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Stereochemical Studies of Monoterpene Compounds. V.⁽¹⁾ The Rotational Conformation of the Acetyl Group of 10-Nor-8-oxomenthols and 10-Nor-8-oxocarvomenthols[2]

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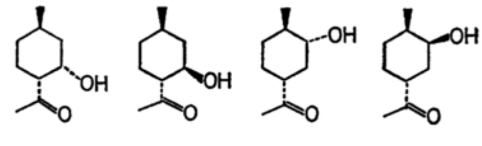
The preferred rotational conformation of the acetyl group of (+)-10-nor-8-oxoneomenthol (I), (−)-10-nor-8-oxomenthol (II), (−)-10-nor-8-oxocarvomenthol (III), and (+)-10-nor-8-oxoneocarvomenthol (IV) has been examined by a combination of conformational analysis by *a priori* calculation and variable-temperature circular dichroism and infrared spectrum measurements. Compound I exhibited an inversion in the sign of the Cotton effect upon a change in the solvent. This phenomenon was interpreted as indicating the conformational change Ia⇄Ib. The cause of the change was ascribed to the formation and subsequent rupture of the intramolecular hydrogen bond. Compound II exhibited a solvent-depending circular dichroism curve similar to the curve of I; this was explained as indicating the existence of a conformational equilibrium between the free conformer, IIa, and the internally-hydrogen-bonded conformers, IIb, IIc, and IId. Furthermore, compounds III and IV were found to take preferentially the IIIa—IIIb and IVa—IVb conformations respectively.

In recent years, optical rotatory dispersion and circular dichroism (CD) measurements have been useful in assigning the rotational conformation of the 17-acetyl group of 20-ketosteroids[3] because of the peculiar sensitivity of this method to subtle conformational alterations. However, the conformation of the acetyl group of the cyclohexane derivatives has not yet been reported. 2- and 3- Acetylcyclohexanols seem to represent an interesting example of such a conformational alteration, since intramolecular hydrogen bonding can be expected in them, together with a rotational conformation of the acetyl group. For this paper the preferred rotational conformation of the acetyl group of (+)-10-nor-8-oxoneomenthol (I), (−)-10-nor-8-oxomenthol (II), (−)-10-nor-8-oxocarvomenthol (III) and (+)-10-nor-8-oxoneocarvomenthol (VI) has been examined by a combination of conformational analysis by *a priori* calculation and variable-temperature CD and infrared (IR) spectrum measurements.

Results and Discussion

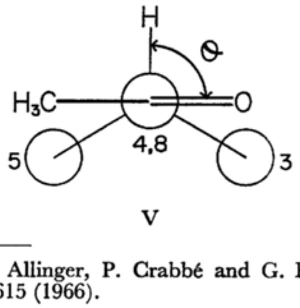
Compounds I, II, III and IV were prepared from (+)-neoisopulegol, (−)-isopulegol, (−)-dihydrocarveol and (+)-neodihydrocarveol respectively by ozonolysis; the configurations are as shown in Fig. 1.



I II III IV

Fig. 1.

In the conformational analysis of compounds I, II, III and IV, the conformation of the cyclohexane ring will be assumed throughout the following discussion to take the 1,4-diequatorial chair-form.[1] We must next consider the problem of the rotational barrier about a bond joining a carbonyl group to a tetrahedral carbon in a molecule of the acetone type. As Fig. 2 shows, the conformational energies of the acetyl group of compounds III and IV were estimated by using the energy functions given by the conformational analysis of the acetyl-side chain of pregnan-20-one.[4]



V

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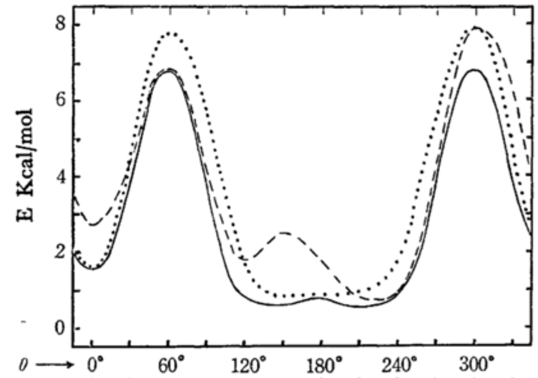
[1] Paper IV of this series: T. Shishibori, This Bulletin, **41**, 1170 (1968).

