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Structure of Curcumenol[1]

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Curcumenol, $C_{15}H_{22}O_2$, a new sesquiterpenic constituent of zedoary, *Curcuma zedoaria* (Zingiberaceae), has been shown to be represented by formula I on the basis of the following evidence. Chemical and physico-chemical properties of curcumenol and its derivatives indicate that curcumenol has a secondary methyl, a vinylic methyl on a trisubstituted double bond in which the carbon bearing a vinyl hydrogen is α to a quaternary carbon, an isopropylidene, and a hemiketal linkage whose carbon terminal is carrying no hydrogen. The carbon skeleton and the location of the hemiketal system have been established by the transformation to S-guaiazulene (V) and to the five-membered ring ketones (VII and VIII), respectively.

By the extraction of the rhizome of zedoary, *Curcuma zedoaria* Roscoe (Zingiberaceae), we have recently isolated, together with zederone[3] and curdione,[4] the sesquiterpenic hemiketal, curcumol, and elucidated its structure as shown in formula XI.[5] In continuation of our work on the analysis of the constituents of zedoary, we have since isolated another sesquiterpenoid hemiketal for which the name curcumenol is given. It will be shown in the present paper that curcumenol is represented by formula I.

Chromatography of the extract of zedoary, carried out in a previous work,[5] was continued to give from the more polar fractions curcumenol which showed mp 118—119° and analyzed for $C_{15}H_{22}O_2$.

The first objective was to confirm the nature of the functional groups. The nuclear magnetic resonance (NMR) spectrum exhibits a quadruplet attributed to a vinyl hydrogen and a doublet associated with a vinyl methyl. Both of the two signals are long-range coupled with each other, and indicate the presence of a trisubstituted ethylenic linkage having a methyl group on it. Further, the splitting pattern of the vinyl proton signal showing no other spin coupling reveals that the second carbon atom flanking the carbon bearing the vinyl hydrogen is quaternary. Two NMR singlets assigned to two olefinic methyls are also observed suggesting the presence of an isopropylidene system which was verified by ozonolysis of curcumenol giving acetone. Curcumenol was hydrogenated over palladium-on-carbon catalyst, there was obtained a saturated tetrahydro-derivative (II), confirming the presence of two ethylenic linkages in curcumenol.

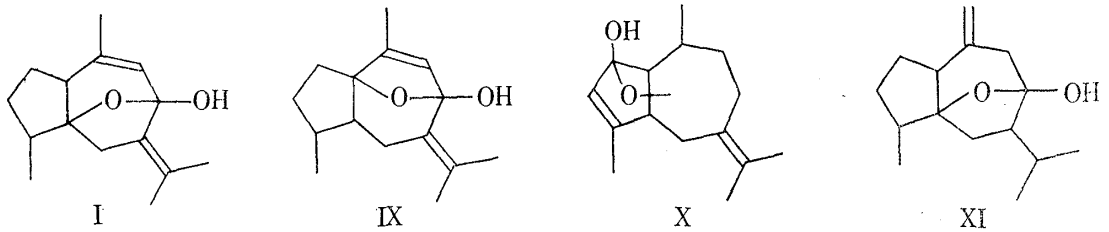
The nature of the oxygen atoms in the molecule was clarified by the subsequent observations. Curcumenol shows an infrared band at 3400 cm^{-1}, and, therefore, contains at least one hydroxyl group. On acetylation curcumenol gave a mono-acetate (III) whose infrared spectrum no longer exhibited hydroxyl absorption. Consequently, curcumenol is deduced

1) This paper constitutes Part XVII in the series on Sesquiterpenoids. Preceding paper, Part XVI: H. Hikino, K. Aota, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **15**, 1929 (1967).
2) Location : *Kita-4-bancho, Sendai.*
3) H. Hikino, S. Takahashi, Y. Sakurai, T. Takemoto, and N.S. Bhacca, *Chem. Pharm. Bull.* (Tokyo), **14**, 550 (1966).
4) H. Hikino, Y. Sakurai, S. Takahashi, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **14**, 1310 (1966); **15**, 1390 (1967).
5) H. Hikino, K. Meguro, Y. Sakurai, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **13**, 1484 (1965); **14**, 1241 (1966).

to be a mono-ol. Since curcumenol shows no infrared absorption due to carbonyl, the remaining one oxygen atom must participate in an ethereal bridge. Connection of the two oxygen functions was achieved as follows. On treatment with methanolic hydrochloric acid curcumenol afforded the methyl ether (IV). This transformation reveals that both the oxidic and hydroxyl groups constitute a hemiketal system. Further, since no signals associated with hydrogens on carbons attached to the ethereal oxygen are visible in the NMR spectrum, the oxidic linkage of curcumenol, therefore, is di-tertiary; the partial structure $\geqslant$C–O–C$\leqslant$OH being present.

