[Chem. Pharm. Bull. 16(8)1605—1607(1968)]

UDC 581.19 : 582.583 : 547.597

Structure of Procurcumenol[1)]

Hiroshi Hikino, Yojiro Sakurai, and Tsunematsu Takemoto

Pharmaceutical Institute, School of Medicine, Tohoku University[2)]

(Received December 19, 1967)

The structure of procurcumenol, a new sesquiterpenic keto–alcohol isolated from zedoary, *Curcuma zedoaria* (Zingiberaceae), has been shown to be I.

In continuation of our investigation on the constituents of zedoary, *Curcuma zedoaria* Roscoe (Zingiberaceae), from which curcumol,[3)] zederone,[4)] curdione,[5)] curcolone,[6)] curcumenol,[7)] furanodiene,[8)] curzerene, curzerenone, and epicurzerenone[9)] have hitherto been isolated, we have further isolated the other new sesquiterpenoid of the molecular formula $C_{15}H_{22}O_2$ for which the name procurcumenol is proposed. In the present paper, we wish to report evidence which indicates the structure I for procurcumenol.

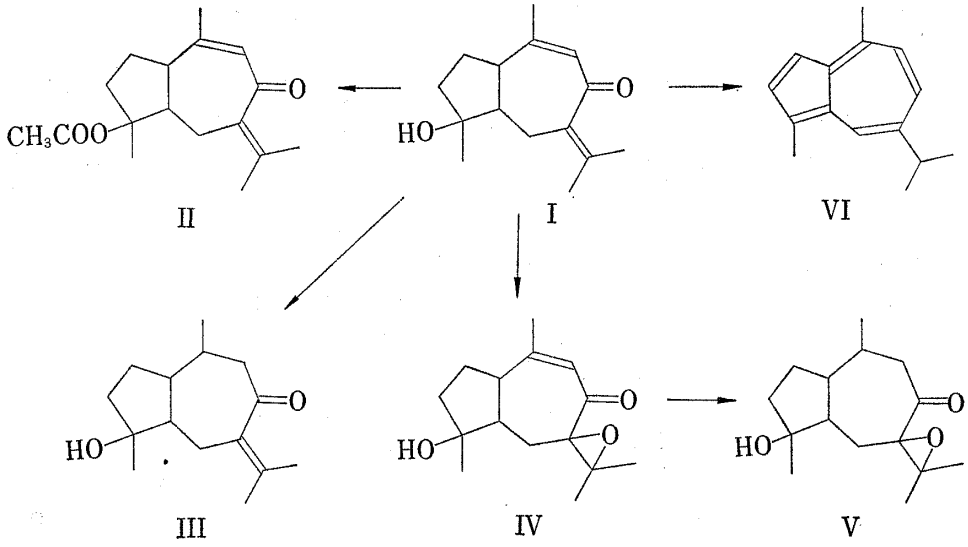
Procurcumenol contains a free hydroxyl group, shown by the infrared absorption (CCl_4) at 3650 and 3460 cm^{-1} and by the formation of the monoacetate (II). Since there is no proton signal in the nuclear magnetic resonance (NMR) spectrum attributable to a hydrogen on an oxygen–bearing carbon, the hydroxyl group is consequently tertiary. A methyl signal as a singlet at 1.14 ppm (CCl_4) suggests that the hydroxyl is situated on a methyl–carrying carbon. The remaining oxygen atom is present as part of a conjugated carbonyl system in a six–membered or larger ring (λ_{max}^{EtOH} 248 mμ, $\nu_{C=O}^{CCl_4}$ 1665 cm^{-1}). Procurcumenol has two double bonds, one of which is present as an isopropylidene group as evidenced by liberation of acetone on ozonolysis. The other double bond is trisubstituted as indicated by the characteristic NMR signals for a vinyl methyl and a vinyl hydrogen. That both the double bonds are conjugated with the carbonyl group was proved by spectral examinations of the following derivatives. Thus partial hydrogenation of procurcumenol resulted in the saturation of the trisubstituted ethylenic linkage to give the dihydro–derivative (III), whose NMR spectrum showed the disappearance of the vinyl methyl signal and the vinyl hydrogen signal in the spectrum of the original ketol (I) and instead the appearance of a secondary methyl signal (3H doublet at 0.84 ppm (CCl_4)). The spectral properties of the dihydro–derivative (III) (λ_{max}^{EtOH} 253 mμ, $\nu_{C=O}^{CCl_4}$ 1675 cm^{-1}) indicate the retention of an enone system. On the other hand, treatment of procurcumenol with perbenzoic acid caused the epoxidation of the isopropylidene grouping affording the epoxide (IV), where the two vinyl methyls of the isopropylidene group in the

