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THE STRUCTURE OF δ-CADINOL[1]

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Abstract—Albicaulol, a crystalline cadinol isolated from the oleoresin of *Pinus albicaulis* and *Pinus armandi*, has been found to be identical with δ-cadinol. The structure of δ-cadinol has been shown to be Δ^4-cadinene-3-ol rather than the Δ^9-structure assigned by Motl, Sýkora, Herout and Šorm.

IN the course of an investigation of the composition of gum terpentines of pine trees, Haagen-Smit, Wang and Mirov[2] isolated a crystalline sesquiterpenic alcohol (m.p. 135°) from the heavy oil fraction of *Pinus albicaulis*. The same alcohol was also found to occur in the oleoresin of *Pinus armandi*[3] and in the heartwood of *Chamaecyparis lawsoniana*.[4] The compound was called "albicaulol" and was shown to possess the formula $C_{15}H_{26}O$ and to have a tertiary hydroxyl group. Through the kind cooperation of Dr. Mirov, a supply of oleoresin from *P. armandi* was made available to us and the structural studies related to albicaulol were initiated.

Albicaulol (V) upon dehydrogenation over 5 per cent palladium-on-carbon yielded cadalene, identified as the trinitrobenzoate and picrate, and upon reaction with hydrogen chloride yielded (−)-cadinene dihydrochloride. The presence of one olefinic linkage was established by hydrogenation of V to a saturated dihydro derivative. As was reported by the earlier workers,[2] the hydroxyl function appeared to be tertiary since most esterification attempts returned only starting material and only when forcing conditions (acetic anhydride at 140°) were used was an acetate obtained. The presence of one double bond, a tertiary hydroxyl function and a cadinene nucleus indicated that albicaulol possessed a cadinol structure.

Of the twelve theoretically possible cadinols which can give rise to (−)-cadinene dihydrochloride, only three isomers have been found in nature, α-cadinol,[6, 7] δ-cadinol,[7–9] and a cadinol of m.p. 78°.[7] Upon comparison of the physical and spectral properties of albicaulol with those of δ-cadinol, it appeared that the materials were identical. The finding of no depression of melting point of a mixture of the two compounds clearly established their identity.[10] The Czech workers have reported[7,8] the structure of δ-cadinol to be I. The location of the double bond was suggested on the basis of infrared spectroscopy and on the basis that δ-cadinol upon ozonization

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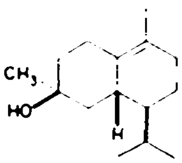
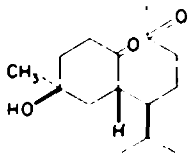
[1] This work was supported in part by the National Science Foundation, Grant G-6212.
[2] A. J. Haagen Smit, T. H. Wang and N. T. Mirov, *J. Amer. Pharm. Assoc.* (*Sci. Ed.*) **40**, 557 (1951).
[3] N. T. Mirov and P. M. Iloff, Jr., *J. Amer. Pharm. Assoc.* (*Sci. Ed.*) **44**, 424 (1955).
[4] G. Kritchevsky and A. B. Anderson, unpublished results.
[5] P. A. Plattner and R. Markus, *Helv. Chim. Acta* **25**, 1674 (1942).
[6] G. Kritchevsky and A. B. Anderson, *J. Amer. Pharm. Assoc.* (*Sci. Ed.*) **44**, 535 (1955).
[7] O. Motl, V. Sýkora, V. Herout and F. Šorm, *Coll. Czech. Chem. Comm.* **23**, 1297 (1958).
[8] V. Herout and V. Sýkora, *Tetrahedron* **4**, 246 (1958).
[9] H. Erdtman, Z. Pelchowicz and J. G. Topliss, *Acta Chim. Scand.* **10**, 1563 (1956).
[10] We are indebted to Professor H. Erdtman for kindly performing this comparison.

yielded a diketo-alcohol which was assigned structure II since the latter material lacked aldehydic properties.

