

IDENTITY OF CADINENOL WITH (\pm)-EPI-CUBENOL

B. TOMITA and Y. HIROSE

Faculty of Agriculture, University of Tokyo, Yayoi, Bunkyo-ku, Tokyo, Japan

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Key Word Index—*Juniperus rigida*; Cupressaceae; cadinenol; (\pm)-*epi*-cubenol; sesquiterpene alcohol.

Abstract—A crystalline sesquiterpene alcohol, 'cadinenol', is identified as (\pm)-*epi*-cubenol.

INTRODUCTION

CADINENOL, $C_{15}H_{26}O$, m.p. 75° , $[\alpha]_D +3.7^\circ$, was initially isolated from *Juniperus communis* L. and named by Šorm *et al.*¹ The same compound has been isolated from *Juniperus rigida* Sieb. et Zucc. by one of the authors,² from *Torreya nucifera* Sieb. et Zucc.,³ from *Schizandra nigra* Maxim.⁴ by Hirose *et al.*, and from *Chamaecyparis formosensis* Matsum. by Toda *et al.*⁵ The identity of these isolates was confirmed by comparison of IR spectra and melting points. However, there are slight differences in specific rotation among these isolates $[\alpha]_D$ 0° ,² $+3.7^\circ$,¹ $+5.02^\circ$.⁵ Though the structure (I) for cadinenol has been proposed,⁵ the authors have found that the IR spectrum of cadinenol obtained from *Juniperus rigida* is in good agreement with that of (–)-*epi*-cubenol from cubeb oil⁶ and with that of cadinenol reported by Šorm. (–)-*epi*-Cubenol is a liquid of $[\alpha]_D -95.7^\circ$. On the other hand cadinenol has been reported to be crystalline with a poor optical rotation. This paper reports the relation between cadinenol and (–)-*epi*-cubenol.

RESULTS AND DISCUSSION

The crystalline sesquiterpene alcohol, $C_{15}H_{26}O$, m.p. 75° , $[\alpha]_D 0^\circ$, isolated from *Juniperus rigida*, together with numerous sesquiterpenes^{7–10} including optical active cubenol (III), was identical with cadinenol by comparison of IR spectra and melting points.¹ In NMR spectrum two secondary methyl groups, an isopropyl group and a methyl group attached to a double bond were observed, besides an olefinic proton. These NMR data were consistent with those of cadin-9-en-1-ol reported⁵ and (–)-*epi*-cubenol.⁶ Since the alcohol is resistant to oxidation with CrO_3 in pyridine and shows no signals in NMR corresponding to the

¹ J. PLIVA, M. HORÁK, V. HEROUT, F. ŠORM, *Die Terpene Sammlung der Spectren und Physikalischen, Konstanten*, Akademie, Berlin (1960).

² Y. HIROSE and T. NAKATSUKA, *The 8th Symposium of Terpene, Essential Oil and Perfume Chemistry by the Chemical Society of Japan*, at Sendai, in Oct., 1964, abstract paper pp. 181–184.

³ T. SAKAI, K. NISHIMURA, H. CHIKAMATSU and Y. HIROSE, *Bull. Chem. Japan* **36**, 1261 (1963).

⁴ K. MORIKAWA, K. NISHIMURA and Y. HIROSE, *Nippon Kagaku Zasshi* **87**, 591 (1966).

⁵ T. TODA, Y. S. CHENG and T. NOZOE, *Chem. Pharm. Bull.* **15**, 903 (1967).

⁶ Y. OHTA and Y. HIROSE, *Tetrahedron Letters* 2073 (1967).