1) This paper constitutes Part XXVI in the series on Sesquiterpenoids. Preceding paper, Part XXV: H. Hikino, D. Kuwano, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 1601 (1968).
2) Location: *Kita–4–bancho, Sendai.*
3) H. Hikino, K. Meguro, Y. Sakurai, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **13**, 1484 (1965); *ibid.*, **14**, 1241 (1966).
4) H. Hikino, S. Takahashi, Y. Sakurai, T. Takemoto, and N.S. Bhacca, *Chem. Pharm. Bull.* (Tokyo), **14**, 550 (1966); *ibid.*, **16**, 1081 (1968).
5) H. Hikino, Y. Sakurai, S. Takahashi, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **14**, 1310 (1966); *ibid.*, **15**, 1390 (1967).
6) H. Hikino, Y. Sakurai, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **15**, 1065 (1967); *ibid.*, **16**, 827 (1968).
7) H. Hikino, Y. Sakurai, S. Numabe, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 39 (1968).
8) H. Hikino, K. Agatsuma, and T. Takemoto, *Tetrahedron Letters*, **1968**, 931.
9) H. Hikino, K. Agatsuma, and T. Takemoto, *Tetrahedron Letters*, **1968**, 2855.

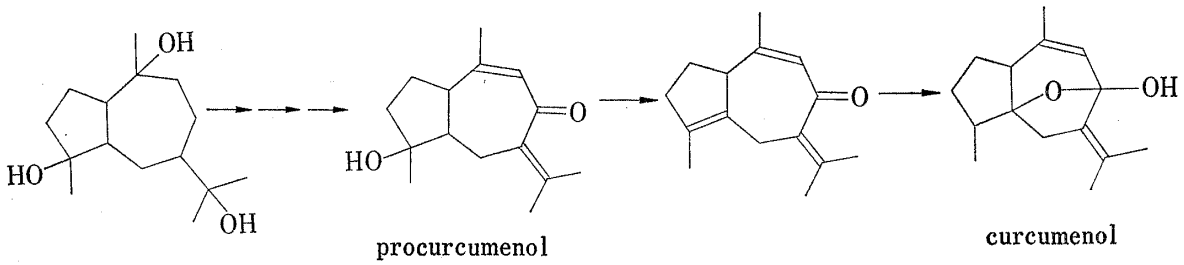
original ketol (I) were replaced by two tertiary methyls on an oxygen-bearing carbon (3H singlets at 1.14 and 1.34 ppm (CCl_4)). The spectral data of the epoxide (IV) (λ_{max}^{EtOH} 245 mμ, $\nu_{C=O}^{CCl_4}$ 1665 cm^{-1}) also demonstrate the retention of an enone moiety. On hydrogenation the epoxide (IV) yielded the dihydro-epoxide (V), the infrared spectrum of which exhibited the presence of a saturated carbonyl group in a six-membered or larger ring ($\nu_{C=O}^{CCl_4}$ 1715 cm^{-1}).

In order to establish the carbon skeleton, procurcumenol was reduced with lithium aluminum hydride to give an isomeric mixture of triols which on dehydrogenation with palladium-carbon furnished S-guaiazulene (VI), indicating that procurcumenol has the guaiane skeleton.

Arrangement of the previous partial structures into this carbon skeleton leads to formula I for procurcumenol.



The structural elucidation of procurcumenol thus provides the missing link in the biogenetic pathway for curcumenol.[6]



Experimental[10]

Isolation of Procurcumenol——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 ovre alumina. Fractions eluted after curcumol[3] and curcumenol[7] with benzene were combined and rechromatographed over silica gel. Elution with benzene—AcOEt (1:1) gave procurcumenol (I) as a colorless oil, $[\alpha]_D$ +140.9 (c=10.5). *Anal.* Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.35; H, 9.69. UV λ_{max}^{EtOH} 248 mμ, IR (CCl_4) cm^{-1}: 3650, 3460 (hydroxyl), 1665 (conjugated carbonyl), NMR: 3H s at 1.14 (CH_3-C≤OH), 6H s at 1.73 (CH_3-C=C), 3H s at 1.87 (CH_3-C=C), 1H br at 5.72

10) Melting points are uncorrected. $[\alpha]_D$s were measured in $CHCl_3$ solution. NMR spectra were run at 60 Mcps in CCl_4 solution unless otherwise indicated. Chemical shifts are expressed in ppm from Me_4Si as internal reference, and coupling constants (J) and band widths at half height (w(h/2)) in cps. Abbreviations: s=singlet, d=doublet, q=quadruplet, and br=broad peak.

(w(h/2)=5, –CO–CH=C–CH_3), NMR (C_6H_6): 3H s at 1.17 (CH_3–C≤OH), 6H s at 1.63 (CH_3–C=C), 3H s at 1.83 (CH_3–C=C), 1H q at 5.91 (J=1.7, –CO–CH=C–CH_3).

