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CRYSTAL STRUCTURE OF HINOKIOL ISOLATED FROM *Isodon henryi*

Bao-Lin Li, Guang-hui Tian, Zhen-guo Zhang, Bo Liang, and Wei Wang

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Hinokiol was isolated for the first time from Isodon henryi *and the structure was elucidated on the basis of IR and NMR spectra analysis. Its molecular configuration, conformation, and crystal structure were also characterized by X-ray structure analysis. The infrequent H-π stacking and hydrogen bonding assemble the molecules of hinokiol into a three-dimensional network structure.*

Key words: hinokiol, *Isodon henryi*, X-ray structure analysis, H-π stacking.

Previously some diterpenoids with various biological activities, such as anti-HIV [1], antitumor, and inhibition of insect growth, were discovered from medicinal plants of *Isodon henryi* [2]. To find new biological activity compounds, recently we continued to investigate the chemical constituents of *Isodon henryi* collected on the Taibai Mountain of Shaanxi Province in China, which led to the first isolation of hinokiol from this plant. Hinokiol (**1**) belongs to the minor diterpenoid constituents in plant, but it showed inhibitive effects for *Staphylococcus aureus*, *Streptococcus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Proteus resp* [3]; it also inhibited *yeast*, *aspergillus*, *strawberry-derived fungus*, some *mushrooms*, etc. [4], and is a crucial antibacterial precursor. The molecular structure and stereochemistry of **1** was studied previously by chemical means, which is an intricate work [5, 6], and by NMR spectra [7]. But those methods did not give an unambiguous confirmation of the configuration and conformation of **1**, so we performed a single-crystal X-ray structure analysis (XSA) of hinokiol. Figure 1 shows the molecular structure of hinokiol from X-ray diffraction analysis.

The fusion of three rings (A, B, C) is evident in the molecular of hinokiol, and only the C ring is the benzene ring as judged from the NMR spectra and the bond lengths and angles obtained from XSA. In this molecule, the A ring is in chair conformation, and the B ring is in the envelope conformation with C6 and C5 deviating from the coplane of C7, C8, C9, C10. The C10 and C7 are coplanar with the C ring, so the envelope conformation B ring is almost coplanar with the C ring except for C5 and C6 of the B ring. There are three asymmetric carbon atoms C3, C5, and C10 in the molecule of **1**. Their configuration is shown in Fig. 1. The hydrogen attached to C5 is in the β-axial orientation, and the hydroxyl at C3 is in the α-equatorial orientation.

The molecules of the title compound are packed in three-dimensional structure in the crystal by H-bonds and H-π stacking. The O-H…O hydrogen bonds between the hydroxyl at C12 and the hydroxyl at C3 of the other molecule [O2…O1 (-x, -1/2+y, 1.5-z): 2.746 Å, H1…O2: 1.943 Å, and angle of O1-H1…O2: 166.33°] lead to **1** in a screw chain arranged along the *b* axis.

It is interesting that H-π stacking emerges in the packing, the hydrogen (H2) of the hydroxyl (O2-H2) at C3 is very near the neighboring benzene ring at the other molecule, and the infrequence of H-π stacking the following properties: the distance between O2 and the center of the benzene ring in the other molecule is 3.808 Å, the distance from H2 to this center is 3.012 Å, and the angle of O2-H2 from the center is 164.47°. The best near distance from H2 to the C ring in the other molecule is 2.537 Å and from O2 to this C ring is 3.247 Å. H-π stacking is another an important intermolecular interaction. In this crystal, H-π stacking interactions contact the screw chain resulting from H-bonds and lead to a three-dimensional network structure.

School of Chemistry and Materials Science, and The Key Laboratory of Medicinal Plant Resource & Natural Pharmaceutical Chemistry of the Ministry of Education, Shaanxi Normal University, Xi′an 710062, P.R. China. Published in Khimiya Prirodnykh Soedinenii, No. 3, pp. 229-230, May-June, 2007. Original article submitted March 15, 2006.

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TABLE 1. Crystal Data and Structure Refinement for Hinokiol

Chemical formula	$C_{20}H_{30}O_2$
Formula weight	302.44
Temperature	273 (2) K
Wavelength	0.71073 Å
Crystal system	orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	a = 7.3811 (7) Å
	b = 11.8183 (12) Å
	c = 19.868 (2) Å
	$\alpha = \beta = \gamma = 90.00°$
Volume	1733.2 (3) $Å^3$
Z, calculated density	4. 1.159 $mg \cdot m^{-3}$
Absorption coefficient	0.072 mm^{-1}
F (000)	664
Crystal size	0.42 × 0.32 × 0.30 mm
θ range for data collection	2.00-25.10°
Limiting indices	-8≤h≤8, -14≤k≤14, -21≤I≤23
Reflections collected/unique	8897/3088[R(int) = 0.0177]
Completeness to q = 25.10°	99.8%
Absorption correction	multi-scan
Max. and min transmission	0.9787 and 0.9704
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3088/0/207
Goodness-of-fit on F^2	1.070
Final R indices [I>2δ (I)]	RI = 0.0297, ωR2 = 0.0787
R indices (all data)	RI = 0.0354, ωR2 = 0.0814
Largest diff. Peak and hole	0.118 and -0.113 e. A^{-3}

