conformational heterogeneity. The wave number of the third band of III is different by 15 cm^{-1} from the low-frequency band of menthol. Hence, the third band of III must be due to an intramolecularly interacted hydroxyl group. Thus, isopulegol (III) is considered to possess two intramolecularly interacted forms as shown in IIIa and IIIb.

The $\varepsilon b/\varepsilon f$ values were 0.9 and 3.5 for III, and 4.8 for IV. Comparison of these values with the value (0.45) of 3-buten-1-ol[10] reveals that the population of the internally hydrogen bonded molecules, such as IIIa and IVa, is larger in isopulegols (III and IV) than in 3-buten-1-ol. This can be explained in the following way. For 3-buten-1-ol, there are three internal rotational degrees of freedom about the alpha and the beta carbon-carbon single bonds and the carbon-oxygen bond. Isopulegols (III and IV) have one less internal rotational degree of freedom, since the incorporation of the C_3–C_4 bond into the

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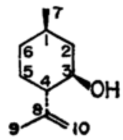
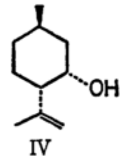
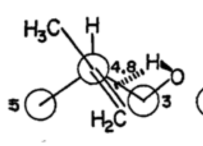
10) This value was calculated from the data of allyl alcohol in Ref. 8.



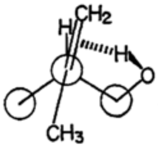
III



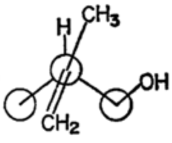
IV



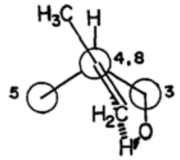
IIIa



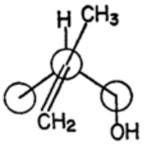
IIIb



IIIc



IVa



IVb

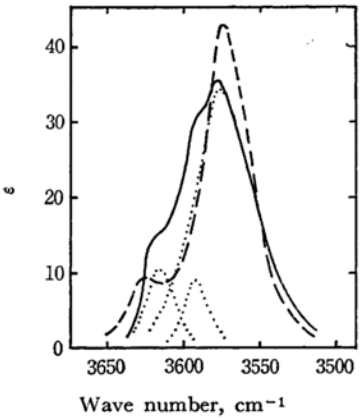
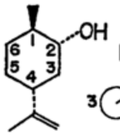


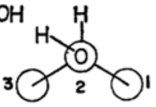
Fig. 1. IR spectra of isopulegol (III) (——; separated ······) and neoisopulegol (IV) (- - -) in 0.005M CCl_4 solution.

cyclohexane ring restrains the rotation of this bond, and this restriction makes the hydroxyl group favorable towards the isopropenyl group. Hence, the opportunity of hydrogen bonding is larger in isopulegols than in 3-buten-1-ol.

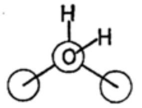
Dihydrocarveol (V), Neodihydrocarveol (VI) and *trans*-β-Terpineol (VII). Dihydrocarveol (V) having an equatorial secondary hydroxyl group showed a peak at 3630 cm^{-1} with a shoulder at 3610 cm^{-1}. This unsymmetrical band is not attributable to the presence of the interaction between the hydroxyl group and the π-electrons, but rather to the presence of isomers (Va, Vb and Vc) due to the rotational conformations of the hydroxyl group about the C–O axis.[11] The corresponding saturated alcohol, carvomenthol, also revealed an unsymmetrical band at 3631 and 3612 cm^{-1}, whereas the epimeric alcohol, neocarvomenthol, showed a symmetrical one at 3633 cm^{-1}. Therefore, the band at 3630 or 3631 cm^{-1} observed in dihydrocarveol (V) and carvomenthol with an equatorial secondary hydroxyl group is attributable to the conformers Va and/or Vb, and the low-frequency bands at 3610 or 3612 cm^{-1} to the conformer Vc. On the other hand, neodihydrocarveol (VI) and *trans*-β-terpineol (VII) showed a symmetrical band at 3633 and at 3617 cm^{-1} respectively, which correspond to the free axial secondary hydroxyl and the free tertiary hydroxyl band.[5-7] Therefore, these alcohols are considered to be internally unbonded.



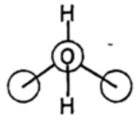
V



Va



Vb



Vc

Thus, the intramolecular interaction between the hydroxyl group and the π-electrons on a double bond of *p*-menth-8-enols takes place only in the case of the hydroxyl group at the α- or β-position to the double bond. This kind of interaction can not be found in the case of hydroxyl group at farther than γ-position.

