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Structure of Curdione.[*2]

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From zedoary, *Curcuma zedoaria* (Zingiberaceae), a sesquiterpenoid curdione, $C_{15}H_{24}O_2$, has been isolated and shown to be germacr-1(10)-ene-5,8-dione (I) based on the following evidence. The presence of a β-methyl-β,γ-unsaturated ketone and an isolated ketone group in the germacrane skeleton has been indicated by spectral determinations of curdione and its reduction product, the diol (IV), which is reversible to curdione on oxidation, and by dehydrogenation of the diol (IV) to S-guaiazulene (VII). The location of the two carbonyls has been established by the transformation of its dihydro-derivative (III) to the enone (VIII) whose structure has been confirmed by its spectral properties and by its conversion into vetivazulene (XI).

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Recently we have been undertaking the chemical study of the crude drug zedoary, the rhizome of *Curcuma zedoaria* Roscoe (Zingiberaceae), and hitherto isolated the new sesquiterpenoids, curcumol[1)] and zederone.[2)] Further investigation have led to the isolation of a new sesquiterpenic diketone which is named curdione. It has been shown in a preliminary communication[3)] that curdione has the structure I. The present paper describes the evidence in full detail.

Curdione, m.p. 61.5~62°, $[\alpha]_D$ +25.6°, possesses the molecular formula $C_{15}H_{24}O_2$.

We first examined the unsaturated character of curdione. The infrared spectrum shows bands at 1667 and 795 cm^{-1} being suggestive of a trisubstituted double bond. Further, the nuclear magnetic resonance (NMR) spectrum exhibits signals at 8.40 and 4.91τ, which originate from a vinylic methyl group and a vinylic hydrogen, respectively; the presence of a trisubstituted ethylenic linkage being deduced. NMR peaks (9.14, 9.08, 9.05τ) further point to the presence of three secondary methyls. The postulated unsaturated feature was supported by the following facts. 1) Peracid oxidation gave two epimeric mono-epoxides (IIa & IIb). The methyl signal at 8.40τ in curdione was shifted to 8.67 and 8.87τ in the epoxides (IIa & IIb), respectively, and that at 4.91τ was also shifted upfield but could not be pointed out clearly by overlapping with the methylene envelope. 2) Catalytic hydrogenation afforded the dihydro-derivative (III), whose NMR spectrum no longer bore peaks attributed to a vinyl methyl and a vinyl hydrogen, but those due to four methyls at 9.25~8.92τ indicating that the vinyl methyl signal in curdione had been altered into this region. Since no further signals ascribable to an unsaturated feature appeared in the spectra and since no color tests for unsaturation were positive, the monoepoxides (IIa & IIb) and the dihydro-derivative (III) are saturated and, therefore, the original substance, curdione, contains only one ethylene bond as its element of carbon-carbon unsaturation. Furthermore, the chemical shifts of the vinyl methyl and the vinyl hydrogen of curdione eliminate any possibilities of conjugation.

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[*2] This paper forms Part XIII in the series on Sesquiterpenoids. Preceding paper, Part XII, H. Hikino, K. Aota, Y. Maebayashi, T. Takemoto: This Bulletin, **15**, 1349 (1967).

1) H. Hikino, K. Meguro, Y. Sakurai, T. Takemoto: This Bulletin, **13**, 1484 (1965); **14**, 1241 (1966).

2) H. Hikino, H. Takahashi, Y. Sakurai, T. Takemoto, N.S. Bhacca: *Ibid.*, **14**, 550 (1966).

3) H. Hikino, Y. Sakurai, H. Takahashi, T. Takemoto: *Ibid.*, **14**, 1310 (1966).

