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Structure of Curcumadiol, a Sesquiterpenoid of *Curcuma zedoaria*[1]

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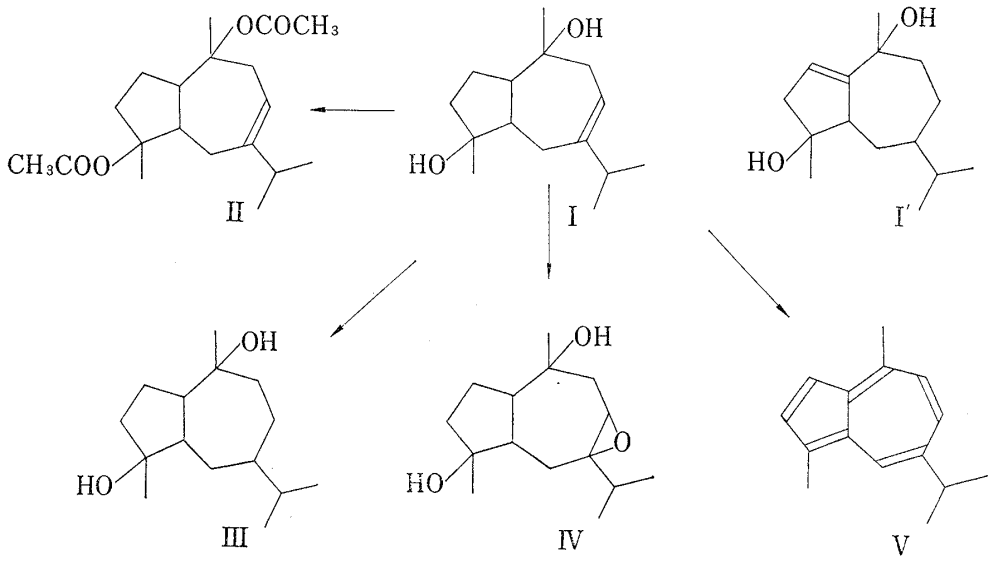
From zedoary, *Curcuma zedoaria* (Zingiberaceae), a new sesquiterpenic diol has been isolated and named curcumadiol whose structure has been deduced as I on the basis of the chemical and physico-chemical study.

We have been recently undertaking investigation of the constituents of the rhizome of *Curcuma zedoaria* Roscoe (Zingiberaceae) and hitherto isolated a number of new sesquiterpenic keto-alcohols having the guaiane skeleton, curcumol,[3] curcumenol,[4] isocurcumenol,[5] and procurcumenol,[6] together with a series of the sesquiterpenoids containing furan nucleus.[7] In continuation of our work has led to the isolation of another new sesquiterpenic diol which is termed as curcumadiol. We now wish to report evidence which demonstrates the structure I for this isoprenoid.

Curcumadiol analyzed for $C_{15}H_{26}O_2$ which was confirmed by the appearance of the molecular ion peak at *m/e* 238 in the mass spectrum. The nuclear magnetic resonance (NMR) spectrum exhibits the presence of two secondary methyls (0.98 ppm) and two tertiary methyls (1.19, 1.25 ppm). Since the protons of the two secondary methyls are spin-coupled to a common hydrogen proton (2.21 ppm), these methyls are involved in an isopropyl group. The infrared (IR) spectrum shows a strong band at 3350 cm^{-1}, curcumadiol having at least one hydroxyl group. In order to clarify the oxygen functions, acetylation was attempted. Thus, on treatment with acetic anhydride in pyridine at room temperature overnight the starting material was recovered. Prolonged treatment under the same conditions formed a monoacetate and the diacetate (II). Therefore, the presence of two hydroxyl groups was established. Since the NMR spectrum of curcumadiol shows no carbinyl proton signal, the two hydroxyls are tertiary. Furthermore, the shielded line positions of the two methyl singlets above mentioned (1.19, 1.25 ppm) indicate that the two tertiary methyls are located on carbons attached to the hydroxyls. In the NMR spectrum, a signal attributable to a vinyl hydrogen is visible (5.51 ppm), indicating that a triply substituted ethylenic linkage is present in curcumadiol. That curcumadiol possesses only one double bond described above was substantiated by its hydrogenation which gave the saturated dihydro-derivative (III) and by its peracid oxidation which afforded the mono-epoxide (IV). Curcumadiol is consequently a bicarbocyclic substance. To establish the carbon skeleton, dehydrogenation of curcumadiol with palladium-on-carbon was carried out to yield S-guaiazulene (V), demonstrating it to have the guaiane skeleton. It follows that the two tertiary hydroxyl groups are located at C-4 and C-10. The remaining problem is, therefore, the situation of the trisubstituted double