10-Nor-8-oxomenthol (VIII) and 10-Nor-8-oxoneomenthol (IX). The spectrum of VIII showed an unresolved band, which can be divided into three by graphical separation (Fig. 2). The peak at 3625 cm^{-1} is attributed to the free hydroxyl group and the peak at 3535 cm^{-1} to the OH···O intramolecularly hydrogen bonded hydroxyl group of the type of VIIIc, in which the hydroxyl group makes bonding to the lone pair electrons on the carbonyl oxygen atom. On the other hand, the intermediate band at 3599 cm^{-1} was separated only by 26 cm^{-1} from the free hydroxyl band. This small separation seems to indicate that the hydroxyl group interact with π-electrons on the carbonyl group,[12] as shown in VIIId and VIIIe. The spectrum of IX showed two peaks at 3626 and 3537 cm^{-1}, the former being attributed to the free hydroxyl group (IXc) and the latter to the intramolecularly hydrogen bonded hydroxyl group of the type IXd in which the hydroxyl group bonds to the lone pair electrons on the carbonyl oxygen atom.

The difference of interactions in VIII and IX was explained as follows: These keto alcohols may take two interconvertible chair-forms VIIIa and VIIIb, and IXa and IXb, respectively. However, the forms VIIIb and IXb containing three or two axial

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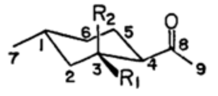
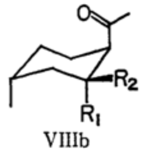
[11] M. Ōki and H. Iwamura, This Bulletin, **32**, 950 (1959).

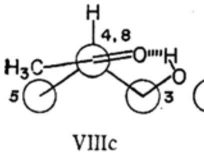
[12] M. Ōki and H. Iwamura, Preprints for the 20th Annual Meeting of the Chemical Society of Japan (April 1967), Part III, p. 128.



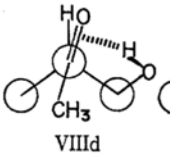
VIIIa (R_1=OH, R_2=H)
IXa (R_1=H, R_2=OH)



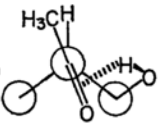
VIIIb
IXb



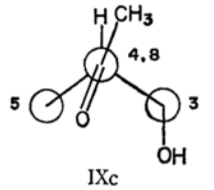
VIIIc



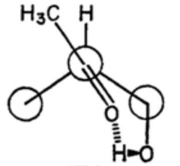
VIIId



VIIIe



IXc



IXd

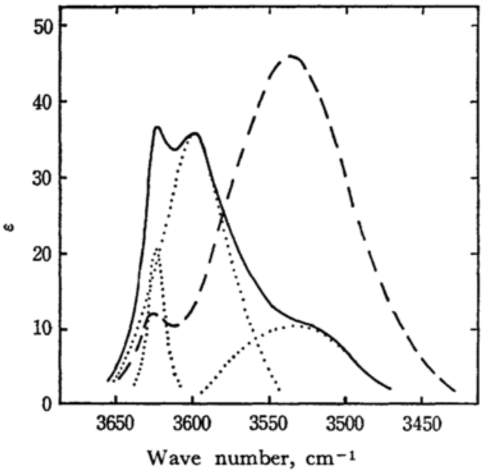
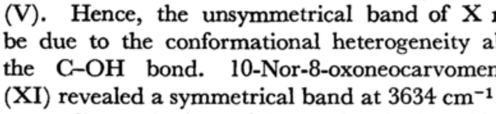


Fig. 2. IR spectra of 10-nor-8-oxomenthol (VIII) (——; separated ······) and 10-nor-8-oxoneomenthol (IX) (- - -) in 0.005M CCl_4 solution.

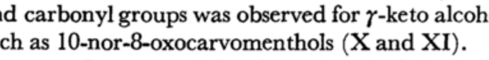
groups are neglected on the basis of the consideration of the thermodynamic stability.[18] Furthermore, the internal rotation of the acetyl group must be considered to explain the difference of the interaction. Intramolecular hydrogen bonding between the axial hydroxyl group and the lone pair electrons on the carbonyl oxygen in IX is favorable in conformer IXd, in which the interaction between the 9-methyl group and the 5-methylene is not present. On the other hand, conformer VIIIc having the short OH···O distance is unfavorable, because the 9-methyl group eclipses the 5-methylene. Therefore, the compound VIII seems to take conformation VIIId or VIIIe, in which no such unfavorable interaction occurs. In these conformations VIIId and VIIIe, the angle made by the direction of the carbonyl n-orbital and the line connecting the hydroxyl hydrogen with the carbonyl oxygen atoms amounts to *ca.* 60°, and the hydroxyl group is thought to interact rather with the π-electrons than with the lone pair electrons of the carbonyl group.