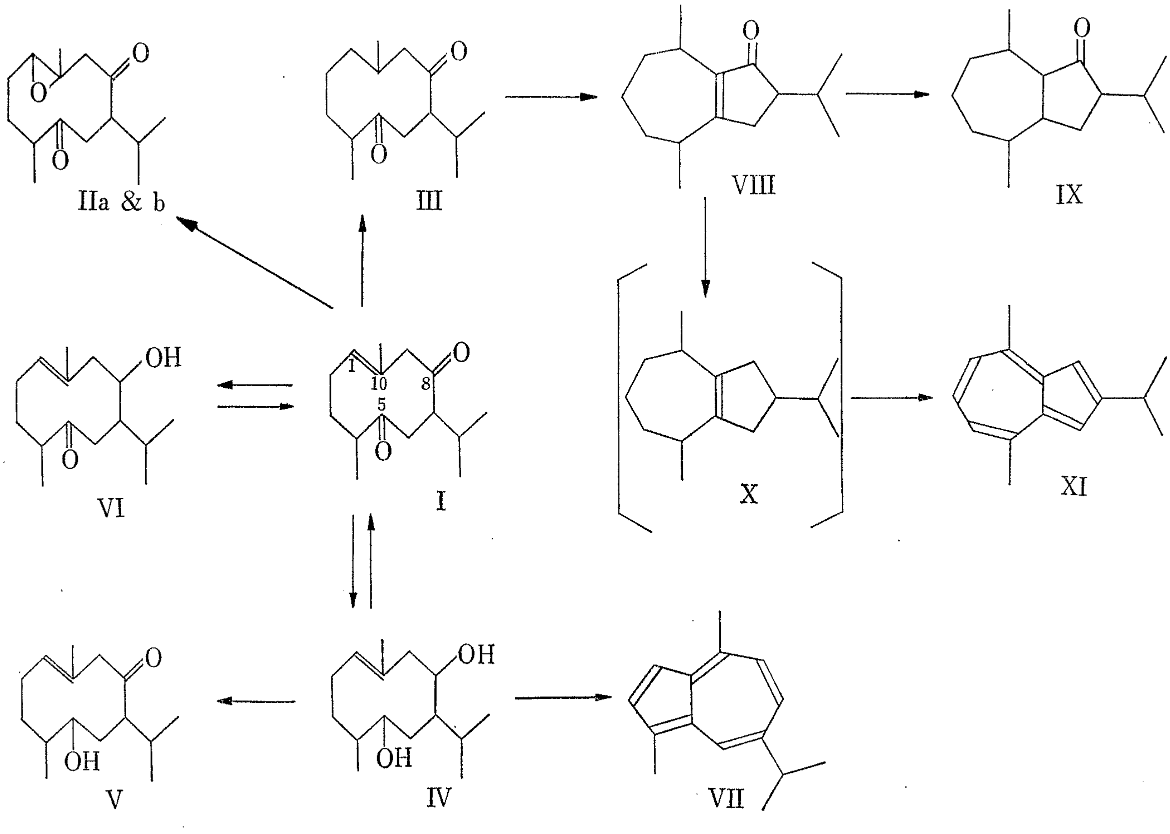
We next turned our attention to the two oxygen atoms in curdione. Infrared bands at 1704 and 1416 cm^{-1} indicate that it contains at least one carbonyl group in a six-membered or larger ring and with a methylene α to it. As the infrared spectrum displayed no absorption around 3500 cm^{-1}, the presence of a hydroxyl grouping appears unlikely. Therefore, the second oxygen atom must be involved either in a carbonyl or in an oxide. In order to establish the second oxygen function, preparation of a 2,4-dinitrophenylhydrazone must be informative. Thus, curdione might afford a bis-2,4-dinitrophenylhydrazone, curdione being a diketone in this case, or a mono-2,4-dinitrophenylhydrazone, whose infrared spectrum should give information about the function of the second oxygen atom. However, attempts to prepare a 2,4-dinitrophenylhydrazone of curdione were unsuccessful. This was later explained by the fact that the carbonyl groups in curdione are oriented in a ten-membered ring (*vide infra*); no ten-membered ring ketones having been known to give 2,4-dinitrophenylhydrazones. Curdione was then reduced with lithium aluminum hydride to yield the diol (IV). The second oxygen function must consequently be a carbonyl or an epoxide. The secondary nature of both hydroxyl groups in the diol (IV) was indicated by the NMR spectrum which showed 1H quadruplets at 6.58 and 5.90τ, both signals being assigned to hydrogens on carbons carrying hydroxyls. Double irradiation at the latter signal made an octet (an AB quadruplet with doubling) at 7.92 and 7.70τ attributable to a methylene grouping collapsed to a quadruplet in an AB type. Therefore, the signal at 5.90τ is an X portion of an ABX spectrum. The presence of the AB part of the ABX spectrum as an octet demonstrates that the methylene protons are coupled only with the hydrogen on carbon bearing the hydroxyl and that the second carbon attached to the methylene is consequently carrying no hydrogens. Further, the second carbon is suggested to be involved in the above described trisubstituted ethylenic linkage judging from the deshielded line positions (7.92 and 7.70τ) of the methylene signals. Oxidation of the diol (IV) with chromic acid gave curdione and the ketol (V), and the latter showed infrared bands at 3410 and 1688 cm^{-1} attributed to a hydroxyl and a carbonyl group, respectively. When compared with the NMR spectrum of the diol (IV), a 1H triplet at 6.78τ observed in that of the ketol (V) suggested that the hydroxyl on carbon β to the ethylenic linkage in the diol (IV) had been oxidized. Reduction of curdione with sodium borohydride yielded another ketol (VI), whose infrared spectrum showed bands at 3500 and 1696 cm^{-1} associated with a hydroxyl and a carbonyl group, respectively, and NMR spectrum exhibited a 1H triplet at 5.88τ. Therefore, it was concluded from the same evidence applied to the ketol (V), that borohydride reduced the carbonyl group β to the ethylene bond in curdione to furnish the ketol (VI). On oxidation with chromic acid the ketol (VI) regenerated the original dione, curdione. Based on the above results curdione has been established as being a diketone.

