Structure of 2′,6′-Dihydroxy-4,4′-dimethoxychalcone

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Abstract. 1-(2,6-Dihydroxy-4-methoxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one, $C_{17}H_{16}O_5$, $M_r = 300\cdot31$, orthorhombic, *Pbca*, $a = 27\cdot903$ (3), $b = 13\cdot958$ (2), $c = 7\cdot662$ (1) Å, $V = 2984$ (1) Å^3, $Z = 8$, $D_x = 1\cdot337$ Mg m^{-3}, $\lambda(\text{Cu } K\alpha) = 1\cdot5418$ Å, $\mu = 0\cdot729$ mm^{-1}, $F(000) = 1264$, $T = 295$ K, $R = 0\cdot040$ for 1702 observed reflections. Two intramolecular hydrogen bonds are observed. The hydroxyl H atom at O(6A) is hydrogen bonded to the C(9) carbonyl group with short distances O(6A)···O(9) = 2·406 (3) and O(9)···H(6A) = 1·38 (3), O(6A)—H(6A) = 1·09 (3) Å, the angle O(6A)—H(6A)···O(9) is 153 (4)°. The other hydrogen bond is of the C—H···O type with distances C(8)···O(2A) = 2·778 (4), H(8)···O(2A) = 2·09 (3) Å and the angle around H(8) is 124 (2)°. Conjugation is observed between the aromatic rings and the central enone system. The molecule is not planar, the angle between the planes of the phenyl rings being 13·1 (4)°. Intermolecular O—H···O bonds with distances O(6A)···O(2A) = 2·689 (2), H(2A)···O(6A) = 1·86 (4) Å and angle O(2A)—H···O(6A) = 176 (4)° form endless chains of molecules along **b**.

Introduction. 2′,6′-Dihydroxy-4′-methoxychalcone [Fig. 1, (I*a*)] and the title compound, 2′,6′-dihydroxy-4′,4-dimethoxychalcone [Fig. 1, (I*b*)] were isolated for the first time from the fern *Pityrogramma chrysophylla* (Nilsson, 1961), where they form the con-

spicuous orange–yellow 'farina' on the lower frond surface. Both compounds are known to be characteristic leaf exudate constituents in a number of ferns (fam. Pteridaceae *sensu* Tyron) (Wollenweber, 1978), but so far only the monomethoxychalcone (I*a*) has been reported to occur rarely in flowering plants (Wollenweber & Dietz, 1981).

In the course of investigating structure–function relationships of allergenic flavonoids and related plant constituents (Schmalle, Jarchow, Hausen & Schulz, 1986), the chalcones (I*a*) (I*b*) and the dihydrochalcone (II) were tested for their allergenicity. (I*a*) and (I*b*) showed a moderate sensitizing capacity, while the dihydrochalcone (II) was a weak sensitizer. Incorrect structural formulae were presented for the chalcones and the dihydrochalcones
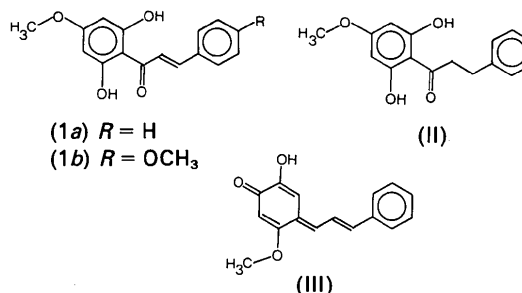

(1*a*) R = H
(1*b*) R = OCH₃

(II)

(III)

Fig. 1. Sensitizing chalcones (I*a*), (I*b*) and a dihydrochalcone (II) compared with the toxic and strong allergenic quinonemethide obtusaquinone (III).

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(Chart II, 11–13) in that paper (Schmalle et al., 1986), as the usual numbering for flavonoids was applied rather than the particular numbering for chalcones/dihydrochalcones. Fig. 1 gives the correct structures of these compounds.

The X-ray structure analysis of (Ib) has been performed in order to compare structural properties of sensitizing flavonoids with chalcones and similar compounds, e.g. obtusaquinone (Karle, Bultman & Jurd, 1976). The latter is known to be a strong contact allergen as determined from occupational contact with the tropical tree Dalbergia retusa Hemsl. (cocobolo) (Hausen & Münster, 1983).

