Stereochemical Studies of Monoterpene Compounds. I. The Conformation of (+)-p-Menthane-3, 4-diol Obtained by the Performic Acid Oxidation of (+)-p-Menth-3-ene

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The hydroxylation of *p*-menth-3-ene with performic acid in the presence of water has been reported by Naves[1] to afford *p*-menthane-*cis*-3, 4-diol (m. p. 76∼77°C) by a comparison of the melting point with that in the literature[*1] cited as footnote 13 in Ref. 1. In the ring-opening reaction of *p*-menthane-3, 4-epoxide using dilute mineral acid, Tanaka[2] obtained a 3, 4-diol[*2] with the same melting point (75∼76°C) as that of the diol obtained by the

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1) Y.-R. Naves, *Helv. Chim. Acta*, **42**, 1174 (1959).

[*1] G. Wagner (1894) obtained (±)-*p*-menthane-3, 4-diol (m. p. 76.5∼77°C) by the potassium permanganate oxidation of *p*-menth-3-ene. J. Böeseken (1923) showed that the hydroxylation of an olefin hydrocarbon by a permanganate reagent proceeds by cis addition. The reports by S. Tanaka (Ref. 2) and by H. Hock and S. Lang (Ref. 3) are also cited.

2) S. Tanaka, *Mem. Coll. Sci. Kyôto Imp. Univ. Series A*, **22**, 97 (1939) (*Chem. Zentr.*, **1940**, **I**, 688).

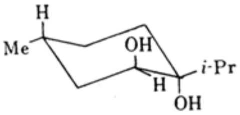
[*2] (+)-*p*-Menth-3-ene ($[\alpha]_D$+107.24°) has been used for preparing the 3, 4-epoxide; the 3, 4-diol is presumed to be dextrorotatory.

potassium permanganate oxidation of *p*-menth-3-ene, while Hock and Lang[3] obtained a (±)-diol melting at 95°C from the 3, 4-epoxide and considered it to be trans. However, there has been no experimental evidence with respect to a spatial arrangement of the two hydroxyl groups. Generally, the hydroxylation[4] of an ethylenic compound with performic acid in the presence of water leads to *trans*-α-glycol by means of the ring opening of the epoxide which is the intermediate product. However, a few exceptions to this stereochemical course in this opening reaction are known.[4c,5] Therefore, we have investigated the conformation of *p*-menthane-3, 4-diol prepared by the same manner as in Naves' report,[1] particularly the hydroxyl groups in it.

(+)-*p*-Menth-3-ene (I) used was prepared by the pyrolysis of methyl (−)-menthylxanthate, but it was accompanied by (+)-*p*-menth-2-ene (28%). The hydroxylation of the sample hydrocarbon was carried out by hydrogen peroxide in an aqueous formic acid at 35°C, giving crude glycol in a 66% yield on the basis of the hydrocarbon. The crude glycol was separated into crystalline (+)-*p*-menthane-3, 4-diol (m. p. 76.5~77°C; a 71% yield based on the crude glycol) and oily (+)-*p*-menthane 2, 3-diol (29%) by elution chromatography on a silica-gel column; no other glycol, i. e., no *cis* or *trans*(diequatorial)-glycol, could be isolated in spite of a careful examination. Each of the diols was shown to be homogeneous by gas phase and chromatostrip chromatography.

(+)-*p*-Menthane-*trans*-3, 4-diol (V). — The crystalline diol was dextrorotatory and showed the same melting point as the previously-described 3, 4-diol,[3*] which is certainly optically inactive, because the *p*-menth-3-ene in Naves' report[1] was prepared from dihydro-α-terpineol by sulfuric acid dehydration. Treatment of the above crystalline diol with 10% sulfuric acid resulted in pinacolic dehydration affording a menthone mixture consisting of (−)-menthone (65%) and (+)-isomenthone (35%). Also, oxidation of the diol with *t*-butyl chromate gave (−)-4-hydroxymenthone. Thus it was confirmed that the hydroxyl groups are situated in both C_3- and C_4-positions.

