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Stable Conformations of Hinokitiol and Tropolone

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Abstract

Hinokitiol (6-isopropyltropolone; IUPAC nomenclature: 2-hydroxy-4-isopropyl-2,4,6-cycloheptatrien-1-one; $C_{10}H_{12}O_2$) has strong insecticidal and phytogrowth-inhibitory activities, and has a much more stable conformation than related brominated compounds. The hinokitiol molecule adopts a planar form and the two O atoms are hydrogen bonded to symmetry-related molecules. Furthermore, the tropolone ring is stacked with another symmetry-related tropolone ring, so that the molecule may be stabilized by resonance energy.

Comment

Hinokitiol (I) (Nozoe, 1936), one of the tropolone (II) (Dewar, 1945) related compounds, was isolated by T. Nozoe from the wood of *Chamacyparis taiwanesis*. Since then the compound has been reported to show the following biological activities: phytogrowth-inhibitory activity (Inamori *et al.*, 1991), antimicrobial effects (Okazaki & Homma, 1953; Taga & Ozaki, 1955; Katsura, Tamura, Hatori & Maeda, 1948; Shibasaki & Terui, 1955; Erdtmann & Gripenberg, 1948), plant growth stimulation, and repellent effects on ticks. (II) was also found to have inhibitory activity on tumour cells *in vitro* (Yamato, Hashigaki, Kokubu, Tsuruo & Tashiro, 1984; Yamato, Hashigaki, Kokubu, Tashiro & Tsuruo, 1986) and exterminatory effects on termites on logs. Recently, the authors reported the inhibitory effect of both compounds on the growth of mammalian cells and on blastogenesis of mouse splenic T cells (Inamori *et al.*, 1993). There have been many reports on the chemical reactions of (II) because of its unique chemical structure. Regarding compound (I), only three structures of hinokitiol derivatives [3,7-dibromohinokitiol (III) (Ito, Fukazawa & Iitaka, 1972*a*); 3,5,7-tribromohinokitiol (IV) and 5,7-dibromohinokitiol (Ito, Fukazawa & Iitaka, 1972*b*)] have been determined by X-ray diffraction methods; furthermore, conformational data about 5,7-dibromohinokitiol were not reported. We cannot clarify the mechanisms of biological activity of hinokitiol, because the structure of hinokitiol is still unknown.

(I)   (II)

(III)   (IV)
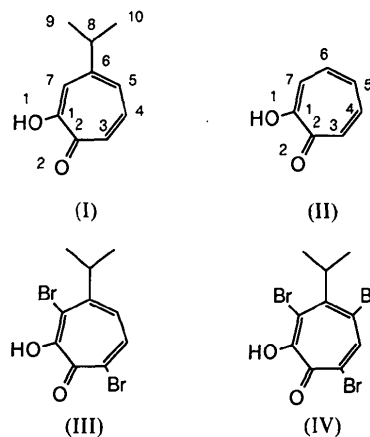
The molecular structure of 4-isopropyltropolone has been reported (Derry & Hamor, 1972). Since hinokitiol is extracted from different material to 4-isopropyltropolone and the activities of those materials are different, we have not compared hinokitiol with 4-isopropyltropolone.

In this work, as a preliminary step to elucidating the relationship between the biological activity of hinokitiol and its conformation, we analysed the structure of hinokitiol by X-ray diffraction. The molecular structure of hinokitiol including H atoms is presented in Fig. 1. Bond distances and angles coincide, to within experimental error, with those of 3,7-dibromohinokitiol and 3,5,7-tribromohinokitiol. Torsion angles involving non-H atoms are listed in Table 2. Side drawings viewed from the C6—C7 bonds of the three compounds are shown in Fig. 2. A stereoscopic diagram of the crystal packing of

hinokitiol is shown in Fig. 3 (c-axis projection). As can be seen from Figs. 1 and 3, the hinokitiol molecule adopts a planar form and the O1 atom of the tropolone ring and the O2 atom of the symmetry-related molecule are hydrogen bonded to each other (O1—H···O2 2.82 Å), forming hydrogen-bond networks in the cell. Furthermore, the tropolone ring is stacked with another symmetry-related tropolone ring at an interplanar spacing of 3.3 Å and the molecule is resonance-energy stabilized. Fig. 2 shows that 3,7-dibromohinokitiol and 3,5,7-tribromohinokitiol form boat conformations with atoms C2, C3, C6 and C7 in the same plane, and atoms C1 and C5 on the upper side of the plane; therefore, these two compounds are not stabilized by stacking interactions.