[2] Presented at the 20th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1967.

[3] G. Snatzke and E. Schwinum, *Tetrahedron*, **22**, 761 (1966), and the references cited therein.

[4] N. L. Allinger, P. Crabbé and G. Perez, *Tetrahedron*, **22**, 1615 (1966).



Compd.	The sign of cotton effect predicted											
I	±	+	+	+	+	+	−	−	−	−	−	−
II	+	+	+	+	+	+	−	−	−	−	−	+
III	+	+	+	+	+	±	−	−	−	−	−	±
IV	+	+	+	+	+	±	−	−	−	−	−	±

Fig. 2. Conformational energies calculated for the rotational conformation of the acetyl groups of I—IV as a function of θ: —— for III and IV, - - - for I, ······ for II. The signs of the Cotton effect predicted for each conformation were estimated from models as illustrated in Fig. 3.

With respect to compounds I and II, the functions of the van der Waals interaction between the C_3-hydroxyl and 9-methyl groups and between the C_3-hydroxyl group and the oxygen of the acetyl group must be superimposed upon the energy function for compound III or IV. The maximum of the former interaction in compound I should come around $\theta=330°$, where θ corresponds to a dihedral angle of V, and should be similar to the 1,3-diaxial hydroxyl-methyl interaction, with a value of 2.1 kcal/mol.⁵⁾ Judging from the distance between the hydroxyl and methyl groups, this value should have fallen to less than 0.35 kcal⁶⁾ at $\theta=270°$ and 30°, but to have a value of more than 0.35 kcal at $\theta=300°$ and 360°. As the interaction between the C_3-hydroxyl group and oxygen of the acetyl group has been unknown, we assumed it to be nearly equal to the 1.9 kcal/mol⁵⁾ given for the 1,3-diaxial hydroxyl interaction. The maximum of this interaction should come around $\theta=150°$. The rest of the curve is taken as proportional to the curve of the methyl-hydroxyl function, displaced appropriately. For compound II, the maximum of the interactions between the C_3-hydroxyl and 9-methyl groups and between the C_3-hydroxyl group and oxygen of the acetyl group are at $\theta=270°$ and 90° respectively. The magnitudes of the interaction are equal to those of I.

If this function represents the relative energy of the conformations, the conformer with $\theta=210°$ to 240° in compound I would be preferred over the conformer with $\theta=120°$ by 1.0 kcal/mol. Concerning compound II, the conformer with $\theta=150°$ to 210° would be preferred over the conformer with $\theta=0°$ by 0.8 kcal/mol.

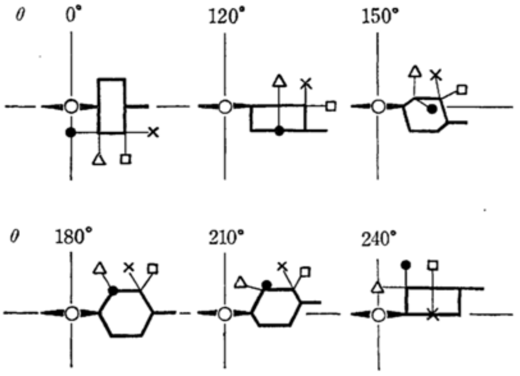


Fig. 3. Illustrations of the octant-rule projections used to predict the Cotton effect of the various rotational conformations of the acetyl group. Only the conformations eventually considered to be preferred are shown. Carbon skeleton is in heavy line; ○ for carbonyl oxygen; ● for OH of I; △ for OH of II; □ for OH of III; × for OH of IV.

Models⁸⁾ of each conformation were examined, and the signs of the Cotton effect were predicted according to the octant rules⁹⁾ (Fig. 3). As shown in Fig. 2, the results showed that the conformers with $\theta=0°$ to 150° should exhibit a positive Cotton effect, and the conformers with $\theta=180°$ to 300°, a negative one, in all compounds.