The melting points of the *p*-menthane-3, 4-diol[4*] (m. p. 76.5~77°C) and its mono-3, 5-dinitrobenzoate (m. p. 150~150.5°C) differ from those of (+)-*cis*-4-hydroxymenthol (m. p. 80~81°C)[6a] and its mono-3, 5-dinitrobenzoate (m. p. 124~125°C)[6a,b] respectively. Moreover, the infrared spectrum of the diol in a highly dilute carbon tetrachloride solution, where intermolecular hydrogen bonding is out of the question, did not show any hydroxyl stretching absorption peak due to an intramolecular hydrogen bond, but only a free hydroxyl stretching absorption peak at 3630 cm^{-1}.[7] It has been established[8] that, at an ordinary temperature, the comparatively bulky isopropyl group in cyclohexane derivatives takes an equatorial conformation, because such conformation seems to be more energetically favored than an axial conformation. Accordingly, from the absence of an intramolecular hydrogen bonding in the 3, 4-diol, the two hydroxyl groups at C_3- and C_4-positions in it should be considered to take a diaxial conformation (V). It was thus shown that the predominant conformation of the hydroxyl groups in this crystalline *p*-menthane-3, 4-diol is in the diaxial trans position.



(V)

The methyl group in the sample *p*-menth-3-ene is considered to retain an equatorial orientation since the hydrocarbon was prepared from methyl (−)-menthylxanthate (1e, 3e, 4e)[9] by thermal decomposition proceeding by cis elimination[10] between the C_3-equatorial xanthate group and C_4-axial hydrogen. Moreover, it is generally accepted[4] that in the hydroxylation reaction of an olefin by performic acid in the presence of water, the intermediate epoxide with a cis configuration is immediately subjected to acid-catalyzed opening reaction by the reaction medium (in this case, formic acid), the opening reaction being initiated by protonation. Thus, the structure of protonated intermediate *p*-menthane-3, 4-epoxide is probably the II in Fig. 1. Generally, the acid-catalyzed opening reaction of cyclohexane epoxides containing no

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[3] H. Hock and S. Lang, *Chem. Ber.*, **75**, 300 (1942).

[4] a) D. Swern, "Organic Reactions," Vol. 7, Ed. by R. Adams, John Wiley and Sons, Inc., New York (1953), p. 378; b) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Company, Inc., New York (1962), p. 356; c) R. E. Parker and N. S. Isaacs, *Chem. Revs.*, **59**, 737 (1959).

[5] Z. Chaubudziński and H. Kuczyński, *Bull. Acad. Polon. Sci., Ser. Sci. Chim.*, **9**, 519 (1961).

[3*] There is no description of the optical property.

[4*] The *trans*-3, 4-diol and its derivatives which are dextrorotatory in optical property have not yet been reported.

[6] a) W. Tagaki and T. Mitsui, *J. Org. Chem.*, **25**, 1476 (1960); b) S. A. Kozhin, S. I. Yakimovich and G. V. Pigulecski, *J. Gen. Chem. USSR* (*Eng. Transl.*), **32**, 2334 (1962).

[7] A. R. H. Cole and P. R. Jefferies, *J. Chem. Soc.*, **1956**, 4391.

[8] H. D. Orloff, *Chem. Revs.*, **54**, 347 (1954).

[9] Ref. 8, p. 366.

[10] a) W. Hückel, W. Tappe and G. Legutke, *Ann.*, **543**, 194 (1940); b) Ref. 4b, p. 232; c) Ref. 8, p. 371.

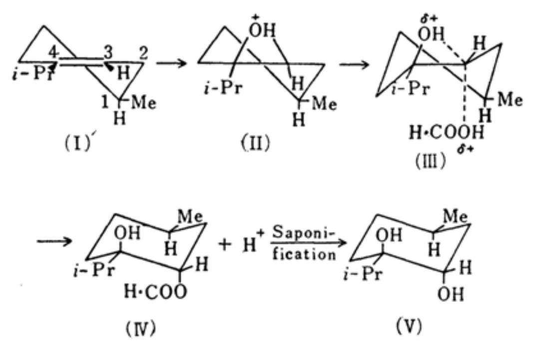
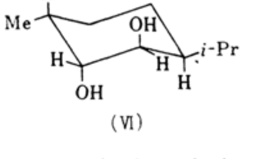


Fig. 1

group capable of exerting any marked polar or conjugative effect proceeds by the S$_N$2 attack of a reagent molecule from the axial side on the epoxide ring carbon atom, and the direction of the ring opening depends, consequently, on the steric factor.[4c] Therefore, the normal isomer corresponding to the attack of formic acid on the least-substituted carbon atom at the 3-position will be formed for the steric hindrance of the bulky isopropyl group, and the inversion of the configuration at the point of attack (the C$_3$-position) occurs because of the approach of the acid on the side opposite the displaced oxygen (cf. III). Thus, the opening reaction produces a monoformate of *p*-menthane-diaxial-3, 4-diol (IV), both alkyl groups of which are equatorial. Alkaline saponification of the formate affords only *trans*-diaxial-3, 4-diol (V).

