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The Configuration of 6,8(9)-*p*-Menthadien-2,4-diols and *p*-Menthane-2,4-diols

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The 6,8(9)-*p*-menthadien-*trans*-2,4-diol (I) and 6,8(9)-*p*-menthadien-*cis*-2,4-diol (II) were obtained by the oxidation of *l*-*cis*-carvyl acetate with selenium dioxide. The hydrogenation of each 6,8(9)-*p*-menthadien-2,4-diol gave a different pair of *p*-menthane-2,4-diols, one pair being *p*-menthane-2,4-diols (III and IV) from *trans*-2,4-diol (I) and the other pair being *p*-menthane-2,4-diols (V and VI) from *cis*-2,4-diol (II). The absolute configurations of the *p*-menthane-2,4-diols (III, IV, V and VI) were assigned as follows on the basis of the chemical evidence, the IR and NMR data, and the Cotton-effect sign of the oxidation products of these isomers: III, (1S : 2R : 4S); IV, (1R : 2R : 4S); V, (1R : 2R : 4R) and VI, (1S : 2R : 4R)-*p*-menthane-2,4-diol. The identification of these diastereoisomeric diols III–VI made possible the assignment of a configuration to diols I and II.

In previous papers[1,2] some 8(9)-*p*-menthendiols and 8(9)-*p*-menthen-aldols were prepared by the oxidation of 8(9)-*p*-menthen-ols and those acetates with selenium dioxide. The configuration of the reaction product was assigned on the basis of the chemical evidence and the IR spectra. Now new diols, 6,8(9)-*p*-menthadien-*trans*-2,4-diol (I) and 6,8(9)-*p*-menthadien-*cis*-2,4-diol (II), have been obtained from *l*-*cis*-carvyl acetate by selenium dioxide oxidation, followed by the saponification of the reaction product.

In a study of the mechanism by which olefins are oxidized with selenium dioxide, Schaefer and Horvath[3] and Olson[4] have shown that selenium dioxide or its conjugate acid acts as an electrophile and attacks a double bond, thus forming a carbonium ion. When Schaefer's mechanism is applied in the case of carvyl acetate the reaction process is as is shown in Fig. 1. This view of the mechanism of the oxidation appears to accord well with that by which the two diols, I and II, are produced.

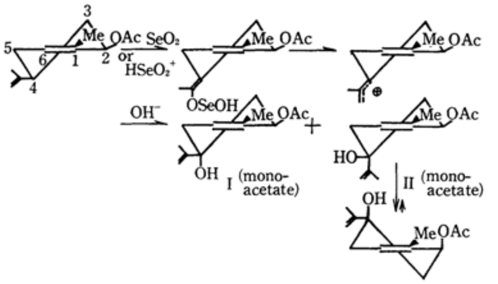

Fig. 1. Oxidation of *l*-*cis*-carvyl acetate.

The hydrogenation of the unsaturated diols, I and II, yielded four diastereoisomeric *p*-menthane-2,4-diols, III, IV, V, and VI. *p*-Menthane-2,4-diol, mp 93—94°C, was prepared by Wallach[5] by the catalytic hydrogenation of the 6-*p*-menthen-2,4-diol obtained by the hydration of sabinol. However, there has been no experimental evidence with respect to a spatial arrangement of the hydroxyl and methyl groups. This paper will report on the preparation and the configuration of these diols, I—VI.

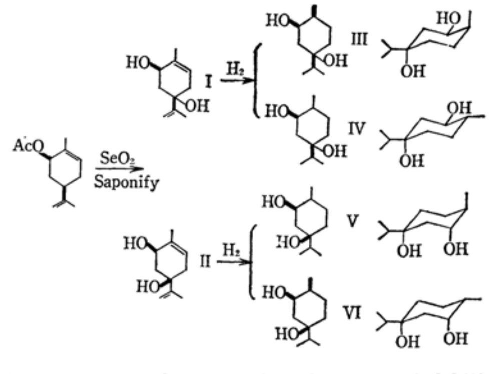

Fig. 2. The configurational assignment of 6,8(9)-*p*-menthadien-2,4-diols (I, II) and *p*-menthane-2,4-diols (III—VI).

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[1] Y. Sakuda, This Bulletin, **34**, 514 (1961).

[2] Y. Sakuda, *J. Sci. Hiroshima Univ.*, **A-II**, **25**, 207 (1961).

