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Structure of Isocurcumenol[1]

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A new sesquiterpenic hemiketal has been isolated from zedoary, *Curcuma zedoaria* (Zingiberaceae), and named isocurcumenol. Chemical and physicochemical studies have established isocurcumenol to be as shown in formula I.

Our recent investigation has shown the presence of the sesquiterpenic hemiketals and ketol possessing the guaiane skeleton, curcumol,[3] curcumenol,[4] and procurcumenol,[5] along with a number of furan-containing sesquiterpenoids[6] in the rhizome of zedoary, *Curcuma zedoaria* Roscoe (Zingiberaceae). Further survey has resulted in the isolation of another sesquiterpenic hemiketal having the guaiane skeleton which we give the term isocurcumenol. The present communication deals with structural elucidation of isocurcumenol (I).

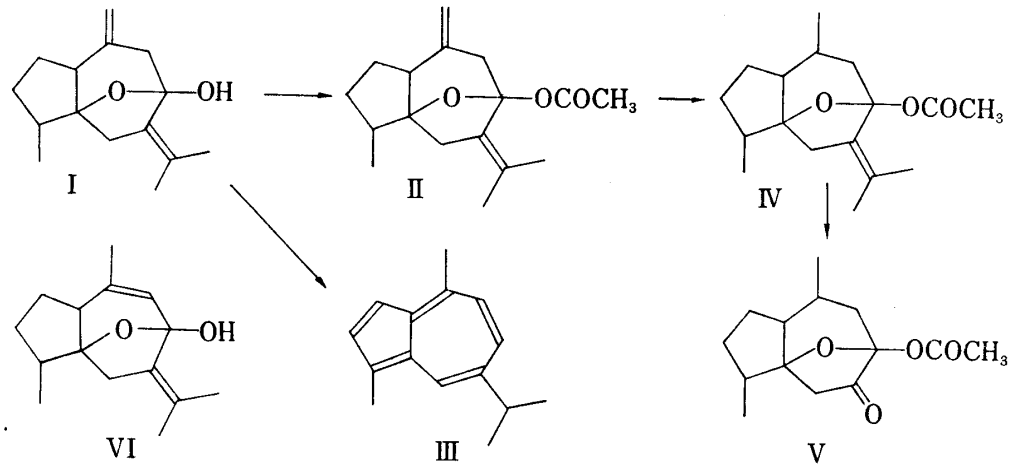

Chart 1

Isocurcumenol analyzed for $C_{15}H_{22}O_2$. The nuclear magnetic resonance (NMR) spectrum indicates the presence of a secondary methyl (0.97 ppm), two vinyl methyls (1.62, 1.79 ppm), and a vinylidene group (4.67 ppm). The last function was confirmed by the infrared absorption (3080, 1649, and 881 cm^{-1}). The infrared spectrum also exhibits a hydroxyl band at 3440 cm^{-1}. In consistent with this, acetylation of isocurcumenol gave a mono-acetate (II) which has no more hydroxyl group. Since isocurcumenol possesses no carbonyl, the remaining one oxygen atom is oxidic. The NMR spectra of isocurcumenol and its acetate (II) show no signals due to hydrogens on carbons bearing oxygen functions. Therefore, the hydroxyl and the ethereal oxygen must be attached to quaternary carbons. When isocurcumenol was

1) This paper is Part XXXII in the series on Sesquiterpenoids. Part XXXI: H. Hikino, T. Kohama, and T. Takemoto, *Tetrahedron*, **25**, 1037 (1969).
2) Location: *Aobayama, 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, Y. Sakurai, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 1605 (1968).
6) *cf.* H. Hikino, K. Agatsuma, and T. Takemoto, *Tetrahedron Letters*, **1968**, 931.

subjected to lithium aluminum hydride reduction followed by dehydrogenation, S-guaiazulene (III) was obtained, demonstrating that isocurcumenol has the guaiane skeleton. These observations together with the common existence of isocurcumenol with curcumenol (VI) in the same plant suggest the structure I for isocurcumenol.

Further chemical evidence, in confirmation, was then sought. Partial hydrogenation of the acetate (II) gave the dihydro-acetate (IV). The infrared and NMR spectra demonstrate the disappearance of the vinylidene and instead the formation of a secondary methyl. Although no definite evidence was available as to whether the dihydro-derivative (IV) was homogeneous or heterogeneous, it was later shown to be an epimeric mixture formed by non-stereospecific hydrogenation of the acetate (II). Thus, ozonolysis of the acetate (IV) gave an oily product which on standing partially crystallized and the crystalline isomer was identified as the five-membered ring ketone (V) previously prepared from curcumenol (VI) in a similar manner.[4]

On the basis of the above evidence the structure of isocurcumenol has been elucidated as represented by formula I. Isocurcumenol is thus a congener of curcumenol (VI) derived from a common precursor.