(+)-*p*-Menthane-*trans*-2, 3-diol (VI).—This was isolated as a minor product and was a viscid oil. The infrared spectrum in a highly dilute carbon tetrachloride solution showed only one peak of a free hydroxyl stretching absorption at 3635 cm^{-1}.[11] This indicates the diaxial orientation of the two hydroxyl groups. Furthermore, the diol gave the same dinitrobenzoate as that of (+)-*trans*-2-hydroxyneomenthol.[11] Therefore, the 2, 3-diol was (+)-*trans*-2-hydroxyneomenthol (VI), which resulted certainly from the *trans*-*p*-menth-2-ene which coexisted in the sample of *p*-menth-3-ene.



(VI)

It appears that the hydroxylation of *p*-menth-2-ene takes place by the attack of formic acid on the C$_2$-position of *p*-menthane-2, 3-epoxide in the same way as with 3, 4-epoxide.

Experimental

Sample.—(+)-*p*-Menth-3-ene (I)[10a,12] (b. p. 168∼169°C, n_D^{25} 1.4492, d_4^{25} 0.8080, $[\alpha]_D^{25}$ +114.8°) was prepared from (−)-menthol by the pyrolysis of methyl (−)-menthylxanthate (m. p. 40.5∼41°C). According to the racemization procedure with *p*-toluenesulfonic acid,[13] the hydrocarbon was shown to be a mixture of (+)-*p*-menth-3-ene (72%) and (+)-*p*-menth-2-ene (28%). However, the isolation of pure *p*-menth-3-ene was so difficult that the hydrocarbon mixture was employed as the sample, without further purification.

Hydroxylation.—Into a mixture of the sample hydrocarbon (73 g.) and 77% aqueous formic acid (370 g.) 30% hydrogen peroxide (83 g.) was stirred drop by drop over a period of 0.5 hr. at 35°C, and then the mixture was maintained under the same conditions for a further 3 hr. The reaction mixture was treated as in Naves' report.[1] The crude glycol monoformate (84 g.) thus obtained was distilled to afford 63.2 g. of the main fraction boiling at 93∼105°C/3 mmHg (reported :[1] b. p. 105°C/3 mmHg for *p*-menthane-3, 4-diol monoformate). The infrared spectrum showed the peaks of ν_{OH} 3503, $\nu_{C=O}$ 1726, ν_{C-O-} 1188, and ν_{C-OH} 991 cm^{-1}. Hydrolysis of the formate with 14% ethanolic potassium hydroxide gave 47.8 g. of a crude glycol boiling at 99∼110°C/3 mmHg; this was a viscid oil which solidified softly after being kept in a refrigerator. The gas chromatogram (3 m. column, Thermol-1 on quartz (150∼200 mesh), 140°C, 50 ml. helium/min.) showed a main peak (t_R=16.3 min.) corresponding to the 3, 4-diol and a small peak (t_R=20.2 min.) corresponding to the 2, 3-diol. The crude glycol was chromatographed on silica-gel. The column was eluted with a mixture of ethyl acetate and *n*-hexane, and the elutes were separated into two fractions.

(+)-*p*-Menthane-*trans*-3, 4-diol (V). — The first elute gave 33.9 g. of a crystalline mass. Recrystallization of the mass from *n*-hexane gave white crystals with a m. p. of 76.5∼77°C ($[\alpha]_D^{25}$ +27.5° (*c* 1, methanol) and +22.3° (*c* 1, chloroform)). The gas phase chromatogram on Thermol-1 packing showed only one peak; moreover, only one spot was observed on the chromatostrip chromatogram[14] (solvent: 20% ethyl acetate in *n*-hexane).

Found: C, 69.81; H, 11.48. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70%.

Mono-3, 5-dinitrobenzoate melted at 150∼150.5°C (recrystallized from petroleum benzine) and showed $[\alpha]_D^{25}$ +36.8° (*c* 1, chloroform).

Found: N, 7.49. Calcd. for $C_{17}H_{22}O_7N_2$: N, 7.65%.