If we admit the presence of an ethylenic linkage and two carbonyl groups, this molecule must then have a monocarbocyclic ring. Dehydrogenation of the diol (IV) with palladium-on-carbon gave S-guaiazulene (VII). This fact confirms that curdione belongs to sesquiterpenoids of the germacrane series which have ten-membered rings.

We then tried to elucidate the relative location of the two carbonyl groups in curdione. The ultraviolet, infrared, and NMR spectra demonstrate the absence of a 1,2- or 1,3-diketone moiety in the molecule. Dihydrocurdione (III) was submitted to alkali treatment which afforded the monoketone (VIII). The presence of a fully substituted α,β-unsaturated carbonyl system in a five-membered ring in the monoketone (VIII) was established by an ultraviolet maximum at 243 mμ, infrared bands at 1694 and 1639 cm^{-1}, and the absence of NMR signals due to vinylic protons. The NMR spectrum further indicated that four secondary methyl groups are contained. Should dihydrocurdione (III) be a 1,4-dione, the transformation of the saturated diketone (III) to the unsaturated monoketone (VIII) can be reasonably explained as an intramolecular aldol condensation. The degradation of the monoketone, which will now be described, further proves the correctness of the presently assigned structure (VIII). Thus, on catalytic hydrogenation the unsaturated ketone (VIII) afforded the saturated ketone (IX) whose infrared absorption at 1733 cm^{-1} confirmed the carbonyl group to be involved in a five-membered ring. Reduction of the monoketone (VIII) with sodium borohydride gave only the starting material (VIII), while reduction with lithium aluminum hydride afforded a product, which had the following properties. The infrared spectrum exhibited weak bands associated with a hydroxyl and a carbonyl in a five-membered ring, and the NMR spectrum disclosed peaks due to four methyl groups in a high-field region but no appreciable peaks attributed to a vinylic methyl, a vinylic hydrogen, and a hydrogen on carbon bearing a hydroxyl. Therefore, the product was considered to be a mixture of a large amount of the hydrocarbon (X) and small amounts of alcohols corresponding to the enone (VIII) and/or the ketone (IX), and a cyclopentanone. The product, without further purification, was dehydrogenated with palladized charcoal furnishing vetivazulene (XI). The above sequence of degradation established the positions of the two carbonyl groups of curdione at C-5 and C-8 in the germacrane skeleton.

The only remaining problem which has to be settled was the orientation of the olefinic linkage in curdione. As has been observed earlier, the linkage is trisubstituted with a metyl on it (NMR spectrum) and not conjugated with a carbonyl group (ultraviolet, infrared, and NMR spectra). Ultraviolet maxima at 299 mμ (log ε 2.40) in curdione and at 306 mμ (log ε 2.41) in the ketol (V) suggest the presence of a β,γ-unsaturated ketone system. This system is further supported by the double resonance experiments of the diol (IV), described above. Therefore, the olefinic bond must be situated at C-1 : C-10.

On the basis of the above facts curdione is concluded to be represented in formula I.



Although a number of sesquiterpenoids of the germacrane skeletone have been recently found in nature, a large majority of them have lactone or furan rings in the molecules. However, curdione, presently isolated, together with germacrone constitute the rare examples as being simple derivatives which have only ethylenic bonds and carbonyl groups in germacrane skeletons.

