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7-Hydroxy-5-methoxy-6,8-dimethylflavanone: a natural flavonoid

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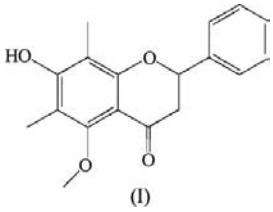
The title flavonoid [systematic name: (2*S*)-7-hydroxy-5-methoxy-6,8-dimethyl-2-phenyl-3,4-dihydrochromen-4(2*H*)-one], $C_{18}H_{18}O_4$, displays statistical conformational disorder, with three conformations of the molecule involving three orientations of the phenyl ring and two orientations of the fused heterocyclic ring. The conformational disorder is correlated with the isomerization equilibrium between the flavanone and chalcone forms. The conformational behaviour has a potential impact on the biological activity of this class of compounds. Moreover, π stacking interactions at van der Waals distances are present between the aromatic rings of chroman-4-one groups of symmetry-related molecules. Apart from these π–π interactions, molecules are linked by strong O—H···O hydrogen bonds between hydroxy and carbonyl groups.

Comment

Flavonoids are of interest because of their antioxidant activity (Pietta, 2000). However, it is now known that the health benefits they provide against cancer and heart disease are the result of other mechanisms (Dixon, 1999; Rice-Evans *et al.*, 1996). More than 5000 different flavonoids have been characterized from various plants and classified according to their chemical structures (Ververidis *et al.*, 2007). Flavanones are one of the subgroups. The title compound, (I), is a natural



(I)

flavanone isolated from the leaves of the South American tree *Couroupita guianensis*. It was reported previously as an anti-hyperglycaemic agent (Hanshella *et al.*, 2005).

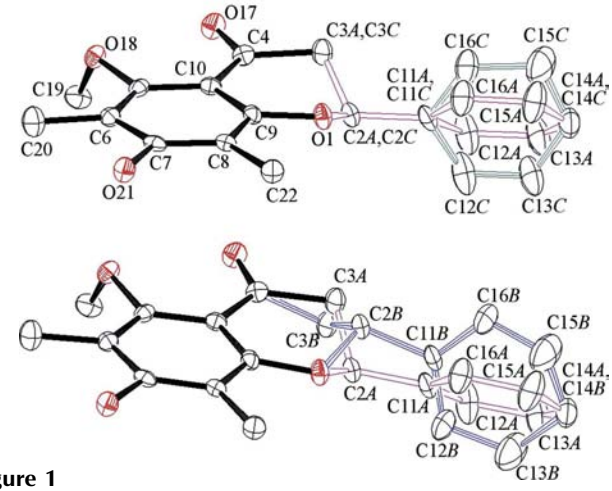


Figure 1
The atom-labelling scheme of (I). Displacement ellipsoids are drawn at the 50% probability level. The suffixes *A*, *B* and *C* denote the corresponding conformations. H atoms have been omitted for clarity.