The next problem was to settle the carbon skeleton. Lithium aluminum hydride reduction followed by dehydrogenation with palladized carbon curcumenol afforded S-guaizulene (V).

After the carbon skeleton of curcumenol has thus been established, arranging the functional groupings described above onto the guaiane skeleton leaves only two possible structures I and IX for curcumenol, since the structure X which has a three or four membered hemiketal ring is highly improbable and can be excluded.

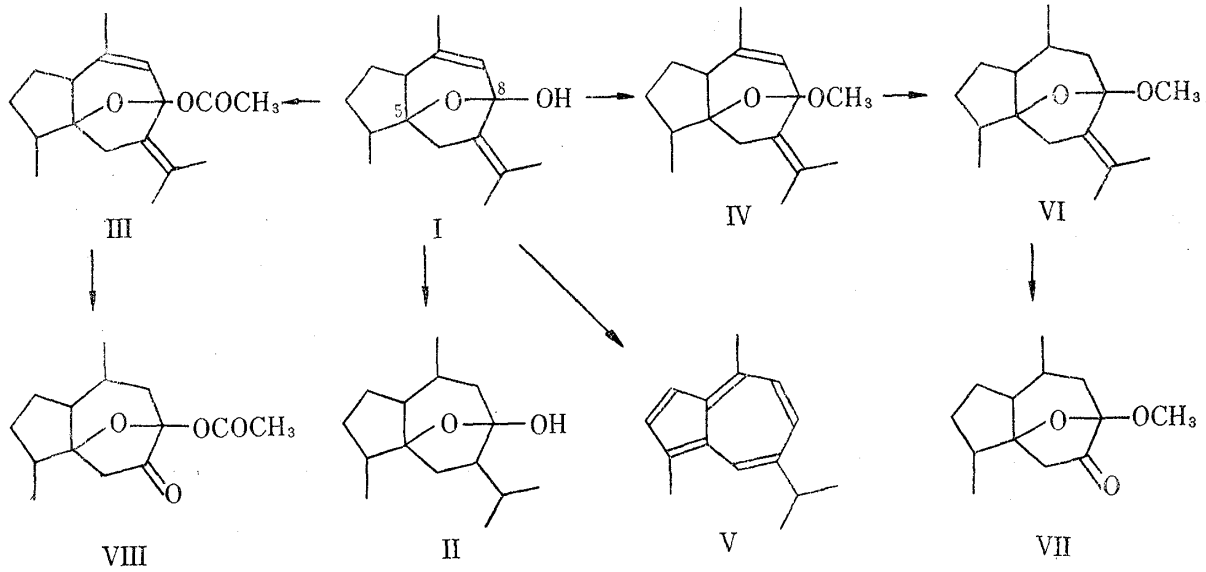


I IX X XI

The decision of the situation of one terminus of the oxide linkage (*i.e.*, the masked hydroxyl) in curcumenol at C-5 was performed in the subsequent way.

Comparison of tetrahydrocurcumenol (II), prepared above, with dihydrocurcumol,[5] which may possibly be identical, revealed that these two compounds were different. They are later considered as being stereoisomers each other.

Methylcurcumenol (IV) was then hydrogenated over palladized charcoal in methanol. The reaction was stopped after one mole of hydrogen had been consumed. The product was indicated by the NMR spectrum to consist of mainly dihydro-derivative (VI), which no longer had a trisubstituted olefinic linkage but an isopropylidene system. The product, without further purification, was subjected to ozonolysis giving the ketone (VII) whose infrared spectrum showed a band at 1768 cm^{-1} indicating that the newly formed carbonyl group was situated in a five-membered ring. The displacement of the carbonyl absorption



III I IV VI

VIII II V VII

for a shorter wavelength was explained by an α-oxygen substitution. However, since the over-all yield of the ketone (VII) from the methyl ether (IV) was very poor, the acetate (III) was also submitted to the same sequence of reactions. Thus, the acetate (III) was partially hydrogenated to yield the dihydrocurcumenyl acetate which on ozonolysis furnished the ketone (VIII). An infrared band at 1769 cm^{-1} shown by the ketone (VIII) demonstrated it to be a five-membered ring ketone with an α-oxygen substitution. These observations thus established that the masked hydroxyl group in curcumenol is located at C-5, since the masked carbonyl group is oriented at C-8.