1) This paper forms Part XXXIX in the series on Sesquiterpenoids. Preceding paper, Part XXXXVIII: H. Hikino, N. Suzuki, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **19**, 87 (1971).
2) Location: *Aoba-yama, Sendai.*
3) H. Hikino, K. Meguro, Y. Sakurai, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **13**, 1484 (1965); **14**, 1241 (1966).
4) H. Hikino, Y. Sakurai, S. Numabe, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 39 (1968).
5) H. Hikino, K. Agatsuma, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 959 (1969).
6) H. Hikino, Y. Sakurai, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 1605 (1968).
7) *cf.*, H. Hikino, K. Agatsuma, C. Konno, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **18**, 752 (1970).



bond. The signal due to the vinyl hydrogen in the NMR spectrum of curcumadiol appears as a single peak with a band width of half height of 5 Hz and the splitting patterns is unclear. On the other hand, the signal due to the hydrogen on carbon carrying the ethereal oxygen in the spectrum of the epoxide (IV) clearly occurs as a doublet of doublets, a fact which demonstrates that a methylene grouping is adjacent to it and consequently the trisubstituted ethylene bond in curcumadiol is not situated at C-5:C-6 nor C-6:C-7 but at C-7:C-8 or C-1:C-2; *i.e.*, curcumadiol should be respresented by formula I or I'. The location of the double bond at C-7:C-8 was deduced as follows. The C-12 and C-13 methyl signals (0.98 ppm) in the NMR spectrum of curcumadiol are more deshielded than those (0.89 ppm) in that of dihydrocurcumadiol (III), and further the C-11 methine hydrogen signal (2.21 ppm) in that of curcumadiol is shifted downfield as compared with that (1.69 ppm) in that of the dihydro-derivative (III). Such observations are well rationalized by the neighboring situation (C-7:C-8) of the double bond with the isopropyl group but not explained by the location (C-1:C-2) of the ethylene linkage far away from the isopropyl.

This conclusion was further substantiated by the finding that, in the mass spectrum of the epoxide (IV), the peak which is attributed to the ion A formed by the pathway shown in Chart 1 occurred at *m/e* 71.0497 (Calcd. for $C_4H_7O^+$: 71.04969).[8]

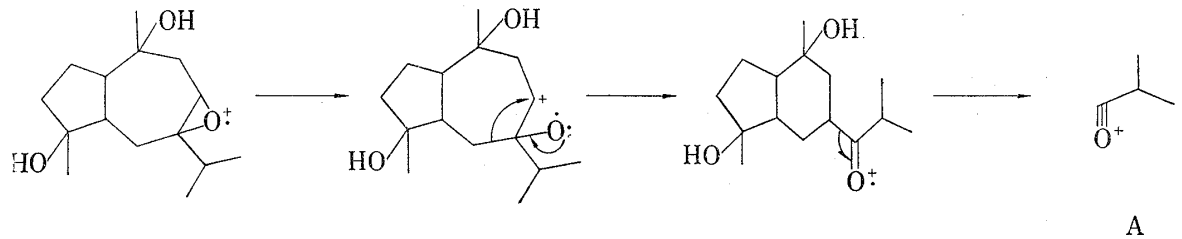


Chart 1

On the basis of the above evidence, the structure of curcumadiol is concluded to be I.