(+)-10-Nor-8-oxoneomenthol (I). As shown in Fig. 4, the CD curves of I exhibited a strong solvent-dependence, that is, a positive Cotton effect in isooctane and in carbon tetrachloride, but a negative one in methanol and in dimethyl sulfoxide. Such an inversion of the sign of the Cotton effect upon a change in solvent can be ascribed to the change in the equilibrium of the rotational conformation of the acetyl group; an inversion of the sign has been observed in α-hydroxycyclohexanone derivatives¹⁰⁾ and explained by the idea that intramolecular hydrogen bonds were present in carbon tetrachloride, but these bonds were ruptured, resulting in a conformational

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5) E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y. (1965), p. 52.

6) The energy of interaction and the distance between an equatorial methyl and an equatorial or axial hydroxyl groups on adjacent carbon atoms in cyclitols are 0.35 kcal/mol⁷⁾ and 2.8 Å respectively.

7) Ref. 5, p. 356.

8) "Dreiding Stereomodels," W. Büchi Manufacture of Glass Apparatus Flawil, Switzerland.

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

10) C. Djerassi, R. Records and B. Bach, *Chem. & Ind.* (*London*), **1961**, 258; K. M. Wellman, W. S. Briggs and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 73 (1965); T. Suga, T. Shishibori and T. Matsuura, *J. Org. Chem.*, **32**, 965 (1967).

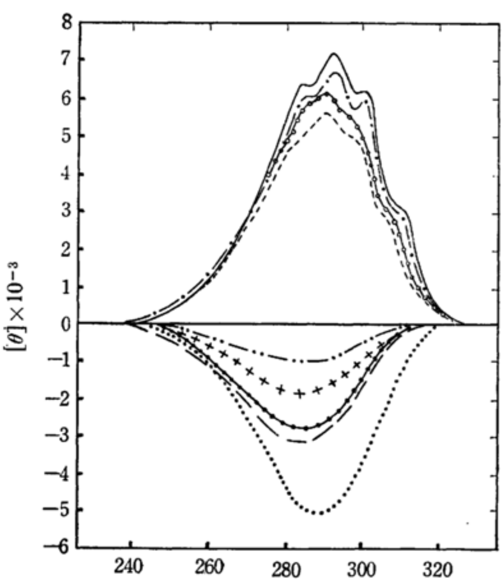
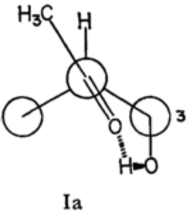


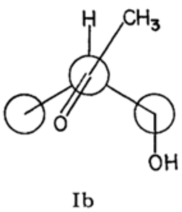
Fig. 4. CD curves of $(+)$-10-nor-8-oxoneomenthol (I) in selected solvents at 23°C: —— in isooctane; —·—· in CCl_4; - - - in $CHCl_3$; -o-o- in CH_2Cl_2; —··— in *t*-BuOH; ++ in *i*-PrOH; -•-•-• in EtOH; — — in MeOH; ······ in $(CH_3)_2SO$.

change in the methanol. A similar change in hydrogen-bonding may occur in compound I.

The IR spectrum of I in a 0.005 M carbon tetrachloride solution showed a concentration-independent band at 3537 cm^{-1} (ε 46) resulting from the hydroxyl function, which is intramolecularly hydrogen bonded with the lone-pair electrons on the carbonyl oxygen atom. This OH···O hydrogen bond is favorable in the Ia conformation with $\theta=150°$. On the other hand, the IR spectrum of I in dimethyl sulfoxide solution exhibited a broad band at 3330 cm^{-1} attributable to the formation of an intermolecular hydrogen bond between the hydroxyl group and the solvent. The CD and IR data, together with the results of conformational analysis (Fig. 2), suggest that the Ia conformer with $\theta=150°$ is preferential in nonpolar solvents, whereas Ib conformer with $\theta=120°$ is preferential in polar ones.