[3] J. P. Schaefer and B. Horvath, *Tetrahedron Letters*, No. 30, 2023 (1964).

[4] D. H. Olson, *ibid.*, No. 19, 2053 (1966).

[5] O. Wallach, *Ann.*, **414**, 203 (1917).

6,8(9)-*p*-Menthadien-*trans*-2,4-diol (I) and -*cis*-2,4-diol (II). *l*-*cis*-Carvyl acetate was oxidized with a solution of selenium dioxide dissolved in *t*-butyl alcohol at room temperature. The diols, I and II, were separated by column chromatography from the saponified product of the less volatile part of the reaction mixture.

6,8(9)-p-Menthadien-trans-3,4-diol (I). The IR spectrum of I showed the bands at 898, 1650, and 3100 cm^{-1} due to the isopropenyl group and that at 3400 cm^{-1} due to the hydroxyl group. The NMR spectrum of I in chloroform-*d*, shown in Fig. 3a, exhibited well-separated signals; this is consistent with that spectrum expected for 6,8(9)-*p*-menthadien-ol.

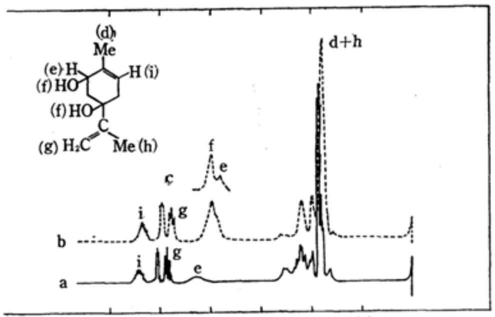

Fig. 3. NMR spectra of (a) I in $CDCl_3$ (——), (b) II in CCl_4 (-----) and (c) fragment of II in CCl_4 $+C_6H_6$ (-----).

6,8(9)-p-Menthadien-cis-2,4-diol (II). The IR spectrum of II showed the bands at 900, 1647, and 3100 cm^{-1} due to the isopropenyl group and that at 3360 cm^{-1} due to the hydroxyl group. The NMR spectrum of II in carbon tetrachloride shown in Fig. 3b was analogous with that of I except for the signal at δ 3.7—4.1 ppm. The NMR spectrum of II, measured in a mixed solvent of carbon tetrachloride and benzene, showed that the absorption at δ 3.7—4.1 ppm appears as two clear splitting signals, at δ 3.60 ppm due to the carbinol proton at the C-2 position and at δ 3.86 ppm due to two hydroxyl protons (Fig. 3c). It was assumed that a strong intramolecular hydrogen bond exists in II from the fact that the OH proton signal of II appeared at a lower field than that of I. The presence of the intramolecular hydrogen bond in II was further evidenced by the measurement of the IR spectra of I and II.[6] The IR spectrum of I in a dilute solution of carbon tetrachloride showed two bands, at 3635 (ε 49) and 3606 (ε 88) cm^{-1}; the lower-frequency band has a weak shoulder at 3590 cm^{-1}. The band at 3635 cm^{-1} is attributed to the free secondary hydroxyl group, and the band at 3606 cm^{-1}, to the hydroxyl group which interacts with the π-electron of the isopropenyl group.[7,8] The IR spectrum of II showed two bands, at 3612(ε 66) and 3550(ε 69) cm^{-1}; the higher-frequency band has a shoulder at 3595 cm^{-1}. The band at 3612 cm^{-1} is attributed to the free tertiary hydroxyl group, and the band at 3550 cm^{-1}, to the OH–O intramolecularly-hydrogen-bonded hydroxyl group. Considering the value of the difference between free and bonded OH bands, it was assumed that II is a *cis*-cyclohexene-1,3(2,4)-diol.[7a] Thus the NMR and IR data provided adequate evidence for determining the configuration of II to be 6,8(9)-*p*-menthadien-*cis*-2,4-diol. Furthermore, the fact that the configuration of each of the diols, I and II, is 6,8(9)-*p*-menthadien-2,4-diol was confirmed by the hydrogenation of I and II.