Experimental[*3]

Isolation of Curdione——The crude drug "Ga-jutsu", the dried rhizomes of *Curcuma zedoaria* Roscoe, was extracted with MeOH. The light petroleum soluble fraction of the extract was steam-distilled. The residue was chromatographed over alumina. Light petroleum-benzene eluate gave a crystalline substance which was crystallized from light petroleum to yield curdione (I) as colorless prisms, m.p. 61.5～62°, $[\alpha]_D$ +25.6°(c=7.0), *Anal.* Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found : C, 76.16; H, 10.27, UV λ_{max} mμ (log ε) : 299 (2.40), IR (KBr) cm^{-1} : 1704 (cyclodecanones), 1667, 795 (trisubstituted ethylene), 1416 (methylene adjacent to carbonyl), NMR : doublet (3H) at 9.14 τ (J=6, $C\underline{H}_3$-CH$\langle$), doublet (3H) at 9.08 τ (J=6, $C\underline{H}_3$-CH$\langle$), doublet (3H) at 9.05 τ (J=5, $C\underline{H}_3$-CH$\langle$), doublet (3H) at 8.40 τ (J=1, $C\underline{H}_3$-C=C$\langle$), slightly multiplying triplet (1H) at 4.91 τ (J=7, $\underline{H}$-C=C$\langle$).

Oxidation of Curdione with Perbenzoic Acid——Curdione (200 mg.) was treated with BzO_2H (120 mg.) in $CHCl_3$ (2 ml.) at 25° for 42 hr. The product was isolated in the usual way and chromatographed over silica gel (5 g.).

Elution with benzene and crystallization from AcOEt gave the mono-epoxide A (IIa) as colorless needles (73 mg.), m.p. 118.5～119.5°, $[\alpha]_D$ +106°(c=2.3), *Anal.* Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found : C, 71.38; H, 9.40, IR (KBr) cm^{-1} : 1701 (cyclodecanones), 1422 (methylene α to carbonyl), NMR ($CDCl_3$): doublet (3H) at 9.12 τ′ (J=6, $C\underline{H}_3$-CH$\langle$), doublet (3H) at 9.05 τ′ (J=6, $C\underline{H}_3$-CH$\langle$), doublet (3H) at 8.90 τ′ (J=6, $C\underline{H}_3$-CH$\langle$), singlet (3H) at 8.67 τ′ ($C\underline{H}_3$-C$\lessdot$O-).

Elution with AcOEt and crystallization from AcOEt afforded the mono-epoxide B (IIb) as colorless needles (34 mg.), m.p. 129～130°, $[\alpha]_D$ −109°(c=3.6), *Anal.* Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found : C, 71.20; H, 9.65. IR (KBr) cm^{-1} : 1706 (cyclodecanones), 1406 (methylene next to carbonyl), NMR ($CDCl_3$) : doublet (3H) at 9.12 τ′ (J=6, $C\underline{H}_3$-CH$\langle$), doublet (3H) at 9.03 τ′ (J=6, $C\underline{H}_3$-CH$\langle$), doublet (3H) at 8.93 τ′ (J=6, $C\underline{H}_3$-CH$\langle$), singlet (3H) at 8.87 τ′ ($C\underline{H}_3$-C$\lessdot$O-).

Hydrogenation of Curdione over Palladized Charcoal in Mathanol——Curdione (1.00 g.) was stirred with 5% Pd-C (1.0 g.) in MeOH under H_2 at room temperature, approximate 1 mole of H_2 being absorbed. The product (0.98 g.) was crystallized from light petroleum yielded dihydrocurdione (III) as colorless needles, m.p. 65.5～66°, $[\alpha]_D$ −32.9°(c=6.7), *Anal.* Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found : C, 76.11; H, 10.92, IR (KBr) cm^{-1} : 1701 (cyclodecanones), 1406 (methylene α to carbonyl), NMR : multiplet (12H) in the region 9.25～8.92 τ ($C\underline{H}_3$-CH$\langle$).