Curcumadiol could be biosynthetically arise from the intermediate cation (VI) as illustrated in Chart 2.

Recently, Brown and Sutherland[9] reported the conversion of germacrene monoepoxide (VII) into the diol (VIII) which appears to be a position isomer of curcumadiol. Since a di-

8) Y. Itagaki, T. Kurokawa, H. Moriyama, S. Sasaki, and Y. Watanabe, *Chem. Ind.*, **1965**, 1654.
9) E.D. Brown and J.K. Sutherland, *Chem. Commun.*, **1968**, 1060.

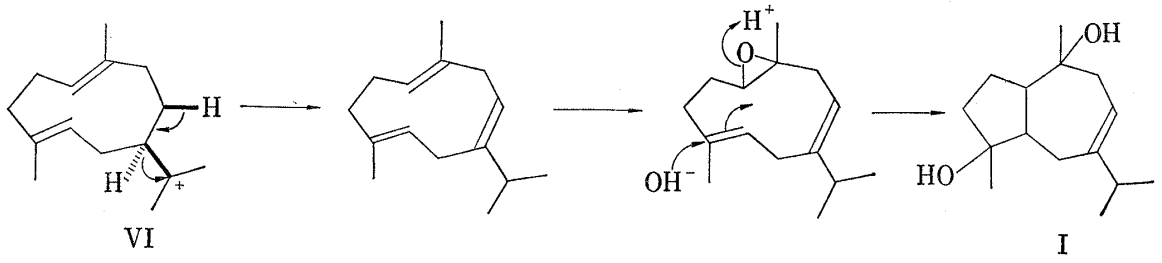
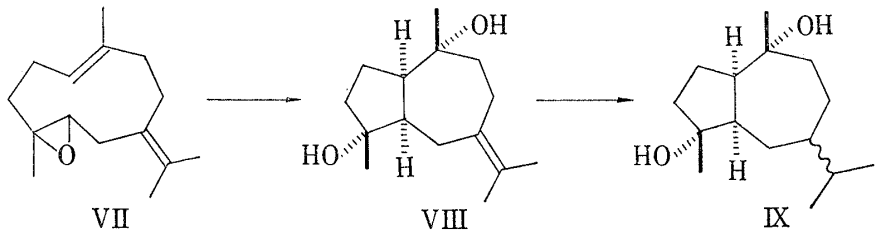


Chart 2

hydro-derivative of the diol (VIII) might be identical with dihydrocurcumadiol (III), the diol (VIII) was hydrogenated to give the dihydro-derivative (IX). Comparison of both dihydro-diols (III and IX) was then performed to reveal that they were not identical. However, the mass spectra of both dihydro-diols (III and IX) were found to be very similar, suggesting that they are stereoisomers.



Experimental[10]

Isolation of Curcumadiol——The crude drug "Ga-jutsu", the dried rhizomes of *Curcuma zedoaria* Roscoe, was extracted with MeOH. The light petroleum soluble portion of the extract was steam-distilled. The residue was chromatographed over alumina. AcOEt eluate was rechromatographed over silica gel. Elution with benzene–AcOEt (1:1) and crystallization from AcOEt gave curcumadiol (I) as colorless prisms, mp 145—145.5°. $[\alpha]_D$ −11.5° (c=1.74, EtOH). *Anal.* Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 76.12; H, 11.16. Mass Spectrum m/e: 238 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3350 (hydroxyl). NMR ($CDCl_3$): 0.98 (6H, d, J=8, $(C\underline{H}_3)_2CH$–), 1.19 (3H, s, $C\underline{H}_3$–C⟨OH), 1.25 (3H, s, $C\underline{H}_3$–C⟨OH), 5.51 (1H, single peak, $W1/2$=5, –CH_2–C$\underline{H}$=C⟨).