***p*-Menthane-2,4-diols III, IV, V and VI.** Upon the hydrogenation of the double bond, each of

TABLE 1. IR AND NMR DATA FOR *p*-MENTHANE-2,4-DIOLS

Diol	IR OH, cm^{-1} Neat	Concn. (mol/l)	CCl$_4$ soln. free(ε)	CCl$_4$ soln. bonded(ε)	NMR, δ ppm 9H C$\underline{H}_3\times3$	1H $\underline{H}$C–OH	2H O$\underline{H}\times2$
III	3280	0.0032	3620(99)		0.88 0.97	4.06[a]	
IV	3280	0.0036	3635(69) 3625(69)		0.88 0.93	3.3[b]	
V	3260	0.0029	3620(69)	3535(90)	0.88 0.97	3.67[a]	3.0[b]
VI	3300	0.0030	3635(48) 3618(48)	3535(100)	0.88 0.97	3.87[a]	3.3[b]

a) Multiplet b) Broad singlet

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6) M. Tichy, "Advances in Organic Chemistry," Vol. 5, Interscience Publishers, New York, N. Y. (1965), p. 115.

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

8) a) M. Ôki, H. Iwamura, J. Aihara and H. Iida, This Bulletin, **41**, 176 (1968). b) T. Shishibori, *ibid.*, **41**, 1170 (1968).

the diols, I and II, would be expected to give two *p*-menthane-2,4-diols, a pair of diastereoisomers epimeric at the C-1 position. Indeed, the I diol gave two products, III and IV, and the II diol gave V and VI. The IR and NMR data for these four diastereoisomeric *p*-menthane-2,4-diols are shown in Table 1. The IR spectra of V and VI in a dilute solution of carbon tetrachloride showed the band at 3535 cm^{-1} due to the intramolecularly-hydrogen-bonded hydroxyl group. Considering the value of the difference between free and bonded OH bands, it was assumed that V and VI are *cis*-cyclohexane-1,3(2,4)-idol.[7a] The NMR spectra of V and VI, measured after adding one drop of concentrated hydrochloric acid to a chloroform-d solution, showed no broad absorption at δ 3.0 or 3.3 ppm. From this fact, the absorption at δ 3.0 or 3.3 ppm was assigned to the OH proton signal. The fact that the OH proton signals of both the V and VI diols appear at a lower field than those of III and IV can account for the presence of strong intramolecular hydrogen bonds in V and VI.

Then it was confirmed that each of four diols, III, IV, V, and VI was diastereoisomeric *p*-menthane-2,4-diol. The IR spectrum of each of the four compounds obtained by the oxidation of III, IV, V, and VI with Jones' reagent[9] showed the band at 1700 cm^{-1} due to the carbonyl group and that at *ca.* 3400 cm^{-1} due to the hydroxyl group. The IR spectrum of the oxidation product of III coincided with that of the oxidation product of V. Each of the four oxidation products of III, IV, V, and VI gave the same 2,4-dinitrophenylhydrazone (2,4-DNP), which was identified as carvenone 2,4-DNP by a direct comparison with an authentic sample. When a mixture of the oxidation product of IV, ethyl alcohol, and sulfuric acid was left to stand overnight under the same conditions as those under which 2,4-DNP was prepared, dehydration occurred and carvenone produced. This fact confirmed that when a 2,4-DNP was derived from each oxidation product of III, IV, V, and VI, dehydration occurred and that, consequently, only carvenone 2,4-DNP was produced from the four oxidation products. From these facts it was concluded that each original diol, III, IV, V, and VI, is diastereoisomeric *p*-menthane-2,4-diol.

Absolute Configuration of *p*-Menthane-2,4-diols III, IV, V and VI. The optical rotatory dispersion spectra of the three oxidation products of III, V, and VI with Jones' reagent are shown in Fig. 4.

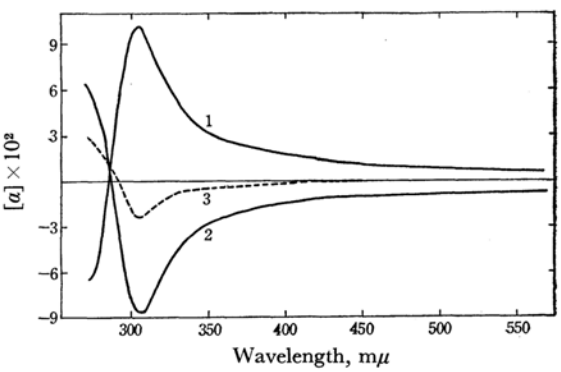

Fig. 4. Cotton effect of the oxidation products of III (curve 1), V (curve 2) and VI (curve 3).