As seen in Fig. 2, the angle between the planes formed by C1, C2 and C7, and C2, C3, C6 and C7 is 19.2° in 3,5,7-tribromohinokitiol, 11.2° in 3,7-dibromohinokitiol and 0° in hinokitiol. The angles
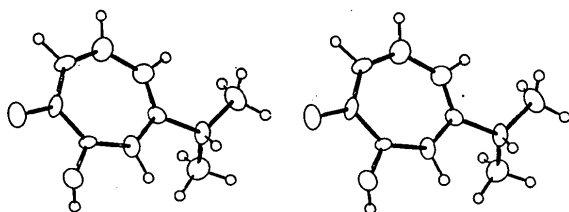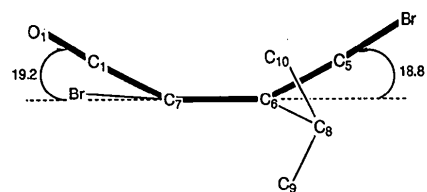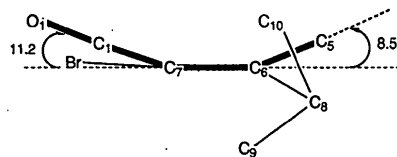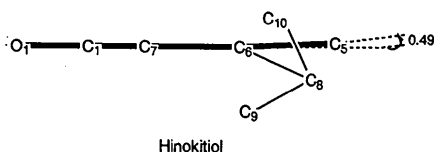

Fig. 3. A stereoscopic packing diagram (PLUTO; Motherwell & Clegg, 1978) of hinokitiol viewed along the c axis.

between the plane formed by C5, C4 and C6, and that formed by C2, C3, C6 and C7 are 18.8, 8.5 and 0.49° for the three compounds, respectively. From these results we believe that the extent of bromination may be very important for the stability and conformational changes in hinokitiol. Investigations of the relationships between the conformation of hinokitiol-related compounds and their various insecticidal and phytogrowth-inhibitory activities, and design of a new compound are in progress.

Fig. 1. An ORTEPII (Johnson, 1976) diagram of hinokitiol.

3,5,7-Tribromohinokitiol

3,7-Dibromohinokitiol

Hinokitiol

Fig. 2. The wire frame models of hinokitiol, 3,7-dibromohinokitiol and 3,5,7-tribromohinokitiol which contain the angles between the plane consisting of atoms C1, C2 and C7, or C5, C4 and C6, and that formed by atoms C2, C3, C6 and C7.
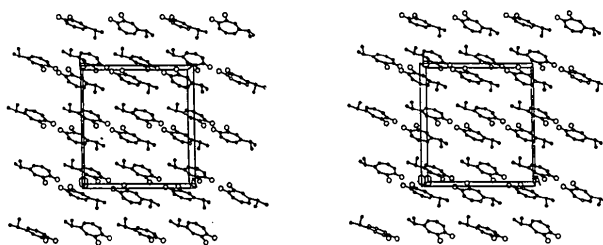
Experimental

Crystal data

$C_{10}H_{12}O_2$	D_x = 1.2428 Mg m^{-3}
M_r = 164.204	Cu $K\alpha$ radiation
Monoclinic	λ = 1.5418 Å
$I2/b$	Cell parameters from 25
a = 15.968 (2) Å	reflections
b = 17.035 (3) Å	θ = 29.49–25.09°
c = 6.453 (1) Å	μ = 6.54 mm^{-1}
γ = 90.75 (1)	T = 293 K
V = 1755.2 (5) Å^3	Platelet
Z = 8	0.50 × 0.50 × 0.20 mm
	Colourless

Data collection

Rigaku automated four-circle diffractometer	1014 observed reflections [$F > 3.0\sigma(F)$]
ω–2θ scans	θ_{max} = 62.5°
Absorption correction:	h = −18 → 18
empirical (North, Phillips & Mathews, 1968)	k = −20 → 0
	l = 0 → 6
T_{min} = 0.83, T_{max} = 0.93	4 standard reflections
2182 measured reflections	monitored every 100
1143 independent reflections	reflections
	intensity variation: 7.8%

