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THE ABSOLUTE STEREOSTRUCTURE OF CURCUMOL ISOLATED FROM *CURCUMA WENYUJIN*

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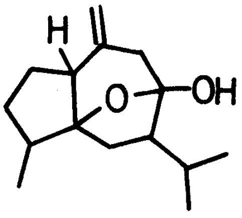
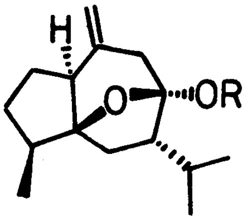
The complete stereostructure of curcumol (1) isolated from *Curcuma wenyujin* was unequivocally determined as shown in **2** on the basis of the CD measurement of norketone (5) and the X-ray analysis of **1** and the *p*-bromobenzoate (4).

KEYWORDS——curcumol; *Curcuma wenyujin*; Zingiberaceae; relative/absolute configuration; norketone; CD; *p*-bromobenzoate; X-ray diffraction

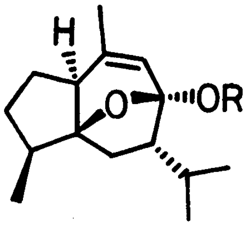
Of the eight Chinese species of the genus *Curcuma* (Zingiberaceae), the rhizomes of five have been used medicinally in China.2) The essential oil prepared from the air-dried rhizome of *C. wenyujin* (温郁金 , 温莪术), which is one of the herbs mentioned above, was found to have antitumor activity.3) Of the various kinds of terpenoid constituents in *Curcuma* rhizomes, curcumol, a major sesquiterpene hemiacetal containing a ring system very similar to that of ambrosic acid,4) was identified in this rhizome2,3) as well as in the rhizomes of *C. zedoaria* Roscoe (莪蒁),5,6) *C. sp.* (川郁金),2) *C. kwangsinensis* (桂莪术),2) and *C. longa* (姜黄).2) The gross structure of curcumol was formulated as **1** based on the physicochemical evidence.5) However, as far as we are aware, no report on the stereostructure of a most interesting component (1) is available, even in regard to the relative configuration. This prompted us to elucidate the stereochemistry of **1** for a basic study of the structure-activity and biogenetic scheme. We describe the complete stereostructure of curcumol (1) in this communication.



1



2: R=H
3: R=$COC_6H_4Br(p)$



4: R=$COC_6H_4Br(p)$

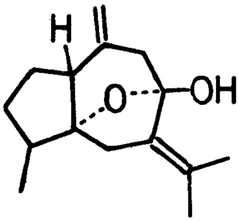


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Chart 1

The physical data on curcumol (1) isolated from the above-mentioned bioactive oil in C. wenyujin are as follows: $C_{15}H_{24}O_2$; mp 141-142°C; $[\alpha]_D^{30}$ -32.26° (c = 2.127, $CHCl_3$) [mp 141-142°C; $[\alpha]_D$ -40.8° (c = 6.7)];$^{5)}$ high-resolution mass (MS) m/z 236.1777 (Theor. 236.1770 for $C_{15}H_{24}O_2$); IR ν_{max}^{KBr} cm^{-1}: 3420 (OH), 3070, 1647, 882 ($>C=CH_2$); ^1H-NMR ($CDCl_3$) δ: 0.87 (3H, d, J = 6.8 Hz, $>HC-CH_3$), 1.00, 1.01 (3H x 2, each d, J = 6.8 Hz, $-CH(CH_3)_2$), 2.51, 2.57 (1H x 2, each d, J = 14.8 Hz, C_9-H), 4.88 (2H, brs, $>C=CH_2$). The crystals grown in ethanol solutions were prisms elongated along the c axis. The crystal data are: $C_{15}H_{24}O_2$, MW = 236, trigonal, space group $P3_2$, lattice constants a = b = 12.387(6), c = 7.866(4) Å, α = β = 90°, γ = 120°, U = 1045 $Å^3$, Z = 3, D_{calc} = 1.125 gcm^{-3}. The intensity data were collected on a Philips PW1100 diffractometer using graphite monochromated CuKα radiation. Of the total of 2323 reflections within the 2θ range 6° through 156°, 1951 were above the 2σ(I) level. The structure was solved by the direct method using a MULTAN program$^{7)}$ and refined by the method of least-squares with block-diagonal matrix approximations. The final R value was 0.046 including 24 hydrogen atoms with isotropic temperature factors.$^{8)}$ The molecular structure of 1 thus obtained is illustrated in Chart 1 and Fig. 1.

These results indicate that the absolute configuration of 1 should be represented as 2 or its mirror image. In order to clarify this point, norketone (5)$^{5)}$ was prepared as a colorless oil by ozonolysis of 1 and subjected to CD spectral determination. The following data were obtained: $C_{14}H_{22}O_3$; $[\alpha]_D^{30}$ -62.76° (c = 0.813, $CHCl_3$); high-resolution MS m/z: 238.1556 (Theor. 238.1563 for $C_{14}H_{22}O_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3568 (OH), 3378 (OH, bonded), 1708 (C=O).

The ozonolysate (5) exhibited a negative Cotton effect, $[\theta]_{294}^{25}$ -1423 (c = 0.01 , dioxane). Application of the octant rule suggests that the absolute configuration of 1 should be expressed as 2 in Chart 1. The α-configuration of the isopropyl side chain in 2 has not always been found in the sesquiterpenoids as expected from the biogenetic viewpoint in higher plants. In addition, the relative configurations at C-1, C-4, C-5 and C-8 of isocurcumenol$^{9)}$ given as 6$^{10)}$ are in sharp contrast to the corresponding stereochemistry of curcumol (2) deduced as described above.