Reduction of Curdione with Lithium Aluminum Hydride——Curdione (530 mg.) was stirred with $LiAlH_4$ (300 mg.) in ether (10 ml.) at 0° for 5 hr. Upon isolation, the product (560 mg.) was crystallized from AcOEt to give the diol (IV) as colorless prisms, m.p. 108～109°, $[\alpha]_D$ −17.3°(c=2.5), *Anal.* Calcd. for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found : C, 74.47; H, 11.64, IR (KBr) cm^{-1} : 3413 (hydroxyl), 1658, 817 (trisubstituted ethylene), NMR ($CDCl_3$, 100 Mc.p.s.) : doublet (3H) at 9.11 τ′ (J=7, $C\underline{H}_3$-CH$\langle$), doublet (3H) at 9.07 τ′ (J=7, $C\underline{H}_3$-CH$\langle$), doublet (3H) at 9.01 τ′ (J=6, $C\underline{H}_3$-CH$\langle$), singlet (3H) at 8.24 τ′ (unresolved, $C\underline{H}_3$-C=C$\langle$), octet (2H) at 7.95, 7.65 τ′ (J_{AB}=13, J_{AX}=5, J_{BX}=3, $\geqslant$C-$C\underline{H}_2$-CH(OH)-), quadruplet (1H) at 6.58 τ′ (J_1=9, J_2=8, $\rangle$CH-C$\underline{H}$(OH)-CH_2-), quadruplet (1H) at 5.90 τ′ (J_1=5, J_2=3, -CH_2-C$\underline{H}$(OH)-CH$\langle$), broad triplet (1H) at 4.68 τ′ (J=7, $\underline{H}$-C=C$\langle$).

Oxidation of the Diol with Chromium Trioxide-Pyridine Complex——The diol (IV) (85 mg.) was treated with CrO_3 (100 mg.) in pyridine (3 ml.) at room temperature for 7 days. The product (81 mg.) isolated by ether extraction was chromatographed over silica gel (3 g.).

Elution with light petroleum-benzene (1:1) gave curdione (I) (38 mg.), colorless prisms (from light petroleum), m.p. 61.5～62°, identified by IR and NMR spectra.

Elution with benzene-AcOEt (1:1) afforded a crystalline mass (42 mg.), which was crystallized from AcOEt to give the ketol (V) as colorless prisms, m.p. 70～71°, $[\alpha]_D$ −303°(c=2.4), UV λ_{max} mμ (log ε) : 306 (2.41), IR (KBr) cm^{-1} : 3420 (hydroxyl), 1688 (cyclodecanone), NMR ($CDCl_3$) : double (3H) at 9.15 τ′ (J=7, $C\underline{H}_3$-CH$\langle$), doublet (3H) at 9.03 τ′ (J=7, $C\underline{H}_3$-CH$\langle$), doublet (3H) at 8.98 τ′ (J=6, $C\underline{H}_3$-CH$\langle$), singlet (3H) at 8.28 τ′ ($C\underline{H}_3$-C=C$\langle$), triplet (1H) at 6.78 τ′ (J=11, $\rangle$CH-C$\underline{H}$(OH)-CH_2-), broad triplet (1H) at 4.59 τ′ (J=7, H-C=C$\langle$).

[*3] Melting points are uncorrected. Rotations were determined in $CHCl_3$ solution and UV spectra in EtOH. NMR spectra were recorded at 60 Mc.p.s. in CCl_4 solution using Me_4Si as internal standard unless otherwise indicated. Chemical shifts are given in τ-values and coupling constants (J) in c.p.s.

Reduction of Curdione with Sodium Borohydride——Curdione (106 mg.) and $\mathrm{NaBH_4}$ (110 mg.) were stirred in MeOH (15 ml.) at room temperature for 100 min. After isolation, the product (112 mg.) was distilled under reduced pressure to yield the ketol (VI) as a colorless oil, $[\alpha]_D$ +74.5°(c=1.8), *Anal.* Calcd. for $\mathrm{C_{15}H_{26}O_2}$: C, 75.58; H, 11.00. Found : C, 74.73; H, 10.82, IR (liquid) $\mathrm{cm^{-1}}$: 3500 (hydroxyl), 1696 (cyclodecanone), NMR : doublet (9H) at $9.07\,\tau$ (J=7, $\mathrm{C\underline{H}_3{-}CH\langle}$), singlet (3H) at $8.12\,\tau$ (unresolved, $\mathrm{C\underline{H}_3{-}C{=}C\langle}$), triplet (1H) at $5.88\,\tau$ (J=4, $\mathrm{>C{-}CH_2{-}C\underline{H}(OH){-}CH\langle}$), broad triplet (1H) at $5.20\,\tau$ (J=7, $\mathrm{\underline{H}{-}C{=}C\langle}$).