In the course of our preliminary work with albicaulol (now δ-cadinol) it was found that the nuclear magnetic resonance spectrum clearly indicated the presence of one vinyl proton (4·43 τ).[11] This conclusion that a trisubstituted double bond was present



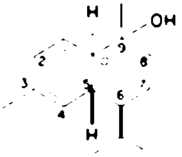
I



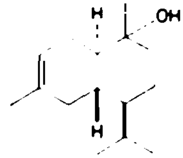
II

was verified when it was found that δ-cadinol upon oxidation with potassium permanganate gave a dihydroxy ketone VI in 59 per cent yield. In order to establish further the identity of our material with that of the Czech workers, the cadinol was osmylated and there was obtained a triol (VII) possessing identical properties with those reported for a similar triol prepared by Motl, Sýkora, Herout and Šorm from δ-cadinol.[7] Repetition of their ozonation experiment, however, failed to yield any crystalline material, and hence evaluation of this important reaction was not possible.

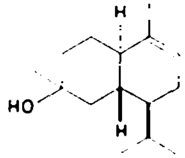
With the present evidence it must be concluded that δ-cadinol possesses a tri- and not a tetra-substituted double bond. Since the alcohol yielded (−)-cadinene dihydrochloride, δ-cadinol must possess the structure III, IV or V (disregarding the stereochemistry of the hydroxyl group).* The structure III can be ruled out on the basis of



III



IV



V

the spin-spin coupling pattern shown by the vinyl proton of the double bond in its NMR spectrum. It was possible to study a closely related model of III since α-cadinol possesses a similar structure, the difference being due to the stereochemistry of the hydroxyl group.[7,12] The NMR spectrum of α-cadinol[13] showed only a singlet (4·52 τ) for the vinyl proton. This finding of a singlet required further consideration since a doublet might have been expected. By examination of a molecular model it is seen that the proton at the ring juncture (C_6) is approximately at a 90° angle to the vinyl proton and when the dihedral angle of two protons which couple is about 90°, the coupling constant is about zero.[14] By consideration of the dihedral angle between the vinyl

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* The numbering of the cadinene nucleus is that normally used for a steroid and differs from the numbering system suggested by Motl, Sýkora, Herout and Šorm.[7]

[11] Originally, Erdtman[9] attributed the absorption at 873 cm^{-1} to a trisubstituted double bond whereas Šorm and his co-workers believed this band was out of the normal range for such a structure.

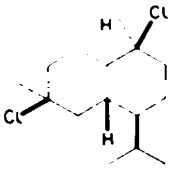
[12] M. D. Soffer, M. Brey and J. Fournier, *Chem. & Ind.* 19 (1958).

[13] Kindly determined by the Stanford Research Institute.

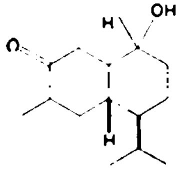
[14] M. Karplus, *J. Chem. Phys.* **30**, 11 (1959).

proton and the quasi-equatorial and the quasi-axial protons on the adjacent carbon, C_1 in IV and C_7 in V, a doublet would be expected. The NMR spectrum of δ-cadinol[13] showed the vinyl proton as a doublet (J = 6·5 c/s). Thus, in view of the different NMR spectra of α- and δ-cadinol, it can be concluded that III cannot represent the formulation of δ-cadinol.

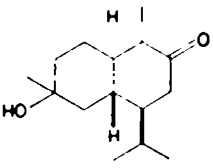
To differentiate between IV and V, the position of the double bond must be located. The usual method of locating such a bond in a cadinene molecule is to insert a methyl group (via epoxidation and Grignard reactions) on the tertiary end of the double bond and to dehydrogenate the resulting material to a methylcadalene.[7,12] However, since the absolute configuration of (−)-cadinene dihydrochloride (VIII) recently has been established,[15] it is possible to employ optical rotatory dispersion measurements to locate the double bond. In the formation of the dihydrochloride VIII from δ-cadinol, the configurations of C_5, C_6 and C_{10} are not affected, and these centers possess the same absolute configuration in δ-cadinol as in VIII. The transformation of the lesser substituted end of the trisubstituted double bond to a carbonyl group, such as in IX or X, would permit the position of the unsaturation to be located since the rotatory dispersion curve of IX should show a negative Cotton effect[16] and X a positive Cotton effect.[17]



VIII



IX



X

Of the various methods available for the conversion of δ-cadinol (V) to a saturated hydroxyketone, the method of choice is hydroboration followed by oxidation. With the hydroboration reaction it is possible to add the equivalent of water to a double bond in an anti-Markownikoff fashion.[18] When δ-cadinol was allowed to react with diborane in diglyme followed by oxidation with hydrogen peroxide the diol XI was obtained in 35 per cent yield. Oxidation of XI with chromic acid yielded the hydroxyketone, X, in 45 per cent yield. The optical rotatory dispersion curve of X showed a positive Cotton effect,[19] establishing the structure of the material as shown. It must be concluded that δ-cadinol possesses the structure V. Although no definite proof is on hand, we agree with the previous workers[7] that the hydroxyl group is most likely axial since it is so difficult to esterify.