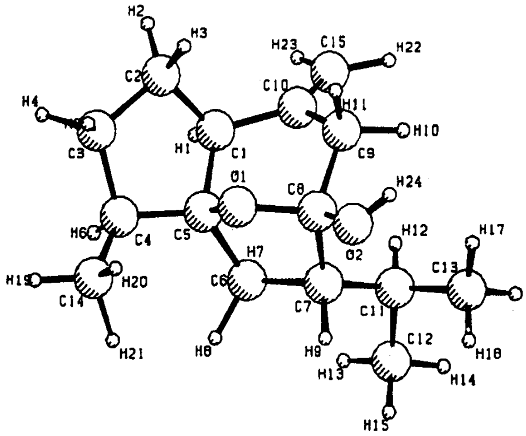

Fig. 1. Perspective View of Curcumol (2)

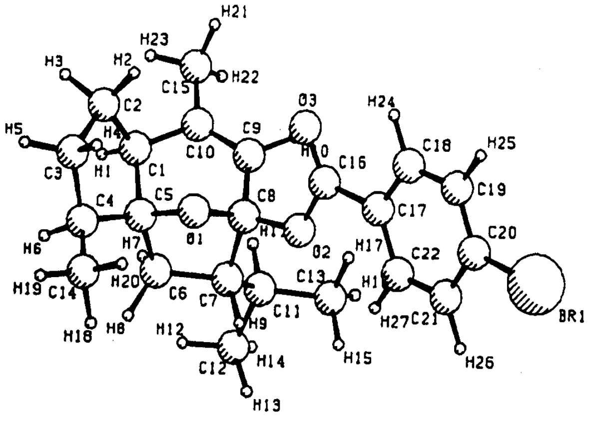

Fig. 2. Perspective View of p-Bromobenzoate (4)

Since we thought it would be safer to acquire further conclusive proof of the absolute configuration of 1, its p-bromobenzoate (4) was prepared (p-BrC_6H_4COCl/pyridine, reflux, overnight) for X-ray crystallographic analysis. A minor crystalline p-bromobenzoate (4) was obtained besides the major oily derivative (3). The data for 4 are: $C_{22}H_{27}O_3Br$; mp 122.5-124.5°C; $[\alpha]_D^{28.8}$ -7.42° (c = 1.885, $CHCl_3$); IR ν_{max}^{KBr} cm^{-1}: 1740 (benzoate C=O), 1594 (arom.); high-resolution MS m/z: 418.1137 (Theor. 418.1135 for $C_{22}H_{27}O_3Br$), 420.1112 (Theor. 420.1115 for $C_{22}H_{27}O_3{}^*Br$); ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, d, J = 6.4 Hz, >CH-CH_3), 0.99, 1.01 (3H x 2, each d, J = 6.4 Hz, -CH$(CH_3)_2$), 1.74 (3H, d, J = 1.2 Hz, $=\overset{|}{C}-CH_3$), 5.65 (1H, d, J = 1.2 Hz, $-HC=\overset{|}{C}-CH_3$), 7.57 (2H, d, J = 8.4 Hz, arom.-H), 7.90 (2H, d, J = 8.4 Hz, arom.-H). For comparison, the following data characteristic of the exo-methylene group of 3 are given: $C_{22}H_{27}O_3Br$; $[\alpha]_D^{30}$ + 46.2° (c = 1.300, $CHCl_3$); IR ν_{max}^{KBr} cm^{-1}: 3080, 1648, 890; ^{1}H-NMR ($CDCl_3$) δ: 4.91 (2H, brs).

The absolute configuration of 4 was determined by the anomalous dispersion of the bromine atom for CuKα radiation. The crystal data are: p-Bromobenzoate (4), $C_{22}H_{27}O_3Br$, MW = 419.4, orthorhombic, space group $P2_12_12_1$, lattice constants a = 13.004(7), b = 13.442(8), c = 11.875(6) Å, U = 2076 Å^3, Z = 4, D_{calc} = 1.342 gcm^{-3}. Intensity data were collected by graphite monochromated CuKα radiation of the total of 2311 reflections measured within the 2θ angle of 156°; 1908 were used for the structure determination as they exceed the 2σ(I) level. The structure was determined by the heavy atom method and refined by the method of least-squares. Of the total of 76 Friedel pairs, 66 pairs clearly showed the absolute configuration. The final R value was 0.043 taking into account the contributions of 27 hydrogen atoms and dispersion corrections. The absolute structure of 4 was deduced as depicted in Chart 1 and in Fig. 2 drawn by the PLUTO program.[11] Hence, the absolute configuration of 1 should be expressed as 2, and is in agreement with that deduced from the CD analysis of 5.

The complete stereostructure of curcumol was thus determined as 2. It is of special interest that curcumol possesses the unusual α-oriented isopropyl side chain.[12] Further study of the biogenetic scheme of 1 is now in progress.

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8) The lists of atomic coordinates, bond lengths and bond angles have been sent to Cambridge Crystallographic Data Centre. Those of $|F_{obs}|$ and $|F_{calc}|$ may be obtained from one of the authors (Y.I.) upon request.

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11) PLUTO, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW.

12) One cannot deny the possibility that curcumol (1), possessing the thermodynamically more stable α-oriented isopropyl side chain, might be derived artificially by epimerization of the hypothetical curcumol having the β-oriented isopropyl group in the course of the distillation of the crude extract obtained from the original plant material.

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