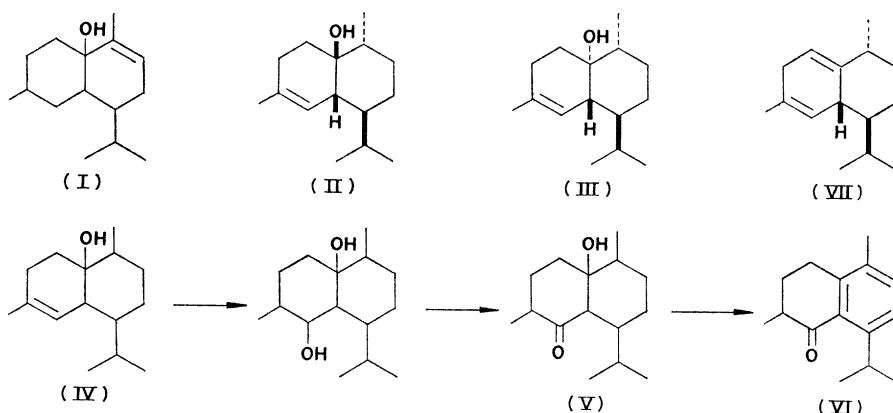
⁷ B. TOMITA, M. HAYASHI and Y. HIROSE, *Mokuzai Gakkaishi* **15**, 341 (1969).

⁸ B. TOMITA, Y. HIROSE and T. NAKATSUKA, *Mokuzai Gakkaishi* **15**, 48 (1969).

⁹ B. TOMITA and Y. HIROSE, *Tetrahedron Letters* 143 (1970).

¹⁰ B. TOMITA, T. ISONO and Y. HIROSE, *Tetrahedron Letters* 1371 (1970).

protons of the carbon atom attached to the hydroxyl group, the alcohol group of cadinenol is tertiary. The cadalenic skeleton^{2,5} was consistent with the spectral data and also with the following evidence.



The hydroxyl ketone (V) obtained by hydroboration of cadinenol followed by oxidation with CrO_3 in pyridine was dehydrogenated with Pd-C at 300° to yield a tetralone (VI), which was in complete agreement with 2,5-dimethyl-8-isopropyl tetralone (VI) by IR, NMR and UV spectra.¹¹ Thus the double bond in cadinenol was situated at the same position in the skeleton as in (–)-*epi*-cubenol (II).⁶

On dehydration with SOCl_2 in pyridine at 0° cadinenol afforded a diene (VII), which was identified by IR and NMR as one of the dienes obtained from cubenol (III) by the same dehydration. It has been reported that (–)-*epi*-cubenol was dehydrated under this condition to give the same diene exclusively.⁶ From these results the stereo-structure of cadinenol was deduced to be identical with (–)-*epi*-cubenol.

(–)-*epi*-Cubenol has the high optical rotation, $[\alpha]_D -95.7^\circ$,⁶ or -100° ,¹² and its dehydrated derivative has also $[\alpha]_D -21.9^\circ$.¹³ On the other hand neither our cadinenol from *Juniperus rigida* nor its dehydrated derivative displays optical rotatory power. The specific rotation of cadinenol has been reported to be $[\alpha]_D 0^\circ$,² $+3.7^\circ$,¹ $+5.02^\circ$.⁵ Considering the optical rotation and spectral identities between cadinenol and (–)-*epi*-cubenol we conclude that cadinenol is really a mixture of (–)-*epi*-cubenol and its enantiomer.

Up to now (–)-*epi*-cubenol has been widely found in nature and (+)-*epi*-cubenol has been recently isolated from *Streptomyces* sp. B-7.¹⁴ It is very interesting that both optically active cubenol and inactive *epi*-cubenol have been isolated from *Juniperus rigida*.

EXPERIMENTAL

Isolation of cadienol and cubenol. Milled wood (air dried, 23 kg) of *Juniperus rigida* from Yamanashi district was extracted with MeOH. The extract (1.7 kg) was treated with *n*-hexane and this soluble portion (1.1 kg) was shaken with 5% NaOH to remove acidic fraction (250 g). The neutral fraction (850 g) was distilled *in vacuo*. The fraction of b.p. $115\text{--}130^\circ$ (5 mm Hg) was chromatographed on alumina using *n*-hexane and EtOAc (1:0, 25:1, 10:1). By preparative GLC (polyethylene glycol 6000 column) the first fraction of alcoholic portion afforded a liquid alcohol, $M^+ 222$, $[\alpha]_D -24^\circ$, $\nu_{\text{max}}^{\text{liq}}$ 3500, 1660, 835 and 802 cm^{-1} , which was identified as cubenol. The eluate after cubenol contained four unknown compounds, one of which was

¹¹ B. A. NAGASAMPAGI, S. DEV, C. RAI and K. L. MURTHY, *Tetrahedron* **22**, 1949 (1966).