The optical rotatory dispersion curve of the dihydroxyketone VI was found to be of a negative Cotton type.[19] This change in sign upon making C_9 fully substituted is expected on the basis of the Octant Rule[20] since a strongly contributing axial group falls into a negative octant. This finding of a negative curve is additional support for the location of the double bond since although the ketone XII derived from an

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[14] V. Sýkora, V. Herout and F. Šorm, *Coll. Czech. Chem. Comm.* **23**, 2181 (1958).

[16] C. Djerassi, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **78**, 6362 (1956); C. Djerassi, *Optical Rotatory Dispersion* pp. 42, 175. McGraw-Hill, New York (1960).

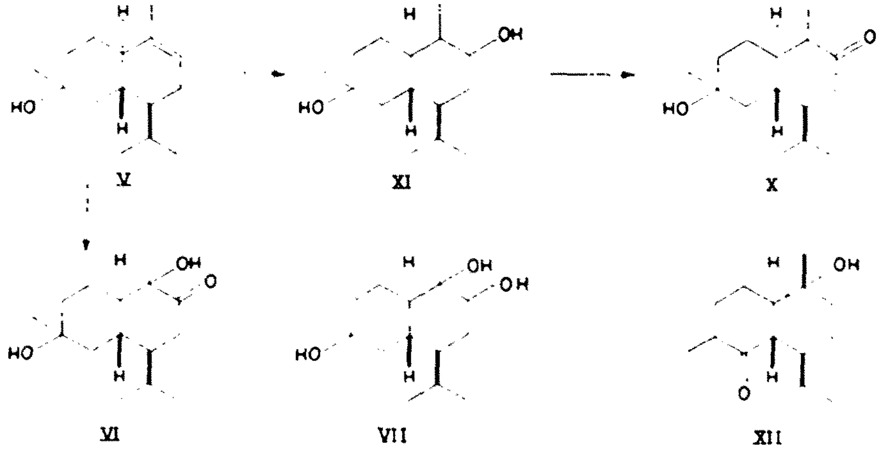
[17] C. Djerassi, W. Closson and A. E. Lippman, *J. Amer. Chem. Soc.* **78**, 3163 (1956).

[18] H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.* **81**, 6428 (1959).

[19] We are indebted to Professor C. Djerassi for this determination.

[20] The use of this rule is summarized in ref. 16, p. 181.

α-cadinol type structure possesses a positive Cotton curve[7,8] as does X, an axial substituent on C_3 falls into a positive octant and no change in sign would be expected. From this dispersion curve of VI it also was possible to assign an axial configuration to the C_9-hydroxyl group in that the position of the first extremum of the dispersion curve was shifted bathochromically 15 mμ from that of the related ketone X. Such a shift has been shown to be characteristic for an axial hydroxyl group adjacent to a ketone.[21]



In view of the revised structure for δ-cadinol it is suggested that the trivial name no longer be employed since it was only assigned to the compound on the basis that it did possess a tetrasubstituted double bond corresponding to a similar bond in δ-cadinene.

EXPERIMENTAL[22]

Isolation of δ-cadinol (*albicaulol*). A 5 gal sample of oleoresin collected from *Pinus armandi* was supplied by the Mutual Security Agency, Taipei, Formosa.[23] The oleoresin was processed as described by Mirov and Iloff[9] and from the heavy oil fraction 8·7 g of δ-cadinol was obtained, m.p. 138–139°, $[\alpha]_D^{22}$ −102·3° (*c*, 3·2, EtOH).

(Found: C, 80·86; H, 12·11. Calc. for $C_{15}H_{26}O$ (222·36): C, 81·02; H, 11·79.)