Experimental. A mixture of (Ia) and (Ib) was separated by thin-layer chromatography and the sample of (Ib) was crystallized from benzene at 255 K. The red crystal used for the measurements had dimensions 0·16 × 0·35 × 0·48 mm. Enraf–Nonius CAD-4 diffractometer, graphite-monochromatized Cu $K\alpha$ radiation. Unit-cell parameters were obtained from least-squares refinement of 23 reflections in the interval $24 < \theta < 42°$. Intensities of 2748 reflections (excluding standards) in the interval $0 < h < 31$, $-15 < k < 3$, $0 < l < 8$ with θ between 2 and 60° were collected using the ω–2θ scan technique. The scan rate varied from 0·3 to 20·0° min^{-1}, maximum measuring time 240 s. Two standard reflections were monitored every 2 h of measuring time, no loss of intensities observed. Orientation was controlled every 500 reflections using four standard reflections. Data reduction led to 2215 unique reflections (1066 reflections averaged, $R_{int} = 0·023$). The data were corrected for Lorentz and polarization effects, but not for absorption effects. 1702 reflections with $I > 3\sigma(I)$ [$\sigma(I)$ based on counting statistics] were considered observed. The phase problem was solved by using the direct-methods program MULTAN80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980). Full-matrix least-squares refinement on F; anisotropic temperature factors for C and O atoms. All H-atom positions were located from difference Fourier maps and were included in the refinements with varying positional and isotropic displacement parameters. 1702 reflections in final refinement cycle; 264 parameters [extinction parameter after Stout & Jensen (1968) converged at 7·6 (1) × 10^{-7}], minimizing $\sum w[(F_o) - (F_c)]^2$ with $w = [\sigma^2(F_o)]^{-1}$, final $R = 0·040$, $wR = 0·042$, $S = 1·19$, $(\Delta/\sigma)_{max} = 0·15$ (H-atom parameter) and 0·12 (non-H-atom parameter), max. height in final difference Fourier synthesis 0·14 e Å^{-3}. Atomic scattering factors and dispersion corrections were taken from International Tables for X-ray Crystallography (1974). All calculations performed on a PDP 11/34 computer using the SDP program system (Frenz, 1983); plots were prepared with ORTEP

Table 1. *Positional and equivalent isotropic thermal parameters* ($Å^2$) *for 2',6'-dihydroxy-4,4'-dimethoxy-chalcone*

	x	y	z	B_{eq}*
O(2A)	0·53225 (7)	0·6172 (1)	0·7192 (3)	4·66 (5)
O(4A)	0·39313 (7)	0·4782 (2)	0·9471 (3)	5·22 (5)
O(6A)	0·50785 (8)	0·2802 (1)	0·6640 (3)	5·30 (5)
O(4)	0·80180 (7)	0·7411 (2)	0·4097 (4)	6·15 (6)
O(9)	0·57900 (8)	0·3508 (1)	0·5417 (3)	5·09 (5)
C(1)	0·6860 (1)	0·5562 (2)	0·4683 (4)	3·96 (7)
C(2)	0·6867 (1)	0·6490 (2)	0·5360 (5)	4·80 (8)
C(3)	0·7257 (1)	0·7073 (2)	0·5158 (5)	5·40 (8)
C(4)	0·7653 (1)	0·6766 (2)	0·4242 (5)	4·46 (7)
C(5)	0·7658 (1)	0·5861 (2)	0·3527 (5)	4·79 (8)
C(6)	0·7262 (1)	0·5276 (2)	0·3753 (5)	4·71 (8)
C(7)	0·6462 (1)	0·4907 (2)	0·4923 (5)	4·45 (7)
C(8)	0·6056 (1)	0·5074 (2)	0·5774 (5)	4·12 (7)
C(9)	0·5693 (1)	0·4331 (2)	0·6006 (4)	3·75 (6)
C(1A)	0·5241 (1)	0·4482 (2)	0·6899 (4)	3·52 (6)
C(2A)	0·5058 (1)	0·5372 (2)	0·7495 (4)	3·62 (6)
C(3A)	0·4625 (1)	0·5440 (2)	0·8318 (4)	3·90 (7)
C(4A)	0·4351 (1)	0·4626 (2)	0·8624 (4)	3·85 (7)
C(5A)	0·4505 (1)	0·3740 (2)	0·8075 (5)	4·18 (7)
C(6A)	0·4938 (1)	0·3678 (2)	0·7212 (4)	4·01 (7)
C(41)	0·8449 (1)	0·7103 (3)	0·3244 (6)	6·20 (9)
C(41A)	0·3629 (1)	0·3977 (3)	0·9771 (6)	6·08 (9)

* $B_{eq} = (4/3)[a^2B(1,1) + b^2B(2,2) + c^2B(3,3)]$.