Ia



Ib

This agrees with the expectation that the population of Ia will increase in a nonpolar solvents, because the destabilizing electrostatic interaction between the carbonyl and hydroxyl groups in Ib is overcome by the formation of an intramolecular hydrogen bond in Ia. On the other hand, methanol and dimethyl sulfoxide are solvents which would be expected to form an intermolecular hydrogen bond with the carbonyl and/or the hydroxyl groups, and the population of Ia decreases concomitantly in a polar solvent because the stabilizing intramolecular hydrogen bond is broken.

A correlation between the rotational strength, R_0^{25}, and Kosower's *Z* values[11] (an empirical index of solvent polarity) is shown in Fig. 5. An anomalous decrease in the rotational strength appears at *Z* values of from 65 to 70. This seems to signify that the intramolecular hydrogen bond of I is broken in solvents with the values of 65—70.

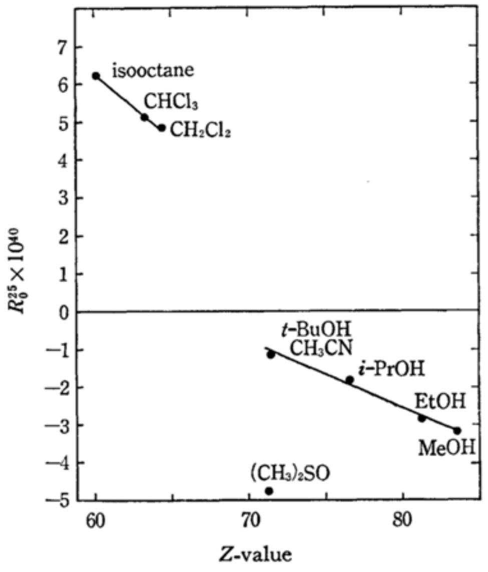


Fig. 5. Plot of rotational strength (R_0^{25}) of $(+)$-10-nor-8-oxoneomenthol (I) in various solvents *vs.* *Z*-value.

The variable-temperature CD curves of I in EPA[12] and in MI[13] are shown in Fig. 6. The CD curves in EPA exhibited a strong negative Cotton effect at −74°C, in contrast with the room-temperature CD curve. This signifies that the negatively rotating conformer, Ib, is energetically more favored at a low temperature in such a polar solvent. The CD curves in MI showed a positive Cotton effect and an increase in strength upon a lowering of the temperature. This implies that the positively-rotating, hydrogen-bonded conformer Ia is favored at a low temperature in a nonpolar solvent.

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[11] E. M. Kosower, *J. Am. Chem. Soc.*, **80**, 3254 (1958).

[12] EPA solvent is composed of ether-isopentane-ethanol in the ratio 5 : 5 : 2 by volume.

[13] MI solvent is composed of methylcyclohexane-isopentane in the ratio 1 : 3 by volume.

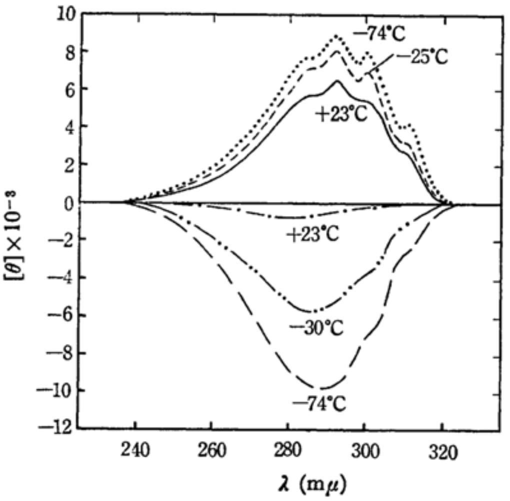
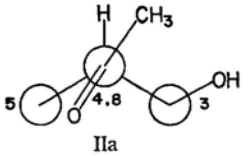
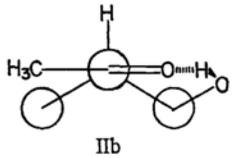


Fig. 6. CD curves of (+)-10-nor-8-oxoneomenthol (I) in EPA (—·—·, —··—, — —) and in MI (——, - - -, ····) at various temperatures.