Evidence so far obtained has led to the expression I for curcumenol.

It is of interest that zedoary contains two sesquiterpenic hemiketals, curcumenol (I) and curcumol (XI), with different degrees of unsaturation.

Experimental[6]

Isolation of Curcumenol——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. After elution of curcumol with benzene,[5] successive elution with the same solvent afforded a crystalline substance which was crystallized from AcOEt to give curcumenol (I) as colorless needles, mp 118.5—119.5°, $[\alpha]_D$ +397°(c=5.1), *Anal.* Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.76; H, 9.46, IR (KBr) cm^{-1}: 3400 (hydroxyl), 1650, 805 (trisubstituted double bond), NMR: doublet (3H) at 9.01τ (J=5, C$\underline{H}_3$-CH<), singlets (3H each) at 8.44, 8.25τ (C$\underline{H}_3$)$_2$C=C<), doublet (3H) at 8.38τ (J=1.4, C$\underline{H}_3$-C=CH-), quartet (1H) at 4.38τ (J=1.4, C$\underline{H}_3$-C=C$\underline{H}$-C<).

Ozonolysis of Curcumenol——Curcumenol (52 mg) in AcOEt (10 ml) was ozonized at 0° for 10 min. After refluxing with H_2O, $KMnO_4$ solution was added to the mixture until no further decolorization occurred, and the mixture was steam-distilled. The distillate was treated with 2,4-dinitrophenylhydrazine-HCl and the precipitate crystallized from EtOH to afford acetone 2,4-dinitrophenylhydrazone as orange needles, mp 125—126°, which showed on mp depression on admixture with an authentic specimen.

Hydrogenation of Curcumenol over Palladized Charcoal in Methanol——Curcumenol (500 mg) was hydrogenated in the presence of 5% Pd-C (500 mg) in MeOH (10 ml). Upon isolation, crystallization from light petroleum yielded a tetrahydro-derivative (II) as colorless needles (60 mg), mp 69.5—71°, $[\alpha]_D$ +45.0° (c=2.4), *Anal.* Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.69; H, 10.94, IR (KBr) cm^{-1}: 3400 (hydroxyl), NMR: multiplet (12H) in the region 9.12—8.92τ (C$\underline{H}_3$-CH<).

Acetylation of Curcumenol——Curcumenol (105 mg) in pyridine (2.5 ml) was refluxed with Ac_2O (2.5 ml) for 4 hr. Working up in the usual manner and crystallization from AcOEt gave curcumenyl acetate (III) as colorless needles (60 mg), mp 80—80.5°, $[\alpha]_D$ +217°(c=6.1), *Anal.* Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 74.20; H, 8.68, IR (KBr) cm^{-1}: 1764, 1215 (acetoxyl), 1667, 838 (trisubstituted double bond), NMR: doublet (3H) at 8.99τ (J=5, C$\underline{H}_3$-CH<), singlet (6H) at 8.42τ ((C$\underline{H}_3$)$_2$C=C<), doublet (3H) at 8.36τ (J=1.3, C$\underline{H}_3$-C=CH-), singlet (3H) at 8.03τ (C$\underline{H}_3$-CO-O-), quartet (1H) at 4.32τ (J=1.3, CH_3-C=C$\underline{H}$-C<).

Methylation of Curcumenol——Curcumenol (140 mg) in conc. HCl (1 ml) and MeOH (9 ml) was let stand at room temperature for 5 days. The mixture was diluted with H_2O, neutralized with $NaHCO_3$, and extracted with ether. The product (130 mg) was distilled under reduced pressure yielding methylcurcumenol (IV) as a colorless oil, n_D^{25} 1.503, $[\alpha]_D$ +528°(c=1.7), *Anal.* Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.35; H, 9.74, IR (liquid) cm^{-1}: 1661, 837 (trisubstituted double bond), NMR: doublet (3H) at 9.01τ (J=5, C$\underline{H}_3$-CH<), singlets (3H each) at 8.40, 8.38τ ((C$\underline{H}_3$)$_2$C=C<), doublet (3H) at 8.32τ (J=1.4, C$\underline{H}_3$-C=CH-), singlet (3H) at 6.81τ (C$\underline{H}_3$-O-), quartet (1H) at 4.44τ (J=1.4, C$\underline{H}_3$-C=C$\underline{H}$-C<).

Reduction with Lithium Aluminum Hydride followed by Dehydrogenation of Curcumenol——Curcumenol (200 mg) in ether (20 ml) was treated with an excess of $LiAlH_4$ at room temperature for 4 days. After isolation in the usual way, the product, without purification, was heated with 10% Pd-C under N_2 at 200° for 2 min. The mixture was extracted with light petroleum and chromatographed over silica gel (6g). Light petroleum eluted S-guaiazulene (V) as a blue oil, identified by TLC and the UV spectrum.