¹² B. A. NAGASAMPAGI, L. YANKOV and S. DEV, *Tetrahedron Letters* 1913 (1968).

¹³ Y. OHTA, K. OHARA and Y. HIROSE, *Tetrahedron Letters* 4181 (1968).

¹⁴ N. N. GERBER, *Phytochem.* **10**, 185 (1971).

isolated by preparative GLC followed by chromatography on silica gel impregnated with silver nitrate. Its IR spectrum in CHCl_3 was in good agreement with that of cadinenol.¹ This alcohol was recrystallized from *n*-hexane and had the following properties: m.p. 75°, $[\alpha]_D$ 0°, *Anal.* Found: C, 81.11; H, 11.68, Calc. for $\text{C}_{15}\text{H}_{26}\text{O}$: C, 81.02; H, 11.79%, MS M^+ 222, $\nu_{\text{max}}^{\text{CHCl}_3}$ 3500, 1667 and 855 cm^{-1} , δ^{CCl_4} 0.80, 0.87 (6H, two doublets, J 6.7 Hz), 0.91 (3H, *d*, J 6.3 Hz), 1.68 (3H, *s*), 5.33 (1H, *m*).

2,5-Dimethyl-8-isopropyl tetralone. The THF solution (10 ml) of cadinenol (0.3 g) was saturated with diborane under N_2 . H_2O (10 ml), 50 ml of 12% NaOH and 10 ml of 30% H_2O_2 were added. After stirring, Et_2O extraction from the solution gave *ca.* 300 mg oil. This oil was dried *in vacuo* and oxidized with CrO_3 (300 mg) and pyridine (3 ml). Usual treatment afforded crystals ($\nu_{\text{max}}^{\text{Nujol}}$ 3500, 1700 cm^{-1}), which was dehydrogenated with Pd-C at 300° for 2 hr. The Et_2O extractives contained several products, as revealed by GLC. The main component separated by preparative GLC has the following properties: MS M^+ 216, $\lambda_{\text{max}}^{\text{EtOH}}$ 252 nm (8300), 300 nm (2180), $\nu_{\text{max}}^{\text{Nujol}}$ 1690, 1580 cm^{-1} , δ^{CCl_4} 1.20 (6H, two doublets, J 6 Hz), 1.19 (3H, *d*, 6.5 Hz), 2.24 (3H, *s*), 7.11 (2H, *s*).

Dehydration of cadinenol. SOCl_2 (0.5 ml) was added to the solution of cadinenol (200 mg) in pyridine (5 ml) maintained at 0°. After 30 min this was poured into H_2O and extracted with Et_2O . The ethereal solution was washed, dried and evaporated to afford a yellow oil, which was chromatographed on alumina. The eluate (100 mg) with *n*-hexane was subjected to GLC, which indicated the presence of a single predominant component. This was purified by preparative GLC and had the following properties: MS M^+ 204, $[\alpha]_D$ 0°, $\nu_{\text{max}}^{\text{liq}}$ 3050, 1665, 945, 885, 820, 785 cm^{-1} , δ^{CCl_4} 0.86, 0.92 (6H, two doublets, J 6.6 Hz), 1.04 (3H, *d*, J 6.5 Hz), 1.68 (3H, *s*), 5.23 (1H, *br s*), 5.43 (1H, *br s*).

Dehydration of cubenol. The same method mentioned above was undertaken and in this case GLC analysis showed the three products previously reported,⁶ each of which was isolated by preparative GLC. The diene of the same retention time as that from cadinenol showed the following properties: MS M^+ 204, $[\alpha]_D$ -20°, $\nu_{\text{max}}^{\text{liq}}$ 3050, 1665, 945, 885, 820, 785 cm^{-1} , δ^{CCl_4} 0.86, 0.92 (6H, two doublets, J 6.6 Hz), 1.04 (3H, *d*, J 6.5 Hz), 1.68 (3H, *s*), 5.23 (1H, *br s*), 5.45 (1H, *br s*).

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