Cadalene from δ-cadinol. A mixture of 520 mg of δ-cadinol and 110 mg of 5% palladium-on-carbon was heated in a bath at 210–220° for 4 hr. After the mixture had cooled to room temperature, 10 ml of 95% ethanol was added, the mixture refluxed for 10 min, the catalyst filtered and the filtrate concentrated to about 3 ml. To 0·5 ml of the ethanolic solution there was added 3 ml of a saturated ethanolic solution of 1,3,5-trinitrobenzene. The solution was warmed on a steam-bath for 2 min and allowed to stand at 0° for 6 hr. The yellow-orange needles of cadalene trinitro benzoate which formed were collected, washed with cold ethanol and dried, m.p. 110–111°, no depression upon admixture with an authentic sample.[24]

To a 1 ml portion of the ethanol solution from the dehydrogenation there was added 1 ml of a saturated ethanol solution of picric acid and the reaction processed as above to yield cadalene picrate, m.p. 114–115°, no depression upon admixture with authentic sample.[24]

( )-*Cadinene dihydrochloride from δ-cadinol.* A solution of 111 mg of δ-cadinol in 15 ml of anhydrous ether was saturated with anhydrous hydrogen chloride at 5° and the solution kept at that

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[21] C. Djerassi, O. Halpern, V. Halpern, O. Schindler and C. Tamm, *Helv. Chim. Acta* **41**, 250 (1958).

[22] Analyses performed by the Microanalytical Laboratory, College of Chemistry, University of California.

[23] We are indebted to Dr. Hubert G. Schenk and Mr. Paul Zengraff of the Mutual Security Agency for their assistance in procuring the oleoresin sample.

[24] Kindly supplied by Dr. P. M. Iloff, Jr.

temperature for 24 hr. The solvent was removed and the dark red viscous residue crystallized upon cooling to 0° and the product was recrystallized from methanol to yield 15 mg of colorless needles, m.p. 117–118°, no depression upon admixture with an authentic sample of (−)-cadinene dihydrochloride.[14]

Dihydro-δ-cadinol. A mixture of 111 mg of δ-cadinol, 1 g of W-2 Raney nickel and 10 ml of ethanol was hydrogenated at room temperature and 1200 lb/in² for 12 hr. The catalyst was filtered, washed thoroughly with ethanol and the filtrate concentrated under reduced pressure. The residue after chromatography on Woelm alumina (Act. I) yielded 71 mg of crude dihydro alcohol, m.p. 69–73°. The solid was fractionally sublimed to yield 49 mg (37%) of a dihydro-δ-cadinol, m.p. 76–77°. The ultraviolet spectrum showed virtually no end absorption, and the NMR spectrum showed no vinyl proton absorption.

(Found: C, 80·43; H, 12·68. Calc. for $C_{15}H_{28}O$ (224·37): C, 80·29; H, 12·58.)

A similar isomer has been obtained by Erdtman[6] along with higher melting materials.[7]

δ-Cadinol acetate. A solution of 111 mg of δ-cadinol, 82 mg of anhydrous sodium acetate and 5 g of redistilled acetic anhydride was heated at 145° for 3 hr. The excess acetic anhydride was removed under reduced pressure and the residue dissolved in ether. The ethereal solution was washed with aqueous sodium bicarbonate, with water and dried. The ether was evaporated and the residual yellow oil chromatographed on Woelm alumina (Act. I) to yield 37 mg of a hydrocarbon, 48 mg of acetate and 4 mg of unreacted starting material. The acetate was rechromatographed and the center cuts were recrystallized from methanol–water (19:1), m.p. 45–46°.

(Found: C, 77·46; H, 10·81. Calc. for $C_{17}H_{28}O_2$ (264·39): C, 77·22; H, 10·67.)

Cadinane-3,9-diol-8-one (VI). To a solution of 111 mg of δ-cadinol in 25 ml of purified acetone cooled in an ice-bath there was added, dropwise with stirring, a solution of 630 mg of potassium permanganate in 10 ml of water. The solution was allowed to warm to room temperature and stirred at that temperature for 10 hr. At the end of this time the unreacted permanganate was destroyed with sodium bisulfite, the manganese dioxide filtered and the filtrate concentrated until all of the acetone was removed. The remaining alkaline aqueous solution was cooled to ice temperature, acidified with 1% hydrochloric acid and extracted with ether. The ethereal solution was washed with dilute sodium bicarbonate, with water and dried. The ether was evaporated and the residual solid recrystallized twice from benzene, yield 74 mg (59%), m.p. 143–144°.