Acetylation of Curcumadiol——a) Curcumadiol (20 mg) in pyridine (1 ml) and Ac_2O (1 ml) was, left standing overnight at room temperature. After isolation in the usual manner, the product was shown to be the starting diol (I). b) Curcumadiol (20 mg) in pyridine (1 ml) and Ac_2O (1 ml) was set aside at room temperature for 14 days. Upon isolation in the customary way, the product was separated by thin-layer chromatography.

The monoacetate, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3640, 3450 (hydroxyl), 1734, 1245 (acetoxyl).

The diacetate (II), Mass Spectrum m/e: 280 (M^+). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740, 1733, 1240 (acetoxyl).

Hydrogenation of Curcumadiol over Platinum in Methanol——Curcumadiol (25 mg) was hydrogenated over PtO_2 (10 mg) in MeOH (5 ml). After work-up in the customary way, the product was crystallized from ether to yield dihydrocurcumadiol (III) as colorless plates (17 mg), mp 97—98°. Mass Spectrum m/e: 240 (M^+), 222, 204, 164, 121, 95, 81, 43. IR ν_{max}^{KBr} cm^{-1}: 3360 (hydroxyl). NMR ($CHCl_3$): 0.89 (6H, d, J=7, $(C\underline{H}_3)_2CH$–), 1.18 (3H, s, $C\underline{H}_3$–C⟨OH), 1.22 (3H, s, $C\underline{H}_3$–C⟨OH).

Epoxidation of Curcumadiol——Curcumadiol (85 mg) was treated with BzOOH (57 mg) in $CHCl_3$ (1.2 ml) at room temperature for 18 hr. The product isolated in the usual way was chromaotgraphed over silica gel (4 g). Elution with benzene–AcOEt (5:1) and crystallization from AcOEt afforded curcumadiol epoxide (IV) as colorless needles (30 mg), mp 83—83.5°. *Anal.* Calcd. for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.41; H, 10.50. Mass Spectrum m/e: 254 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3530 (hydroxyl). NMR (CCl_4, 100 MHz):

10) Melting points are uncorrected. NMR spectra were recorded at 60 MHz unless otherwise indicated. Chemical shifts are expressed in ppm downfield from Me_4Si as internal reference and coupling constants (J) and band width at half height ($W1/2$) in Hz. Abbreviations: s=singlet, d=doublet, and dd=doublet of doublets.

0.99 (6H, d, J=7, $(C\underline{H}_3)_2C\underline{H}$–), 1.14 (3H, s, $C\underline{H}_3$–C(OH)), 1.27 (3H, s, $C\underline{H}_3$–C(OH)), 3.42 (1H, dd, J=2.5, 7, $-CH_2-$ $C\underline{H}$——C–).
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Dehydrogenation of Curcumadiol with Palladium-on-Carbon——Curcumadiol (50 mg) was heated with Pd–C (35 mg) under N_2 at 310—320° for 2 min. The product was extracted with light petroleum and chromatographed over alumina (1 g). Elution with light petroleum gave S-guaiazulene (V) as a blue oil. UV λ_{max}^{EtOH} nm: 235, 245, 284, 289, 303, 450, 603. The trinitrobenzene adduct, prepared in the customary manner, crystallized from MeOH as maroon needles, mp 139—141°. Identity was confirmed by usual criteria.

Hydrogenation of the Diol from Germacrene Monoepoxide——The diol (VIII) (4 mg) was hydrogenated at atmospheric pressure over PtO_2 (2 mg) in MeOH (2 ml). Upon isolation, the product was crystallized from light petroleum to furnish the dihydrodiol (IX) as colorless needles (2 mg), mp 113—115°. Mass Spectrum m/e: 240 (M^+), 222, 204, 164, 121, 95, 81, 43. IR ν_{max}^{KBr} cm^{-1}: 3360 (hydroxyl).

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