The oxidation product of III exhibits a strong positive Cotton effect, the oxidation product of V exhibits a strong negative Cotton effect, and the oxidation product of VI exhibits a weak negative Cotton effect. Considering the Cotton-effect signs of these oxidation products, it was concluded that the oxidation products of III and V are enantiomer, and that the oxidation product of V possesses an axial methyl group at the C-1 position and that the oxidation product of VI possesses an equatorial methyl group at the C-1 position. Assuming that the conformations of these original diols are maintained throughout the oxidation procedure with Jones' reagent, the absolute configuration of each diol, III, IV, V, and VI, was assigned as is shown in Fig. 1; that is to say, III, IV, V and VI are (1S : 2R : 4S), (1R : 2R : 4S), (1R : 2R : 4R), and (1S : 2R : 4R)-*p*-menthane-2,4-diol respectively.

Experimental

The NMR spectra were recorded with a Varian A-60 NMR spectrometer using TMS as the internal standard. The IR spectra in the 2500—4000 cm^{-1} region were determined with a Perkin-Elmer Model 621 grating spectrophotometer using a stoppered sodium chloride cell with a path length of 2.00 cm. The ORD spectra were determined in methanol with a Nippon Bunko ORD/UV-5 spectropolarimeter. The reaction products were analyzed by gas chromatography using a diethylene glycol succinate column at 150 and 190°C.

Samples. *l-cis-Carvyl Acetate.* *l-cis*-Carveol was prepared from *l*-carvone by reduction with lithium aluminium hydride[10] and was purified *via* its 3,5-dinitrobenzoate. Physical constants:[11] mp 23—24°C, bp 81—82°C/2 mmHg, n_D^{25} 1.4955, d_4^{25} 0.9524, $[\alpha]_D$ −24.4. *l-cis*-Carvyl acetate was prepared by refluxing the pure *l-cis*-carveol thus obtained with acetic anhydride and with anhydrous sodium acetate. Bp 90—92°C/2 mmHg, n_D^{25} 1.4731, d_4^{25} 0.9689, $[\alpha]_D$ −42.9.

6,8(9)-*p*-Menthadien-*trans*-2,4-diol(I) and -*cis*-2,4-diol (II). These two diols were prepared from *l-cis*-carvyl acetate by selenium dioxide oxidation as follows.

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[9] K. Bowden, I. M. Hellbron, E. H. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, **1946**, 39.

[10] R. H. Reitsema, *J. Am. Chem. Soc.*, **75**, 1996 (1953).

[11] R. G. Johnston and J. Read, *J. Chem. Soc.*, **1934**, 233.

A solution of *l-cis*-carvyl acetate (97 g, 1/2 mol) in benzene (97 g) was stirred, drop by drop, into a solution of selenium dioxide (28 g, 1/4 mol) dissolved in *t*-butyl alcohol (225 g, 3 mol). The temperature of the reaction mixture rose to 45°C. The mixture was then left to stand at room temperature overnight. After the solvent had been removed, the remaining product was distilled under reduced pressure, giving two fractions: 1 (bp 65—90°C/2 mmHg (28 g)) and 2 (bp 91—110°C/2 mmHg (19.2 g)). Fraction 1 consisted mainly of unchanged carvyl acetate. Fraction 2 was saponified and was then chromatographed on a silica-gel column, giving I and II. The yield of I plus II was 10% based on the sample used. I, mp 107—108°C, $[\alpha]_D+20.0$ (*c* 3.7, ethanol). Found: C, 71.62; H, 9.87%. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.58%. II, bp 110—111°C/2 mmHg, n_D^{25} 1.5045, d_4^{25} 1.0508, $[\alpha]_D$ +14.0 (*c* 11.8, ethanol).