Experimental[7]

Isolation of Isocurcumenol——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. Elution with benzene gave a mixture of isocurcumenol, curcumol,[3] and curcumenol[4] which was rechromatographed on silicagel. Fractions obtained before the elution of curcumol and curcumenol were combined and crystallized from AcOEt to afford isocurcumenol (I) as colorless needles, mp 139—141°, $[\alpha]_D$ +34.0° (c=10.0, $CHCl_3$), *Anal.* Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.61; H, 9.45. IR (KBr) cm^{-1}: 3440 (hydroxyl), 3080, 1649, 881 (vinylidene), NMR: 3H d at 0.97 (J=6, $C\underline{H}_3$-CH〈), two 3H s at 1.62, 1.79 (($C\underline{H}_3$)$_2$C=C〈), 2H br peak at 4.67 (w(1/2h)=5, $C\underline{H}_2$=C〈).

Acetylation of Isocurcumenol——Isocurcumenol (216 mg), Ac_2O (5.2 ml), and pyridine (5.2 ml) were heated under reflux for 3 hr. The product was worked up in the customary manner to afford isocurcumenyl acetate (II) as a colorless oil (239 mg), IR (CCl_4) cm^{-1}: 3100, 1650, 891 (vinylidene), 1770, 1206 (acetoxyl), NMR: 3H d at 0.98 (J=6, $C\underline{H}_3$-CH〈), two 3H s at 1.61, 1.63 (($C\underline{H}_3$)$_2$C=C〈), 3H s at 1.99 ($C\underline{H}_3$-CO-O-), 2H m at 4.68 (w(1/2h)=7, $C\underline{H}_2$C〈).

Lithium Aluminum Hydride Reduction followed by Dehydrogenation of Isocurcumenol——Isocurcumenol (54 mg) in ether (5 ml) was treated with $LiAlH_4$ (60 mg) under stirring for 1.5 hr at room temperature. Working up in the usual way gave a reduced product (49 mg). The product (30 mg) was heated with Pd-C (10%, 30 mg) under N_2 at 290—310° for 3 min. Extraction with light petroleum and chromatography over alumina (2g) afforded S-guaiazulene (III) as a blue oil, UV λ_{max}^{EtOH} mμ: 244, 286, 289, 305.

The 1,3,5-trinitrobenzene adduct, prepared in the usual manner, crystallized from EtOH as maroon needles, mp 142—144°. The identity was confirmed by the usual criteria.

Hydrogenation of Isocurcumenyl Acetate over Palladium-Carbon in Methanol——The acetate (II) (220 mg) in MeOH (2.5 ml) was hydrogenated in the presence of Pd-C (5%, 0.25 g). Isolation yielded the crude epimeric mixture of the dihydrocurcumenyl acetates (IV) as a colorless oil, NMR: 3H d at 0.93 (J=6, $C\underline{H}_3$-CH〈), 3H d at 0.98 (J=6, $C\underline{H}_3$-CH〈), 6H br s at 1.62 (($C\underline{H}_3$)$_2$C=C〈), 3H s at 1.90 ($C\underline{H}_3$-CO-O-).

Ozonolysis of the Dihydroisocurcumenyl Acetates——The epimeric mixture of the dihydro-acetates (IV) (143 mg) in AcOEt (10 ml) was ozonized at −40° for 30 min. The reaction mixture was hydrogenated over Pd-C (5%, 22 mg). After isolation, the product was chromatographed over silica gel (4 g). Elution with light petroleum-benzene (1:1) furnished the epimeric mixture of the ketones (V) as a colorless oil (71 mg), NMR: 6H m in the region 0.9—1.2 ($C\underline{H}_3$-CH〈), 3H s at 1.97, 2.04 ($C\underline{H}_3$-CO-O-), which crystallized on standing. Crystallization from AcOEt gave one epimer of the ketones (V) as colorless prisms (50 mg), mp 65—66°, IR (KBr) cm^{-1}: 1768, 1224 (acetoxyl), 1757 (five-membered ring ketone with α-oxygen substitution), NMR: 3H d at 0.99 (J=6, $C\underline{H}_3$-CH〈), 3H d at 1.06 (J=6, $C\underline{H}_3$-CH〈), 3H s at 2.04 ($C\underline{H}_3$-CO-O-). The identity with the crystalline ketone (V) derived from curcumenol (VI)[4] was confirmed in the usual criteria.

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7) Melting points are uncorrected. NMR spectra were determined at 60 MHz in CCl_4 solution. Chemical shifts are given in ppm downfield from Me_4Si as internal reference, and coupling constants and band-widths at half height (w(1/2h)) in Hz. Abbreviations: s=singlet, d=doublet, m=multiplet, and br=broad.