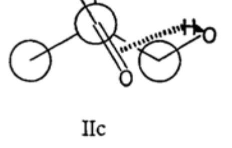
(−)-10-Nor-8-oxomenthol (II). The IR spectrum of II showed two peaks, at 3625 (ε 20) and 3599 cm^{-1} (ε 35), and a shoulder at 3535 cm^{-1} (ε 9) in a 0.005 M carbon tetrachloride solution. The band at 3625 cm^{-1} was attributed to such a free hydroxyl group as in the IIa conformation with θ=150°—210°, and the weak band at 3535 cm^{-1} to such an OH···O-type intramolecular hydrogen bond as in the IIb conformation with θ=90°. The band at 3599 cm^{-1} was also ascribed to an intramolecular, hydrogen-bonded hydroxyl group, and the small shift ($\Delta\nu$=26 cm^{-1}) of this band from the free hydroxyl band seems to indicate that the hydroxyl group interacts with the π-electrons on the carbonyl group,[14] as in IIc and/or IId. The IR spectrum in a dimethyl sulfoxide solution revealed the same results as in compound I.



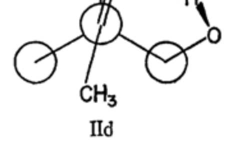
IIa



IIb



IIc



IId

As Fig. 7 shows, the CD curves of II exhibited a solvent-dependence similar to those of I, but the negative curve was observed only in dimethyl sulfoxide. This phenomenon can be explained in terms of the conformational equilibrium, IIa⇄IIb, IIc and IId, resulting from the formation and the subsequent rupture of the intramolecular hydrogen bond, in view of the IR-spectra results described above. The acetyl group of II would preferentially exist in positively-rotating, internally-bonded conformations, IIb, IIc, and IId, in a nonpolar solvent. In a polar medium, the stabilizing intramolecular hydrogen bond is broken and the population of the IIb, IIc, and IId conformations decreases, in contrast to the increasing population of the negatively-rotating conformer, IIa, with θ=150—210°. Thus, a decrease in the rotational strength of the positive curve was observed upon changing from a nonpolar solvent to a polar one, and a negative curve appeared in dimethyl sulfoxide (Fig. 7). As shown in Fig. 8, the CD curves of II in EPA exhibited a weak positive Cotton effect at +23°C and a weak negative one at −74°C. This signifies that the nonbonded conformer, IIa, is energetically favorable at a low temperature in a polar medium.

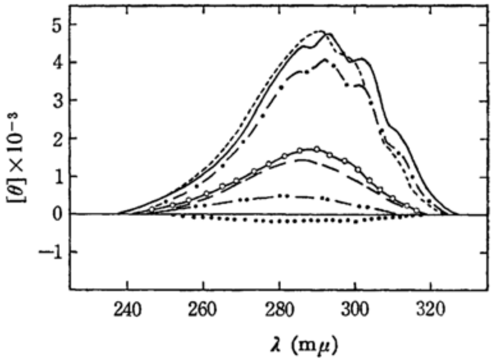


Fig. 7. CD curves of (−)-10-nor-8-oxomenthol (II) in selected solvents at 23°C: —— in isooctane; —·—· in CCl_4; - - - in $CHCl_3$; -○-○- in dioxane; —··— in *t*-BuOH; — — in MeOH; ···· in $(CH_3)_2SO$.

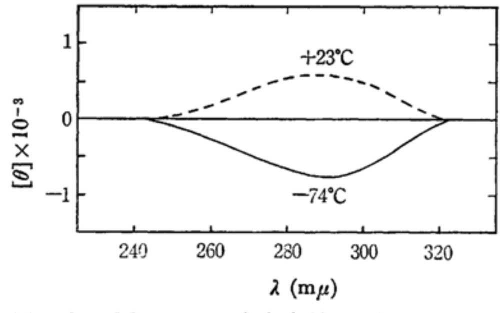


Fig. 8. CD curves of (−)-10-nor-8-oxomenthol (II) in EPA at +23°C and −74°C.