Acetylation of Procurcumenol——Procurcumenol (200 mg) in Ac_2O (4 ml) was refluxed in the presence of AcONa (200 mg) for 1 hr. Upon isolation, the product (200 mg) was chromatographed over silica gel (10 g). Elution with benzene and distillation under reduced pressure gave procurcumenyl acetate (II) as a colorless oil (90 mg), $[\alpha]_D$ +116.4° (c=3.4). *Anal.* Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.59; H, 8.81. UV λ_{max}^{EtOH} 245 mμ, IR (CCl_4) cm^{-1}: 1738, 1239 (acetoxyl), 1659 (conjugated carbonyl), NMR: 3H s at 1.41 (CH_3–C≤$OCOCH_3$), 6H s at 1.73 (CH_3–C=C), 3H s at 1.84 (CH_3–C=C), 3H s at 1.91 (CH_3COO–), 1H br at 5.71 (w(h/2)=4, –CO–CH=C–CH_3), NMR (C_6H_6): 3H s at 1.36 (CH_3–C≤$OCOCH_3$), 6H s at 1.58 (CH_3–C=C), 3H s at 1.70 (CH_3COO–), 3H s at 1.85 (CH_3–C=C), 1H br at 5.93 (w(h/2)=5, –CO–CH=C–CH_3).

Ozonolysis of Procurcumenol——Procurcumenol (200 mg) in AcOEt (10 ml) was ozonized at 0° for 10 min. The mixture was refluxed with water (10 ml). To the water layer separated was added $KMnO_4$ and the mixture was distilled. The distillate was treated with 2,4-dinitrophenylhydrazine–HCl solution, and the deposited precipitate was crystallized from EtOH to give acetone 2,4-dinitrophenylhydrazone as orange needles, mp 125—125.5°. Identity was confirmed by the usual criteria.

Partial Hydrogenation of Procurcumenol over Palladium-Carbon in Methanol——Procurcumenol (400 mg) was hydrogenated over 5% Pd–C (500 mg) in MeOH (20 ml). After the consumption of 1 mole (44 ml) of H_2, the mixture was worked up in the customary manner. The product (380 mg) was chromatographed over silica gel (14 g) and elution with benzene—AcOEt (1:1) gave dihydroprocurcumenol (III) as a colorless oil, $[\alpha]_D$ −26.2° (c=2.4). IR (CCl_4) cm^{-1}: 3640, 3470 (hydroxyl), 1675, 1614 (conjugated carbonyl), NMR: 3H d at 0.84 (J=6, CH_3–CH⟨), 3H s at 1.11 (CH_3–C≤OH), 6H s at 1.80 ((CH_3)$_2$C=C⟨), NMR (C_6H_6): 3H d at 0.83 (J=6, CH_3–CH⟨), 3H s at 1.10 (CH_3–C≤OH), 3H s at 1.71, 3H s at 1.94 ((CH_3)$_2$C=C⟨).

Epoxidation of Procurcumenol with Perbenzoic Acid——Procurcumenol (300 mg) and BzO_2H (200 mg) in $CHCl_3$ (3 ml) were set aside at room temperature for 4 days. Upon isolation, the product (310 mg) was chromatographed over silica gel (10 g). Elution with benzene—AcOEt (1:1) afforded procurcumenol monoepoxide (IV) as a colorless oil, $[\alpha]_D$ +71.9° (c=1.8). UV λ_{max}^{EtOH} 245 mμ, IR (CCl_4) cm^{-1}: 3630, 3480 (hydroxyl), 1665, 1635 (cycloheptenone), NMR: 3H s at 1.05 (CH_3–C≤OH), 3H s at 1.14, 3H s at 1.34 ((CH_3)$_2$-C⟨O⟩C⟨), 3H s at 1.95 (CH_3–C=CH–), 1H q at 5.70 (J=1, –CO–CH=C–CH_3).

Hydrogenation of Procurcumenol Monoepoxide over Palladium-Carbon in Methanol——The epoxide (IV) (100 mg) was hydrogenated over 5% Pd–C (300 mg) in MeOH (15 ml). After isolation, the product (90 mg) was chromatographed over silica gel (4 g). Elution with benzene—AcOEt (1:1) yielded dihydroprocurcumenol monoepoxide (V) as a colorless oil, IR (CCl_4) cm^{-1}: 3620, 3530 (hydroxyl), 1715 (cycloheptanone), NMR: 3H s at 0.99 (CH_3–C≤OH), 3H d at 1.12 (J=5, CH_3–CH⟨), 3H s at 1.12, 3H s at 1.38 ((CH_3)$_2$C⟨O⟩C⟨).

Lithium Aluminum Hydride Reduction followed by Dehydrogenation of Procurcumenol——Procurcumenol (530 mg) in ether (10 ml) was treated with $LiAlH_4$ (250 mg) at 0° for 2 hr. Isolation in the usual way afforded the product (490 mg) which gave a number of spots on TLC.

The product (50 mg) was heated with 10% Pd–C (30 mg) under N_2 at 300—305° for 2 min. This was repeated once more. The combined product in light petroleum was chromatographed over silica gel (5 g). Elution with the same solvent furnished S-guaiazulene (VI) as a blue oil, UV λ_{max}^{EtOH} 244, 287, 290, 303, 353, 366 mμ, which was dissolved in EtOH, treated with 1,3,5-trinitrobenzene, and crystallized from EtOH to give S-guaiazulene 1,3,5-trinitrobenzene adduct as maroon needles (50 mg), mp 149—149.5°. Identification was carried out in the usual criteria.

Acknowledgement Microanalyses and NMR measurements were performed by Analytical Laboratories, this Institute, to whom thakns are due.