(Johnson, 1971). The final atomic parameters are listed in Table 1.*

Discussion. Bond distances and angles are given in Table 2. The atom numbering of the molecule is shown in Fig. 2. The conformation of the molecule as well as bond lengths and angles are in good agreement with other chalcone structures (e.g. Rabinovich & Shakked, 1974, and references cited therein; Green, Rabinovich, Shakked, Hope & Swanson, 1981; Roychowdhury, 1984). The molecule consists of two phenyl planes connected via the enone plane. The shortening of each of the C(1)—C(7) and C(1A)—C(9) single bonds to 1·450 (4) Å is due to the conjugation of the C(7)=C(8) and C(9)=O(9) double bonds with the aromatic rings B and A, respectively. With respect to the enone moiety C(7), C(8), C(9), O(9), the molecule adopts the cis conformation about C(8)—C(9) which is observed for most of the chalcone structures (Rabinovich & Shakked, 1974). The deviations of O(4), C(41), C(7), C(8), C(9) and O(9) from the plane of ring B are 0·008 (3), −0·073 (4), −0·049 (3), −0·066 (4), −0·184 (4) and −0·321 (4) Å, respectively. The plane of the enone system shows maximum values of deviation of 0·011 (3) Å for C(8) and

Table 2. *Bond distances* (Å) *and angles* (°) *for 2',6'-dihydroxy-4,4'-dimethoxychalcone*

C(2A)—O(2A)	1·359 (3)	C(4)—C(5)	1·377 (4)
C(4A)—O(4A)	1·357 (4)	C(5)—C(6)	1·385 (4)
C(41A)—O(4A)	1·424 (5)	C(7)—C(8)	1·328 (4)
C(6A)—O(6A)	1·357 (3)	C(8)—C(9)	1·461 (4)
C(4)—O(4)	1·364 (4)	C(1A)—C(9)	1·450 (4)
C(41)—O(4)	1·435 (4)	C(1A)—C(6A)	1·425 (4)
C(9)—O(9)	1·264 (3)	C(1A)—C(2A)	1·419 (4)
C(1)—C(2)	1·395 (4)	C(2A)—C(3A)	1·366 (4)
C(1)—C(6)	1·388 (4)	C(3A)—C(4A)	1·389 (4)
C(1)—C(7)	1·450 (4)	C(4A)—C(5A)	1·375 (4)
C(2)—C(3)	1·368 (4)	C(5A)—C(6A)	1·380 (4)
C(3)—C(4)	1·377 (4)		

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C(1)—C(2)—C(3)	121·4 (3)	C(2A)—C(1A)—C(6A)	114·9 (3)
C(2)—C(3)—C(4)	120·7 (3)	C(2A)—C(1A)—C(9)	126·3 (3)
C(3)—C(4)—C(5)	119·8 (3)	C(6A)—C(1A)—C(9)	118·7 (3)
C(3)—C(4)—O(4)	115·8 (3)	C(1A)—C(2A)—C(3A)	121·9 (3)
C(5)—C(4)—O(4)	124·4 (3)	C(1A)—C(2A)—O(2A)	118·0 (3)
C(41)—O(4)—C(4)	117·7 (3)	C(3A)—C(2A)—O(2A)	120·1 (3)
C(4)—C(5)—C(6)	118·9 (3)	C(2A)—C(3A)—C(4A)	120·5 (3)
C(5)—C(6)—C(1)	122·7 (3)	C(3A)—C(4A)—C(5A)	120·8 (3)
C(6)—C(1)—C(2)	116·5 (3)	C(3A)—C(4A)—O(4A)	115·1 (3)
C(1)—C(7)—C(8)	127·2 (3)	C(5A)—C(4A)—O(4A)	124·1 (3)
C(7)—C(1)—C(2)	123·3 (3)	C(4A)—C(5A)—C(6A)	118·5 (3)
C(7)—C(1)—C(16)	120·2 (3)	C(5A)—C(6A)—C(1A)	123·4 (3)
C(7)—C(8)—C(9)	121·8 (3)	C(5A)—C(6A)—O(6A)	117·7 (3)
C(8)—C(9)—O(9)	117·0 (3)	C(1A)—C(6A)—O(6A)	118·9 (3)
C(8)—C(9)—C(1A)	123·9 (3)	C(7A)—O(4A)—C(41A)	117·5 (3)
C(1A)—C(9)—O(9)	119·1 (3)		
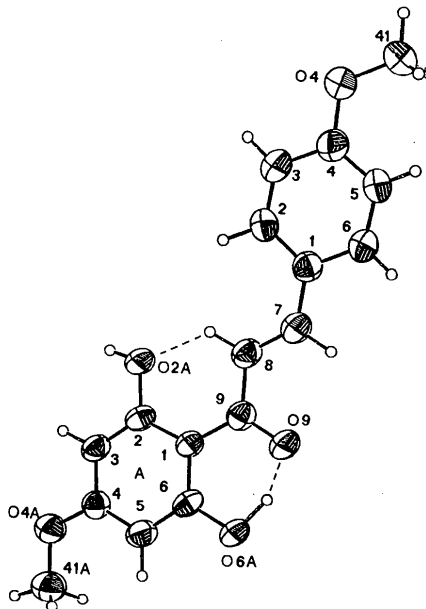
Fig. 2. Atom numbering and molecular conformation of 2',6'-dihydroxy-4,4'-dimethoxychalcone. The thermal ellipsoids are drawn at the 50% probability level (Johnson, 1971). Intramolecular hydrogen bonds are indicated by broken lines.