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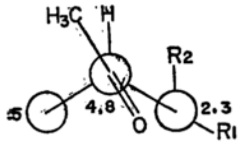
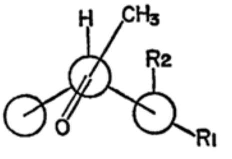
14) M. Ōki and H. Iwamura, Preprints for the 20th Annual Meeting of the Chemical Society of Japan, Tokyo (April, 1967), Part III, p. 128.

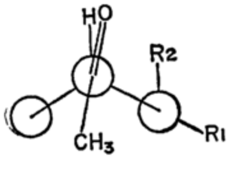
(−)-10-Nor-8-oxocarvomenthol (III) and (+)-10-Nor-8-oxoneocarvomenthol (IV). Furthermore, the rotational conformation of the acetyl group of III and IV has been examined. The IR spectra of III and IV in a 0.005 M carbon tetrachloride solution exhibited only a free hydroxyl band at 3630 (ε 42) and 3634 cm^{-1} (ε 80) respectively, showing the absence of a hydrogen bond between the carbonyl and hydroxyl groups. Thus, the rotational conformation of the acetyl group of III and IV is not affected by the hydrogen bond, and the acetyl group may be expected, from the conformational analysis (Fig. 2), to be situated near $\theta=120$—240° or 0°.



IIIa: R_1=OH, R_2=H
IVa: R_1=H, R_2=OH



IIIb
IVb



IIIc
IVc

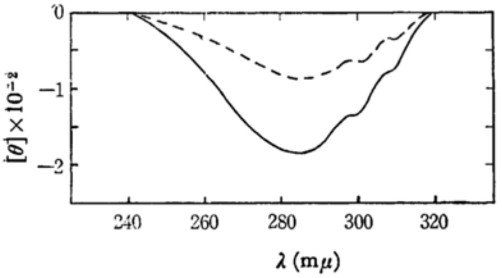


Fig. 9. CD curves of (−)-10-nor-8-oxocarvomenthol (III) in EPA at +23°C and −74°C.

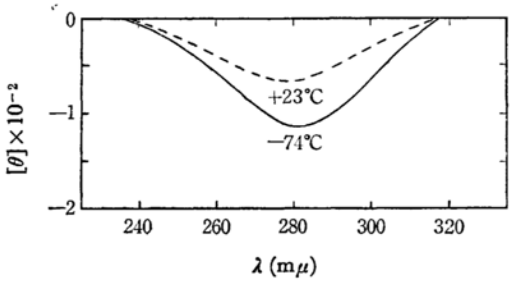


Fig. 10. CD curves of (+)-10-nor-8-oxoneocarvomenthol (IV) in EPA at +23°C and −74°C.

The CD curves of III in EPA showed a small increase in molecular ellipticity upon lowering of the temperature (Fig. 9). The CD curves of IV in EPA showed a similar tendency (Fig. 10). These results imply that the less stable, positively-rotating conformers, IIIc and IVc, with $\theta=0°$, diminish, and that the stable ones, IIIa—IIIb and IVa—IVb, with $\theta=120$—240°, are favored at a low temperature.

Experimental

Materials. The (+)-10-nor-8-oxoneomenthol (I), (−)-10-nor-8-oxomenthol (II), (−)-10-nor-8-oxocarvomenthol (III), and (+)-10-nor-8-oxoneocarvomenthol (IV) were the same as were prepared in a preceding paper1) of this series.

Spectral Measurements. The IR spectra in the hydroxyl-stretching region were measured with a Perkin-Elmer Model 621 Grating Infrared Spectrometer. A salt absorption cell, 20 mm long, was used, and the concentration of the solution was 0.005 mol/*l* at which value the association of the solute is negligible. The measurements were made at 25°C. The CD curves were obtained by a Japan Spectroscopic Co., Ltd., automatically-recording spectropolarimeter, Model ORD/UV-5, equipped with a circular dichroism attachment. The low-temperature CD curves were obtained by the same spectrometer, using a low-temperature CD cell15) designed and constructed by the authors. These measurements were carried out using a cell 10 mm long and *c* 0.1.

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15) T. Suga and T. Shishibori, JASCO Report (published by Japan Spectroscopic Co., Ltd., Tokyo), to be presented.