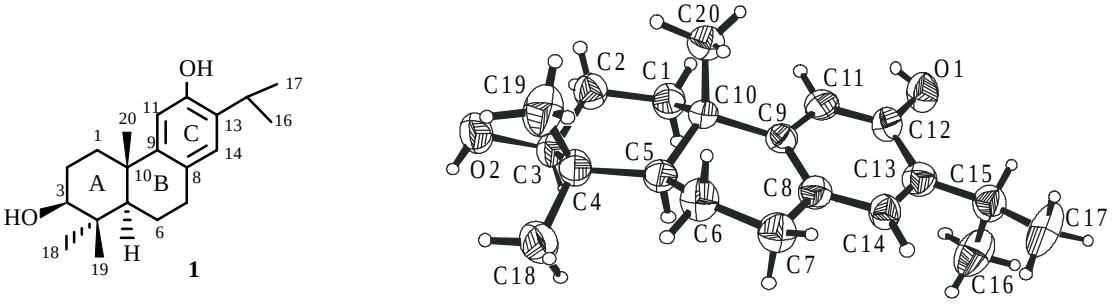

Fig 1. The molecular structure of hinokinol showing 50% probability displacement ellipsoids

EXPERIMENTAL

The leaf and branch of *Isodon henryi* (Hemsl.) Kudo were collected from the Taibai Mountain of Shaanxi Province in China, July 2005, and identified by comparing them with a voucher specimen (SNU 97-08-03, Li) deposited at the Biology Department of Shaanxi Normal University, Xi′an, China. All chemicals used were of analytical reagent grade and were used directly. The dry powders (12.6 kg) of the leaf and branch of *Isodon henryi* were extracted for 36 h with 75% ethanol (11 L) three times. The ethanol-soluble portion of the extraction mixture was dried on a rotary evaporator under reduced pressure and subjected to silica-gel (200~300 mesh, 3.1 kg) column chromatography (1200 cm × 175 cm). The column was eluted with $CHCl_3$, $CHCl_3$–Me_2CO (9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9), and Me_2CO. Each eluent was collected as a 250 mL fraction. All components were also purified by silica-gel column. Hinokiol was eluted and obtained from the fraction with $CHCl_3$–Me_2CO (8:2) and recrystallized from methanol to yield colorless prism crystals (1.37 g).

The IR was recorded as KBr pellets on a Nicolet 170SX FT-IR spectrophotometer. The melting point was determined using a WRS-113 digital melting point instrument (the thermometer was not emended). The ^{1}H NMR, ^{13}C NMR, and 135° DEPT spectra were recorded on a Bruker AM-300 spectrometer with TMS as internal reference and acetone-d_6 as solvent. Hinokiol was assigned the molecular formula $C_{20}H_{30}O_2$, mp: 233–235°; IR (ν_{max} ,KBr, cm^{-1}): 3510, 3280, 2930, 1600, 1410, 1450, 1500, 1210. Its ^{1}H NMR (acetone-d_6, 300 MHz, ppm) spectrum showed the following δ: 6.77 (1H, br.s, H-11), 6.72 (1H, s, H-14), 3.33(1H, dd, H-3α), 3.30 (1H, dd, H-7β), 2.81 (1H, dd, H-6α), 2.79 (1H, m, H-7α), 1.25, 1.18 (each 3H, d, Me-17, Me-16), 1.14, 1.05, 0.869 (each 3H, s, Me-20, Me-18 and Me-19). ^{13}C NMR δ: 37.0 (t, C-1), 27.8 (t, C-2), 77.5 (d, C-3), 38.8 (C-4), 50.2 (d, C-5), 19.0 (t, C-6), 29.9 (t, C-7), 131.8 (s, C-8), 147.5 (s, C-9), 38.8 (C-10), 110.5 (d, C-11), 152.3 (s, C-12), 125.2 (C-13), 126.1 (d, C-14), 29.2 (d, C-15), 22.1 (q, C-16), 22.0 (q, C-17), 24.3 (q, C-18), 15.2 (q, C-19), 26.5 (q, C-20). The type of carbon atoms substitution was determined by 135° DEPT experiment. These data were in agreement with the hinokiol structure data in the literature [7, 8].

The crystals of hinokiol for X-ray diffraction analysis were obtained by slow evaporation from methanol solution after five days at room temperature. The data were collected with graphite-monochromated Mo/Kα radiation (λ = 0.71073 Å) on a Bruker Smart-1000 CCD diffractometer at room temperature. The structure was solved using direct methods and refined by full-matrix least-squares techniques. All non-hydrogen atoms were assigned anisotropic displacement parameters in the refinement. All hydrogen atoms were added at calculated positions and refined using a riding model. The structure was refined on F^2 using the SHELXTL-97; the final R index (on F^2) was 0.0297. The crystals used for the diffraction study showed no decomposition during data collection. The crystal data and some details of the structure determination are summarized in Table 1. Data from the X-ray structure analysis were deposited as a CIF-file in the Cambridge crystallographic Data Center (No. CCDC 299271).

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