Refinement

Refinement on F	$w = 1/[\sigma^2(F_o) - 4.06302F_o$
R = 0.0564	$+ 0.17053F_o^2]$
wR = 0.0576	$(\Delta/\sigma)_{max}$ = 0.11
S = 1.232	$\Delta\rho_{max}$ = 0.31 e Å^{-3}
1014 reflections	$\Delta\rho_{min}$ = −0.11 e Å^{-3}
110 parameters	Atomic scattering factors
Only coordinates of H atoms refined	from International Tables for X-ray Crystallography (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å²)

$$B_{eq} = (4/3)\Sigma_i\Sigma_j\beta_{ij}\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	B_{eq}
O2	0.7270 (3)	0.0274 (3)	0.6011 (8)	4.2 (3)
O1	0.6228 (3)	0.0094 (3)	0.8948 (8)	3.9 (3)
C1	0.5954 (3)	0.0490 (4)	0.726 (1)	2.2 (3)
C2	0.6560 (3)	0.0577 (4)	0.560 (1)	3.0 (3)
C3	0.6380 (4)	0.0959 (5)	0.364 (1)	3.4 (4)
C4	0.5679 (4)	0.1329 (4)	0.296 (1)	4.0 (4)
C5	0.4903 (4)	0.1456 (4)	0.405 (1)	3.5 (4)
C6	0.4648 (4)	0.1187 (4)	0.597 (1)	2.4 (3)
C7	0.5136 (3)	0.0750 (4)	0.743 (1)	2.9 (3)
C8	0.3787 (3)	0.1378 (4)	0.679 (1)	3.1 (3)
C9	0.3148 (4)	0.1656 (5)	0.517 (1)	4.3 (4)
C10	0.3837 (4)	0.1971 (6)	0.852 (1)	5.3 (5)

Table 2. *Geometric parameters* (Å, °)

O2—C2	1.279 (8)	C4—C5	1.44 (1)
O1—C1	1.359 (8)	C5—C6	1.38 (1)
C1—C2	1.447 (9)	C6—C7	1.437 (9)
C1—C7	1.390 (9)	C6—C8	1.514 (9)
C2—C3	1.46 (1)	C8—C9	1.54 (1)
C3—C4	1.36 (1)	C8—C10	1.51 (1)
O1—C1—C2	115.1 (4)	C4—C5—C6	129.5 (4)
O1—C1—C7	113.8 (4)	C5—C6—C7	127.0 (4)
C2—C1—C7	131.1 (4)	C5—C6—C8	120.5 (4)
O2—C2—C1	113.7 (4)	C7—C6—C8	112.4 (4)
O2—C2—C3	122.8 (4)	C1—C7—C6	129.0 (4)
C1—C2—C3	123.5 (4)	C6—C8—C9	115.7 (4)
C2—C3—C4	131.0 (4)	C6—C8—C10	111.3 (4)
C3—C4—C5	128.6 (5)	C9—C8—C10	109.2 (5)
O1—C1—C2—O2	−0.8 (5)	C3—C4—C5—C6	−5.6 (8)
O1—C1—C2—C3	178.0 (7)	C4—C5—C6—C7	4.8 (7)
C7—C1—C2—O2	178.1 (8)	C4—C5—C6—C8	−178.4 (8)
C7—C1—C2—C3	−3.0 (6)	C5—C6—C7—C1	−1.2 (7)
O1—C1—C7—C6	179.6 (8)	C8—C6—C7—C1	−178.2 (8)
C2—C1—C7—C6	0.6 (7)	C5—C6—C8—C9	17.6 (6)
O2—C2—C3—C4	−178.0 (1)	C5—C6—C8—C10	−107.8 (7)
C1—C2—C3—C4	3.3 (8)	C7—C6—C8—C9	−165.2 (7)
C2—C3—C4—C5	0.9 (7)	C7—C6—C8—C10	69.4 (6)

Intensities were measured with a scan rate of 6° min⁻¹ in θ and a scan width of $\Delta\theta = (1.1 + 0.15\tan\theta)°$. Background intensities were measured for 3 s at the end of each scan. The structure was solved by direct methods using *MULTAN*87 (Debaerdemaeker, Germain, Main, Tate & Woolfson, 1987). The initial *E* map gave partial structure around the tropolone skeleton. Positions of the remaining non-H atoms were located stepwise from the subsequent Fourier syntheses. The structure was refined by a block-diagonal least-squares procedure. *The Universal Crystallographic Computation Program System – Osaka* (1979) was used for all calculations.

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Non-Steriodal Anti-Inflammatory Drugs. III. Structure of Indoprofen: 2-[4-(1-Oxo-2-isoindolinyl)phenyl]propionic Acid

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Abstract

Indoprofen, 4-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)-α-methylbenzeneacetic acid, $C_{17}H_{15}NO_3$, a nonsteroidal anti-inflammatory agent, falls into the class of phenylpropionic acids that includes ibuprofen, ketoprofen and flubirprofen. It adopts a planar conformation apart from the carboxylic acid group. There is a small twist of 8.8 (2)° between the mean planes of the isoindolinyl and phenyl rings. The rotation of the carboxyl group out of the plane of the adjacent phenyl ring seems to be connected with anti-inflammatory activity and is similar to that found in other 2-phenylpropionic acids. A pair of