(Found: C, 70·64; H, 10·11. Calc. for $C_{15}H_{26}O_3$ (254·36): C, 70·83; H, 10·30.)

The compound gave a positive test with periodic acid. The infrared spectrum of the material in chloroform showed the following bands: 3480 and 3340 cm^{-1} (hydroxyl), 1685 cm^{-1} (carbonyl). The optical rotatory dispersion of VI in methanol (*c*, 0·12) was as follows: $[\alpha]_{700}$ 10°, $[\alpha]_{589}$ 15°, $[\alpha]_{310}$ −170° (min), $[\alpha]_{272}$ +420° (max), $[\alpha]_{250}$ +370°; no change upon addition of acid.

Cadinane-3,8,9-triol (VII). A solution of 444 mg of δ-cadinol in 10 ml of dioxane containing three drops of pyridine was added to a solution of 650 mg of osmium tetroxide in 10 ml of dioxane and the resulting solution allowed to stand in the dark for 7 days. Hydrogen sulfide was bubbled into the solution for 15 min and the resulting black slurry filtered. The solid was washed with hot ethyl acetate and the combined filtrate concentrated to dryness. The residual thick oil (515 mg) was crystallized from benzene–petroleum ether to yield 448 mg of white needles, m.p. 147–157°, which was recrystallized twice from the same solvent pair, yield 361 mg (70·5%), m.p. 160·5–161·5° (lit.[7] m.p. 157°).

(Found: C, 70·10; H, 10·90, Calc. for $C_{15}H_{28}O_3$ (256·37): C, 70·27; H, 11·01).

The combined mother liquors upon concentration gave 38 mg of an isomeric triol, m.p. 139·0–140·0°. The product was recrystallized from benzene, m.p. 139·0–140·0, yield 25 mg (4·5%).

Cadinane-3,8-diol (XI). Following the procedure of Brown and Subba Rao[16], a solution of 630 mg of δ-cadinol in 10 ml of diglyme was allowed to react with 420 mg of sodium borohydride and 4·5 g of boron trifluoride etherate. After 1½ hr, the reaction mixture was hydrolyzed with ice-water. When hydrogen evolution ceased, 50 ml of 3 N sodium hydroxide was added and 2·5 ml of 30% hydrogen peroxide added dropwise. After 30 min the reaction mixture was poured into 200 ml of water and processed as usual. The residual oil partially crystallized on cooling. The solid was separated and the filtrate was dissolved in a small volume of ether and upon cooling more solid was deposited. Concentration of the ethereal solution yielded additional material. The combined solids were recrystallized from petroleum ether, yield 237 mg (35%), m.p. 126·5–127·5°.

(Found: C, 74·68; H, 11·63. Calc. for $C_{15}H_{28}O_2$ (240·37): C, 74·95; H, 11·74.)

Cadinane-3-ol-8-one (X). To a solution of 130 mg of cadinane-3,8-diol (XI) in 15 ml of glacial acetic acid there was added, dropwise with stirring, a solution of 40 mg of chromium trioxide in 0·2 ml of water and 0·3 ml of glacial acetic acid over a 5 min period. The resulting dark brown solution was diluted with 15 ml of water and extracted with benzene. The benzene extract was washed with sodium bicarbonate, with water and the solvent evaporated. The crystalline residue was recrystallized twice from petroleum ether, yield 59 mg (54%), m.p. 85·0–86·0°, ν_{max}^{KBr} 3420, 1695 cm^{-1}.

(Found: C, 75·70; H, 11·22. Calc. for $C_{15}H_{26}O_2$ (238·36): C, 75·58; H, 11·00.)

The optical rotatory dispersion of X in methanol (*c*, 0·08) was as follows: $[\alpha]_{700}$ +10°, $[\alpha]_{589}$ +25°, $[\alpha]_{306}$ −360° (max), $[\alpha]_{263}$ 110° (min).