Pinacolic Dehydration. — A mixture of (+)-*p*-menthane-3, 4-diol (0.5 g.) and 10% sulfuric acid (5 ml.) was refluxed for 2 hr. and then steam-distilled. The distillate gave a menthone mixture (0.36 g.). The infrared spectrum corresponded to

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[11] P. R. Jefferies and B. Milligan, *J. Chem. Soc.*, **1956**, 2363.

[12] L. Tschugaeff, *Ber.*, **32**, 3332 (1899).

[13] J. P. Wibaut, H. C. Beyerman and H. B. Van Leeuwen, *Rec. trav. chim.*, **71**, 1032 (1952).

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

that[15] of a mixture of (−)-menthone and (+)-isomenthone. The composition (mentioned above) of the menthone mixture was calculated from its optical rotation value, $[\alpha]_D^{20}$ +15.2° (*c* 2, methanol), using $[\alpha]_D^{20}$ −25° (*c* 2, methanol) for (−)-menthone and $[\alpha]_D^{20}$ +90° (*c* 2, methanol) for (+)-isomenthone. Only (−)-menthone 2, 4-dinitrophenylhydrazone (m. p. and mixed m. p. 145~145.5°C) was prepared.

Oxidation with t-Butyl Chromate (The Formation of 4-Hydroxymenthone).—A *t*-butyl chromate solution[16] was prepared from chromic trioxide (1.75 g.), *t*-butyl alcohol (3.5 g.) and benzene (20 ml.). The 3, 4-diol (3.0 g.) in benzene (15 ml.) was oxidized with this oxidant at 25~30°C for 2 hr. Then a neutral reaction mixture (2.7 g.) obtained was fractionated into 1.3 g. of a keto alcohol (n_D^{25} 1.4641; d_4^{25} 0.9906; $[\alpha]_D^{25}$ −96.7°; IR (liq. film): 3493 (OH), 1709 (C=O), 1430 (-CH_2-CO-), 1154 (OH) cm^{-1}) and 1.3 g. of unchanged diol by elution chromatography on a silica-gel column using ethyl acetate—*n*-hexane as an eluant.

Treatment of the keto alcohol with 2 N hydrochloric acid solution of 2, 4-dinitrophenylhydrazine gave (−)-4-hydroxymenthone 2, 4-dinitrophenylhydrazone (m. p. 102.5~103°C; UV: λ_{max}^{alc} 360 mμ, ε=22400; Found: N, 15.73. Calcd. for $C_{16}H_{22}O_5N_4$: N, 15.99%). On the other hand, (±)-*p*-menth-3-en-5-one 2, 4-dinitrophenylhydrazone (m. p. and mixed m. p. 147.5~148.5°C) was produced on treating it with an ethanol-sulfuric acid solution of 2, 4-dinitrophenylhydrazine.[17]

(+)-*p*-Menthane-*trans*-2, 3-diol (VI).—In the elution chromatography of the crude glycol described above, the second elute gave a viscid oil (13.8 g.), which was confirmed to be homogeneous by gas phase and chromatostrip chromatography as in the case of V. The oil showed $[\alpha]_D^{25}$ +37.2° (*c* 1, chloroform) (reported;[11] $[\alpha]_D^{20}$ +40.8°) and gave di-*p*-nitrobenzoate, m. p. 173.5~174°C (reported[11]: m. p. 174°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. The wave number accuracy at 3500 cm^{-1}: ±3 cm^{-1}. Temperature: 20°C. Solvent: carbon tetrachloride. Cell: 20 mm. long. Sample concentration: 0.003 mol.

Summary

The conformational analysis of (+)-*p*-menthane-3, 4-diol, which had been obtained by the hydroxylation of (+)-*p*-menth-3-ene with performic acid in the presence of water, has been performed mainly by means of infrared spectra. It has been shown that the two hydroxyl groups at the C_3- and C_4-positions take a diaxial conformation, that they are, accordingly, trans to each other, and that the methyl group presumably holds an equatorial orientation. It has also been found that *p*-menthane-*trans*(diaxial)-2, 3-diol results from the *p*-menth-2-ene coexisting in the sample of *p*-menth-3-ene. A stereochemical course of the hydroxylation reaction has been discussed.

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[15] Y.-R. Naves and J. Lecomte, *Bull. soc. chim. France*, **1955**, 792.

[16] Cf. T. Suga, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **80**, 918 (1959); S. M. Linder and F. R. Greenspan, *J. Org. Chem.*, **22**, 949 (1957).

[17] P. R. Jefferies and B. Milligan, *J. Chem. Soc.*, **1956**, 4390.