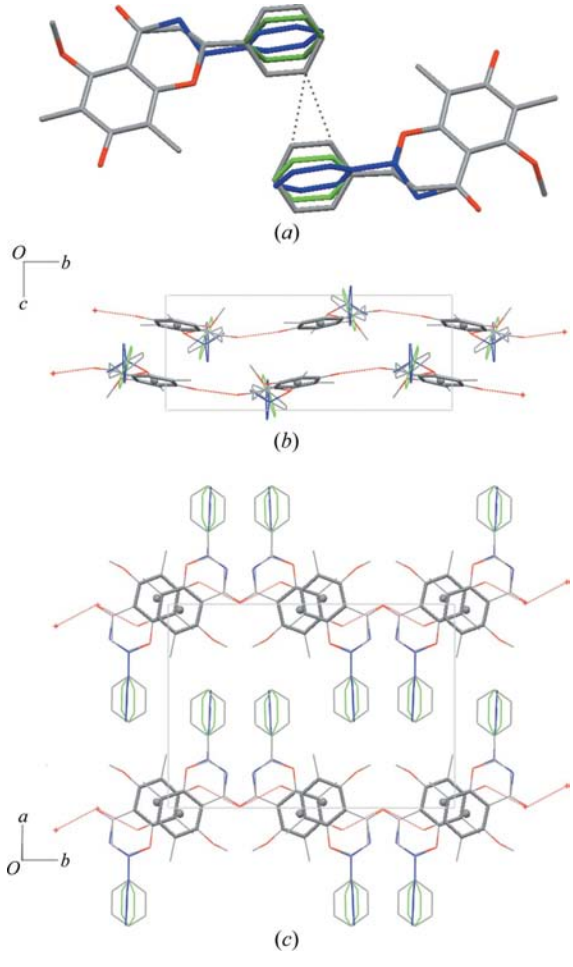


Figure 2
(*a*) Intermolecular short contacts between one molecule of conformation *A* of (I) (coloured grey in the electronic version of the paper) and another molecule with the same conformation at $(-x+1, -y, -z+1)$. (*b*) The crystal packing of (I), showing the hydrogen-bond network (dashed lines, in red in the electronic version of the paper). (*c*) The aromatic rings that constitute the weak intermolecular π–π interactions, and their calculated centroids where highlighted. (Conformations *B* and *C* are coloured blue and green, respectively, in the electronic version of the paper.)

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The two most similar structures reported in the Cambridge Structural Database (CSD; Allen, 2002), *viz.* (−)-6-bromocryptostrobin (Byrne *et al.*, 1982) and 6,8-dimethylpinocembrin (Tanrisever *et al.*, 1987), contain a disordered phenyl group. In the case of (I), it was necessary to include three different disordered conformations (labeled *A*, *B* and *C* in Fig. 1) involving three orientations of the phenyl ring and two orientations of the fused cyclohexyl ring in order to obtain a good refinement. According to the $(-x + 1, -y, z + 1)$ symmetry operation, conformation *A* by itself would exhibit overly short intermolecular contacts. Obviously these contacts cannot be real and we must consider these three conformations to correspond to a statistical disorder behaviour (Fig. 2*a*). The classical Cremer & Pople (1975) analysis of the heterocyclic nonplanar ring gives the ring-puckering parameters φ = 286.6 (5)° and θ = 53.9 (5)° and the puckering amplitude Q = 0.498 (5) Å for conformations *A* and *C*, and φ = 87.9 (10)°, θ = 131.0 (10)° and Q = 0.521 (13) Å for conformation *B*. Thus, the ring conformation varies between an envelope (*E*) for *A* and *C* and a symmetrical half-chair (*H*) for *B*. Such a pattern of conformational equilibrium for flavanone derivatives has been described in solution (Toth *et al.*, 2001) but not in the solid state as far we could find for previously reported flavanone derivatives. This behaviour seems to be associated with the isomerization equilibrium between the flavanone and chalcone forms (Gonzalez *et al.*, 2002). On this basis, (I) should be a good precursor for the chalcone opened chemical form, which has been reported as an antitumor agent (Ye *et al.*, 2005).

The structures of a number of flavanones (derived from 2,3-dihydro-2-phenylchromen-4-one) have been reported in the CSD. We can estimate the concordance between some internal geometric parameters of our structure and the data from 82 structures that include the flavanone chemical skeleton. In Fig. 3 we can see good concordance between some torsion angle values of the statistical conformations *A* and *C* of (I). It is of note that each torsion angle displays a bimodal distribution, indicating that the two conformations of the above-mentioned heterocyclic nonplanar ring are almost equally probable in flavanones. This behaviour suggests the movement of the involved bonds, and hence the isomerization equilibrium should be usual for flavanones.