(1R : 2R : 4R)-*p*-Menthane-2,4-diol (V) and (1S : 2R : 4R)-*p*-Menthane-2,4-diol (VI). A solution of II (1.6 g) in ethanol (50 cc) containing Raney Ni (*ca.* 2 g) was shaken for 8 hr at 40—60°C under a 100—110 atm. H_2 pressure. The total semisolid hydrogenation product (1.6 g) gave two peaks corresponding in those retention times to V and VI on the gas chromatogram. The area ratio of the peaks of V and VI was 7 : 2. After the filtration of the liquid compound, the remaining crystals were recrystallized from hexane. Three recrystallizations gave needles of V, mp 76.5°C. Found: C, 69.22; H, 11.48%. Calcd for $C_{10}H_{20}O_2$: C, 69.76; H, 11.62%. The liquid filtrate was chromatographed on an alumina column. Elution with a methanol-ether mixture (1 : 30) gave 35 fractions, which were then analyzed by gas chromatography. Fractions 1—16 consisted of the solvent alone. Fractions 17—20 gave the liquid diol, VI. Found: C, 70.30; H, 11.62%. Calcd for $C_{10}H_{20}O_2$: C, 69.76; H, 11.62%. Fractions 21—35 gave mixtures of V and VI.

(1S : 2R : 4S)-*p*-Menthane-2,4-diol (III) and (1R : 2R : 4S)-*p*-Menthane-2,4-diol (IV). *trans*-Diol (I) was hydrogenated in the same way as was *cis*-diol (II) described above. The total crystalline hydrogenation product gave two peaks, corresponding in retention time to the two *p*-menthane-2,4-diols, III and IV, on the gas chromatogram. The area ratio of the peaks of III and IV was 1 : 4. The product was recrystallized from hexane, hexane - ethyl acetate (4 : 1), ether, benzene, and hexane - ethyl acetate (9 : 1) successively. Twenty-three recrystallizations gave white flakes of III, mp 153°C. Found: C, 70.00; H, 11.72%. Calcd for $C_{10}H_{20}O_2$: C, 69.76; H, 11.62%. After the solvent had been removed from the combined mother liquors, the remaining product was chromatographed on an alumina column. Elution with a methanol-ether mixture (1 : 30) gave 55 fractions, which then were analysed by gas chromatography. Fractions 1—16 consisted of the solvent alone. Fractions 17—26 gave white needles of IV, mp 115—116°C. Found: C, 69.84; H, 11.72%. Calcd for $C_{10}H_{20}O_2$: C, 69.76; H, 11.62%. Fractions 27—55 gave mixtures of III and IV.

Oxidation of Four *p*-Menthane-2,4-diols, III, IV, V, and VI, with Chromic Acid. A solution of chromic trioxide (46 mg, 0.46 mmol), concentrated sulfuric acid (0.1 cc), and water (0.5 cc) was added, over a ten minutes period, to a solution of V (38 mg, 0.22 mmol) dissolved in acetone (1 cc), and then cooled to 0°C, while the mixture, cooled in an ice-water bath, was being stirred vigorously. The mixture was then poured into ice water and extracted with ether. The evaporation of the ether gave a viscous oil (35 mg) which showed characteristic absorptions at 1700 cm^{-1} due to the carbonyl group and at 3400 cm^{-1} due to the hydroxyl group. The 2,4-DNP of this carbonyl compound was prepared in the usual way; mp 165—166°C, UV λ_{max}^{alc} 387 mμ. Found: N, 16.69%. Calcd for $C_{16}H_{23}O_5N_4$: N, 16.80%. This 2,4-DNP was identified as carvenone 2,4-DNP by a mixed-melting-point determination and by a direct comparison of the IR spectra. The III, IV, and VI diols were oxidized in the same way as in the case of V. The 2,4-DNP of each of these three oxidation products was prepared and melted at the same mp, 165—166°C; all were identified as carvenone 2,4-DNP.

Dehydration of Oxidation Product of the IV Diol. From the fact that each of the four oxidation products of III, IV, V, and VI gave the same 2,4-DNP, it was assumed that dehydration occurred when the 2,4-DNP was derived. To confirm this, the following experiment was carried out. A solution of the oxidation product (50 mg) of IV with chromic trioxide, ethanol (3 cc), concentrated sulfuric acid (0.2 cc), and water (0.3 cc) was left to stand at room temperature overnight. This conditions were the same as in the case of the derived 2,4-DNP. After water had been added, the reaction mixture was extracted with ether. The extract was chromatographed on a silica-gel column. Elution with petroleum ether - ethyl acetate (9 : 1) gave carvenone as an initial elute; it was identified by its UV spectrum, λ_{max}^{alc} 234 mμ, and 2,4-DNP; mp 165—166°C.

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