10-Nor-8-oxocarvomenthol (X) and 10-Nor-8-oxoneocarvomenthol (XI). The spectrum of 10-nor-8-oxocarvomenthol (X) showed an unsymmetrical band at 3630 cm^{-1} with a weak shoulder at 3608 cm^{-1}. The shape of this band as well as the wave number of the peak and the shoulder are very similar to those of carvomenthol and dihydrocarveol (V). Hence, the unsymmetrical band of X must be due to the conformational heterogeneity about the C–OH bond. 10-Nor-8-oxoneocarvomenthol (XI) revealed a symmetrical band at 3634 cm^{-1} corresponding to the free axial secondary hydroxyl band. No intramolecular interaction between the hydroxyl and carbonyl groups was observed for γ-keto alcohols such as 10-nor-8-oxocarvomenthols (X and XI).

***cis*- and *trans*-*p*-Menthane-3,8-diols (XII and XIII).** The spectrum of XII gave two bands at 3615 and 3522 cm^{-1}; the higher frequency band has a shoulder at *ca.* 3622 cm^{-1}. Concerning the *cis*-diol XII with the secondary axial hydroxyl group, the band at 3615 cm^{-1} is attributed to the free tertiary hydroxyl group in XIIa, while the weak band at 3622 cm^{-1} is due to the free secondary hydroxyl group in XIIb. This is supported by the fact that these frequencies agree with those of the ordinary



XIIa		XIIb



XIIIa		XIIIb

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[13] The differences in free energy between the equatorial and axial forms of the hydroxyl and methyl groups are -0.7[14] and -1.7 kcal/mol respectively. The energy of 1,3-diaxial interaction between the 7-methyl and hydroxyl groups in conformer VIIIb is 1.9—2.4 kcal/mol.[14] As the difference has been unknown for the acetyl group, we assumed to be nearly equal to -1.8 kcal/mol[14] given for the ethyl group. The difference of the conformational energy for VIIIa—VIIIb and IXa—IXb was estimated as -5.2 and -2.8 kcal/mol,[15] respectively. These differences would give a room temperature equilibrium mixture containing >99% of VIIIa or IXa, and <1% of VIIIb or IXb.

[14] E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc. New York, N. Y. (1965), pp. 44 and 52.

[15] Estimated approximately by adding the corresponding values for a hydroxyl, a methyl and an acetyl groups, and for the 1,3-diaxial interaction between the hydroxyl and methyl groups, since such summations have been said to be approximately correct in some cases.[16]

[16] Ref. 14, p. 58.

free tertiary hydroxyl and secondary hydroxyl groups.[5-7] The strong band at 3522 cm^{-1} is attributable to both the bonded secondary and tertiary hydroxyl groups in XIIa and XIIb respectively. On the other hand, the spectrum of XIII showed two resolved peaks at 3614 and 3509 cm^{-1}. The band at 3614 cm^{-1} is assigned to the band due to the free tertiary hydroxyl group in XIIIa and the strong band at 3509 cm^{-1} is mainly due to the bonded secondary hydroxyl group in XIIIa, since the band corresponding to the free hydroxyl is absent. Therefore, the preferential formation of the hydrogen bond seems to be in the case, where the secondary hydroxyl group is bonded to the oxygen atom of the tertiary hydroxyl group.

Experimental

Infrared Measurements. The infrared absorption was measured with a Perkin-Elmer Model 621 Grating Infrared Spectrometer, the spectral slit width being 3.5 cm^{-1} in the region required. Spectro Grade carbon tetrachloride was used as a solvent. A salt absorption cell, 2 cm in length, was used and the concentration of the solution was 0.005 mol/*l* at which the association of the solute negligible. Measurements were made at 25°C.

***trans-* and *cis-p*-Menth-8-en-4-ols (I and II).** These *p*-menth-8-en-4-ols (I and II) kindly supplied by Dr. Klein were prepared from 4(8)-*p*-menthene by the photosensitized oxidation.[17]

(−)-Isopulegol (III) and (+)-Neoisopulegol (IV). These two alcohols were isolated by the partial esterification of an isopulegol mixture.[18] III showed the following properties: bp 65—66°C/3 mmHg, n_D^{25} 1.4684, d_4^{25} 0.9062, $[\alpha]_D^{25}$ −22.51° (homog.) (lit.,[18] n_D^{26} 1.4690, d_4^{26} 0.9062, $[\alpha]_D^{26}$ −23.6°), 3,5-dinitrobenzoate of III, mp 104—105°C (lit.[18] mp 104—104.5°C). IV showed the following properties: bp 81—81.2°C/9 mmHg, n_D^{25} 1.4695, d_4^{25} 0.9115, $[\alpha]_D^{25}$ +33.27° (homog.) (lit.,[18] n_D^{26} 1.4708, d_4^{26} 0.9121), 3,5-dinitrobenzoate of IV, mp 133—134°C (lit.,[18] 133—133.5°C).