Oxidation of the Ketol with Chromium Trioxide-Pyridine Complex——The ketol (VI) (150 mg.) and $\mathrm{CrO_3}$ (140 mg.) in pyridine (3.5 ml.) were set aside at room temperature for 40 hr. Worked up in the customary manner, the main product (80 mg.) was separated by preparative TLC to yield curdione (I), colorless prisms (from light petroleum), m.p. 61~61.5°, identified by IR and NMR spectra.

Dehydrogenation of the Diol with Palladized Charcoal——The diol (IV) (39 mg.) was heated with 10% Pd–C (25 mg.) under $\mathrm{N_2}$ at 300° for 3 min. The mixture in light petroleum, after removal of the catalyst by filtration, was adsorbed on silica gel (1 g.). Elution with light petroleum gave S-guaiazulene (VII) as a blue oil, identified by TLC and the UV spectrum.

The 1,3,5-trinitrobenzene adduct crystallized from EtOH as dark maroon needles, m.p. 143.5°, UV $\lambda_{\max}$ mμ : 243.5, 283, 291, 305, 334.5, 350, 357, 389, *ca.* 600; the spectrum being superimposable with an authentic spectrum.

Alkali Treatment of Dihydrocurdione——Dihydrocurdione (III) (60 mg.) and NaOH (25 mg.) in $\mathrm{H_2O}$ (1 ml.) and dioxane (1 ml.) were heated on a steam-bath under $\mathrm{N_2}$ for 1 hr. The ether extract (61 mg.) was distilled under diminished pressure to give the cyclopentenone (VIII) as a colorless oil, $[\alpha]_D$ +24.6°(c=5.2), *Anal.* Calcd. for $\mathrm{C_{15}H_{24}O}$: C, 81.76; H, 10.98. Found : C, 82.64; H, 11.09, IR (liquid) $\mathrm{cm^{-1}}$: 1694, 1639 (cyclopentenone), NMR : doublet (3H) at $9.26\,\tau$ (J=6, $\mathrm{C\underline{H}_3{-}CH\langle}$), doublet (6H) at $9.02\,\tau$ (J=7, $\mathrm{C\underline{H}_3{-}CH\langle}$), doublet (3H) at $8.79\,\tau$ (J=7, $\mathrm{C\underline{H}_3{-}CH\langle}$).

Hydrogenation of the Cyclopentenone over Palladized Charcoal in Methanol——The cyclopentenone (VIII) (40 mg.) was hydrogenated over 5% Pd–C (60 mg.) in MeOH (5 ml.) at room temperature. Isolation in the usual manner gave the cyclopentanone (IX) as a colorless oil, IR (liquid) $\mathrm{cm^{-1}}$: 1733 (cyclopentanone).

Reduction with Lithium Aluminum Hydride followed by Dehydrogenation with Palladized Charcoal of the Cyclopentenone——The cyclopentenone (VIII) (190 mg.) and $\mathrm{LiAlH_4}$ (200 mg.) were stirred in ether (10 ml.) at room temperature for 2 hr. Working up in the customary way gave the product (tetranitromethane test : positive) whose VPC showed three peaks, IR spectrum ($\mathrm{CCl_4}$) exhibited weak bands at 3570, 3360 (hydroxyl), 1723 (cyclopentanone), and NMR spectrum disclosed a multiplet (12H) in the region 9.32~$8.95\,\tau$ but any appreciable peaks due to a vinyl methyl, a vinyl hydrogen, and a hydrogen on carbon bearing a hydroxyl.

The product (40 mg.), without further purification, was heated with 10% Pd–C (32 mg.) under $\mathrm{N_2}$ at 300~310° for 3 min. The mixture was dissolved in light petroleum and the catalyst was filtered off. The filtrate was percolated through silica gel (1 g.). Elution with light petroleum gave vetivazulene (XI) as a violet oil, identified by TLC and the UV spectrum.

The 1,3,5-trinitrobenzene complex crystallized from EtOH as dark maroon needles, m.p. 155~156°, UV $\lambda_{\max}$ mμ : 245.5, 283, 290, 307, 334, 348, 545; the spectrum being identical with an authentic specimen.

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