1,3,5-Trinitrobenzene adduct crystallized from EtOH as dark maroon needles, mp 147°, UV λ_{max}^{EtOH} 244, 285, 289, 304, 349, 367, *ca.* 600 mμ, which was undepressed in mp on admixure with an authentic specimen.

Partial Hydrogenation of Methylcurcumenol over Palladized Charcoal in Methanol——Methylcurcumenol (IV) (360 mg) in MeOH (25 ml) was hydrogenated using 5% Pd-C (500mg); the reaction was stopped after

6) Melting points are uncorrected. Specific rotations were determined in $CHCl_3$ solution. NMR spectra were recorded at 60 Mcps in CCl_4 solution using Me_4Si as internal standard. Chemical shifts are expressed in τ units and coupling constants (J) in cps.

1 mole of H_2 had been absorbed. Isolation in the usual manner gave the crude dihydromethylcurcumenol (VI) as a colorless oil, NMR: doublet (3H) at 9.08τ (J=6, C$\underline{H}_3$–CH$\langle$), doublet (3H) at 9.02τ (J=5, C$\underline{H}_3$–CH$\langle$), unresolved peak (1H) at *ca.* 8.35τ (($C\underline{H}_3)_2C{=}C\langle$), singlet (3H) at 6.92$\tau$ (C$\underline{H}_3$–O–), no olefinic hydrogen signal.

Ozonolysis of Dihydromethylcurcumenol——The crude dihydromethylcurcumenol (VI) (290 mg), without further purification, was dissolved in AcOEt (20 ml), treated with ozonized oxygen at 0° for 1 hr, and hydrogenated over 5% Pd–C. Upon isolation, the product (300 mg) was chromatographed over silica gel (13 g). Elution with light petroleum and distillation under diminished pressure furnished the ketone (VII) as a colorless oil (10 mg), IR (liquid) cm^{-1}: 1768 (five-membered ring ketone with α-oxygen substitution), NMR: doublet (3H) at 9.00τ (J=6, C$\underline{H}_3$–CH$\langle$), doublet (3H) at 8.09τ (J=6, C$\underline{H}_3$–CH$\langle$), singlet (3H) at 6.77τ (C$\underline{H}_3$–O–).

Partial Hydrogenation of Curcumenyl Acetate over Palladized Charcoal in Methanol——The acetate (III) (600 mg) in MeOH (25 ml) was hydrogenated in the presence of 5% Pd–C (0.5 g) at room temperature. After the consumption of 1 mole of H_2, the catalyst was removed by filtration and the filtrate on evaporation gave the crude epimeric mixture of the dihydrocurcumenyl acetates as a colorless oil (607 mg), NMR: multiplet (6H) in the range 9.27—8.99τ (C$\underline{H}_3$–CH$\langle$), singlet (6H) at 8.40τ (($C\underline{H}_3)_2C{=}C\langle$), singlet (3H) at 8.08$\tau$ (C$\underline{H}_3$–CO–O–), no vinylic hydrogen signal.

Ozonolysis of the Dihydrocurcumenyl Acetates——The crude epimeric mixture of the dihydrocurcumenyl acetates (607 mg) in AcOEt (20 ml) was ozonized at −5° for 2 hr. The reaction mixture was hydrogenated over 5% Pd–C (30 mg). Isolation of the product (580 mg) in the customary manner, chromatography over silica gel (15 g), elution with light petroleum, and distillation under reduced pressure yielded the epimeric mixture of the ketones (VIII) as a colorless oil (130 mg), NMR: multiplet (6H) in the range 9.12—8.91τ (C$\underline{H}_3$–CH$\langle$), singlet (3H) at 7.98τ (C$\underline{H}_3$–CO–O–), which crystallized on standing. Crystallization from AcOEt furnished one epimer of the ketones (VIII) as colorless prisms, mp 66—67°, $[\alpha]_D$ +7.4° (c=2.3), *Anal.* Calcd. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 67.08; H, 8.18, IR (CCl_4) cm^{-1}: 1769 (five-membered ring ketone with α-oxygen substitution), 1725, 1225 (acetoxyl), NMR: doublet (3H) at 9.01τ (J=5, C$\underline{H}_3$–CH$\langle$), doublet (3H) at 8.94τ (J=5, C$\underline{H}_3$–CH$\langle$), singlet (3H) at 7.97τ (C$\underline{H}_3$–CO–O–).

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