(−)-Dihydrocarveol (V). This alcohol was prepared from (−)-carvone by the reduction with sodium-aqueous ammonia[19] and had following properties: bp 99—99.5°C/10 mmHg, n_D^{25} 1.4725, d_4^{25} 0.9162, $[\alpha]_D^{25}$ −34.15° (homog.) (lit.,[19] n_D^{23} 1.4748, d_{20}^{23} 0.9202, $[\alpha]_D^{23}$ −33.25°), 3,5-dinitrobenzoate of V, mp 122—123°C (lit.,[19] mp 121.5—122.5°C).

(+)-Neodihydrocarveol (VI) and *trans-β*-terpineol (VII). These alcohols were prepared from (+)-limonene monoxide by the reduction with lithium aluminum hydride.[20] The former VI was isolated from a reduction product by converting into the *p*-nitrobenzoate derivative followed by hydrolysis and showed the following properties: bp 107—107.9°C/19 mmHg, n_D^{25} 1.4763, d_{41}^{25} 0.9225, $[\alpha]_D^{25}$ +35.16° (homog.) (lit.,[20a] n_D^{20} 1.4798, d_4^{25} 0.9337, $[\alpha]_D^{25}$ +32.8°), *p*-nitrobenzoate of VI, mp 106—107°C (lit.,[20] 106°C).

The unesterified portion of the reduction product was fractionally distilled under a reduced pressure, and afforded *trans-β*-terpineol (VII): bp 100—100.5°C/17 mmHg, mp 30—31°C, n_D^{25} 1.4746, d_4^{25} 0.9230, $[\alpha]_D^{25}$ 0° (lit.,[20a] mp 31—31.5°C n_D^{20}, 1.4749, d_4^{25} 0.9235).

(−)-10-Nor-8-oxomenthol (VIII). A solution of 1.0 g of III was ozonized in glacial acetic acid. The reaction mixture was stirred with zinc powder (1.0 g), 20 m*l* of ether, and 15 m*l* of water for 2 hr. The usual work-up gave 0.56 g of VIII: mp 45—46°C, $[\alpha]_D^{25}$ −48.5° (*c* 0.34, methanol), 3,5-dinitrobenzoate of VIII, mp 152—153°C (Found: C, 54.68; H, 5.20%).

Found: C, 69.38; H, 10.52%. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32%.

(+)-10-Nor-8-oxoneomenthol (IX). (+)-Neoisopulegol (IV) (1.0 g) was ozonized in glacial acetic acid (20 m*l*). On treatment as in the case of VIII, the ozonized mixture gave 0.8 g of IX: mp 59—60°C, $[\alpha]_D^{25}$ +17.7° (*c* 0.37, methanol), 3,5-dinitrobenzoate, mp 93—94°C (Found: C, 54.96; H, 5.37%).

Found: C, 68.90; H, 10.48%. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32%.

(−)-10-Nor-8-oxocarvomenthol (X). When (−)-dihydrocarveol (V) (2.0 g) was ozonized in glacial acetic acid in the same way as in the case of VIII, it gave a crystalline mass (1.1 g) of X: mp 58—59°C, $[\alpha]_D^{25}$ −43.1° (*c* 0.21, methanol), 3,5-dinitrobenzoate, mp 126—126.5°C (Found: C, 54.77; H, 5.42%).

Found: C, 69.42; H, 10.50%. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32%.

(+)-10-Nor-8-oxoneocarvomenthol (XI). On ozonization in the same way as in the case of VIII, (+)-neodihydrocarveol (VI) (2.0 g) gave 1.2 g of XI as an oil: bp 107—108°C/2 mmHg, n_D^{25} 1.4732, d_4^{25} 1.0165, $[\alpha]_D^{25}$ +29.41° (homog.); 3,5-dinitrobenzoate, mp 136—137°C (Found: C, 54.58; H, 5.39%).

***cis-* and *trans-p*-Menthane-3,8-diols (XII and XIII).** These diols kindly supplied by Dr. Arai were prepared from (+)-citronellal by the acid-catalyzed cyclization[21]; XII, mp 73—74°C; XIII, mp 60—61°C.

The author wishes to express his hearty gratitude to Professor Tamon Matsuura and to Dr. Takayuki Suga for their guidance and encouragement, to Dr. E. Klein of DRAGOCO, Holzminden, for a gift of *p*-menth-8-en-4-ols, to Dr. Mannosuke Arai of Tohoku University, for *p*-menthane-3,8-diols, to Takasago Perfumery Co., Ltd., Tokyo, for spearmint oil and isopulegol, to Hasegawa Co., Ltd., Tokyo, for limonene. Microanalyses were performed at Faculty of Pharmacy of Kyoto University, Kyoto.

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