C(9). The deviations from the plane of ring A for O(6A), O(9), C(9), O(2A) and O(4A) are 0·048 (4), 0·100 (3), −0·013 (4), 0·020 (3) and −0·010 (3) Å. Selected dihedral angles are between the plane of ring B and the enone, 6·4 (3)°, between ring B and ring A, 13·1 (4)°, and between the enone and ring A, 6·7 (3)°.

A common feature of chalcone structures is their enone entity O=C—C=CHR. Experiments confirm that such groups in low-molecular-weight compounds (*e.g.* sesquiterpene lactones, quinones) can be attacked by nucleophiles to yield covalently bonded adducts (*e.g.* Kupchan, Fessler, Eakin & Giacobbe, 1970; Dupuis, Mitchell & Towers, 1974; Dupuis, Benezra, Schlewer & Stampf, 1980; Liberato, Byers, Dennick & Castagnoli, 1981). In the case of a contact allergy the nucleophiles are most probably functional groups of amino acids of receptor proteins, *e.g.* —SH of cysteine or —NH$_2$ of lysine. The assumption that the allergenic property of a compound is a result of a nucleophilic attack on the O=C—C=CHR entity rationalizes the sensitizing capacity of the title compound and structurally related chalcones. The strong allergenic quinone-methide obtusaquinone [Fig. 1, (III)] exhibits a similar shape and conformation to those found in the chalcones; the allergenic requisite O=C—C=CHR, however, is located in the quinonoid ring and occurs in the *trans* conformation about C(8)—C(9). In *O*-methylobtusaquinone (Palmer, Wong & Jurd, 1973), the position for the nucleophilic attack, C(5),

is hindered by the C(8) methyl group with the probability of diminishing or loss of its allergenic property.

A very short intramolecular hydrogen bond is observed for the title compound, O(6A)···O(9) = 2·406 (3), H(6A)···O(9) = 1·38 (3) Å. Other examples of very short intramolecular hydrogen bonds were discussed for lithium hydrogen phthalate–methanol (Adiwidjaja & Küppers, 1978) and for lithium maleate dihydrate (Popelier, Lenstra & Geise, 1989). The other intramolecular hydrogen bond (Fig. 2) is of the type C—H···O with C(8)···O(2A) and H(8)···O(2A) distances of 2·778 (4) and 2·09 (3) Å, respectively, the angle around H(8) being 124 (2)°. Only one intermolecular hydrogen bond of the form O(2A)—H(2A)···O(6A) is observed in the structure, forming endless chains of molecules along b. The distances O(2A)···O(6A) and H(2A)···O(6A) are 2·689 (2) and 1·86 (4) Å, symmetry operation 1 − x, 0·5 + y, 1·5 − z; the angle around H(2A) is 176 (4)°.

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Structure of 2-Methoxy-6-nonyl-1,4-benzoquinone, C₁₆H₂₄O₃, a Synthetic Contact Allergen Related to the Naturally Occurring Primin

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Abstract. $C_{16}H_{24}O_3$, $M_r = 264 \cdot 36$, triclinic, $P\bar{1}$, $a = 4 \cdot 167$ (1), $b = 9 \cdot 658$ (1), $c = 19 \cdot 093$ (1) Å, $\alpha = 89 \cdot 66$ (1), $\beta = 87 \cdot 27$ (1), $\gamma = 79 \cdot 07$ (1)°, $V = 753 \cdot 65$ (1) Å³, $Z = 2$, $D_x = 1 \cdot 165$ Mg m⁻³, λ(Cu $K\alpha$) $= 1 \cdot 5418$ Å, $\mu = 0 \cdot 595$ mm⁻¹, $F(000) = 288$, $T = 295$ K, R is 0·047 for 1682 observed unique reflections. The angle between the quinone ring plane and the mean plane defined by the aliphatic nonyl chain atoms is 17·4 (3)°. The average C_{sp^3}—C_{sp^3} bond distance and corresponding angle of the side chain are 1·522 (3) Å and 113·2 (2)°. The average dimensions of the quinone ring are C—C 1·485 (3), C=C 1·337 (3), C=O 1·209 (3) Å, C—C—C 118·4 (2), C=C—C 120·8 (2), O=C—C 120·8 (2)°. Neighboring molecules form dimers across centres of symmetry which are linked by C—H···O hydrogen