The molecules of (I) are linked by O—H···O hydrogen bonds between the hydroxy group of one molecule and the carbonyl O atom of an adjacent molecule to form chains running along the *b* axis (Fig. 2*b*). The crystal stability of (I) seems to be enhanced by weak intermolecular interactions. Classical π–π contacts are present between the aromatic rings of neighbouring chroman-4-one groups (Table 3). These interactions generate stacked molecules running almost

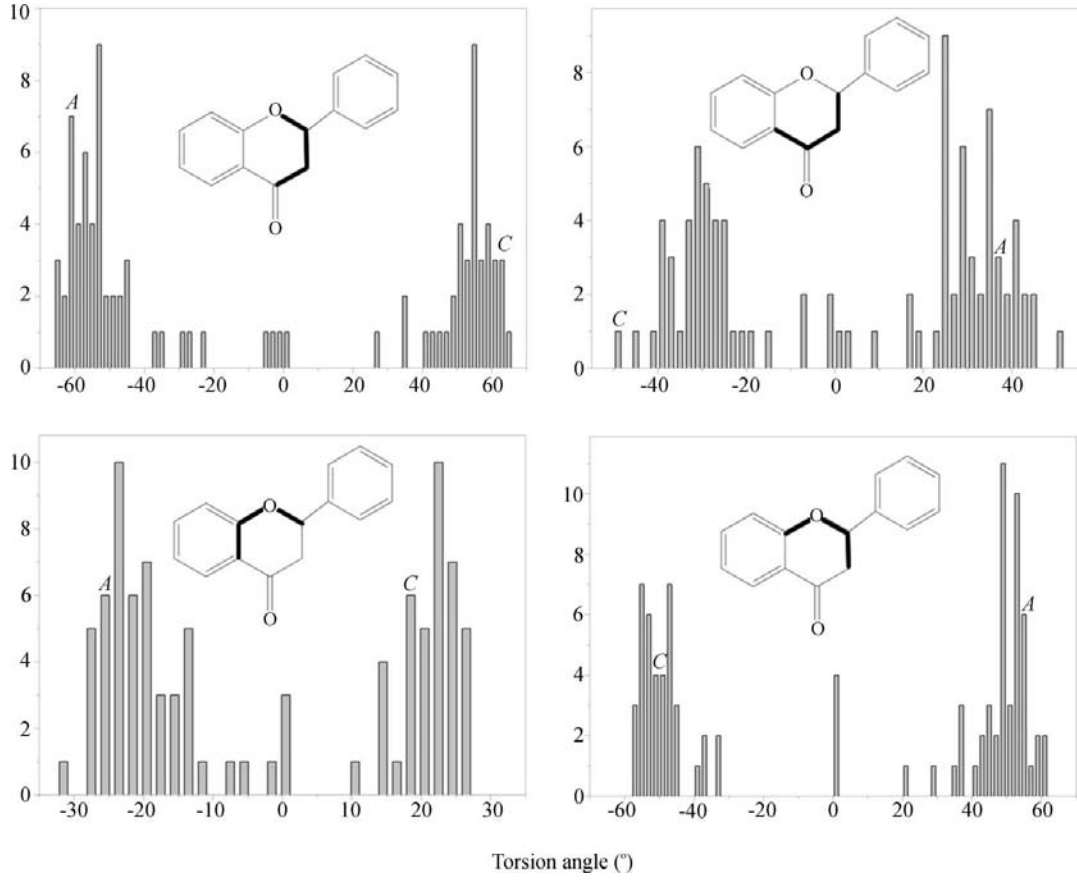

Figure 3
The frequencies of torsion angle values from CSD data. The torsion angles correspond to the highlighted atoms on the flavanone skeleton shown in each graph. The CSD search was related to the flavanone's chemical scheme. Labels *A* and *C* indicate the calculated angles corresponding to conformations *A* and *C* of (I), respectively.

parallel to the [001] crystal plane (Fig. 2*c*). This type of interaction seems to be common in flavanones since 11 of the 82 structures in the CSD display geometric parameters giving optimal π–π binding energy (McGaughey *et al.*, 1998), *i.e.* the aromatic rings stack almost parallel (with a dihedral angle between stacking planes of less than 1°) with centroid–ring distances of less than 4 Å, as in (I).

The strategy of self-assembly through these weak and strong interactions is of central importance for efficient and specific biological reactions, and for the design of new supramolecules possessing interesting physical or chemical properties. As an example, despite the fact that (I) exhibits a high degree of disorder, the crystals were stable and their diffraction was good. This behaviour has encouraged us to undertake a polymorph screening, in order to obtain different types of solid state and, therefore, different types of biochemical behaviour. Such studies will be reported in future publications.

Experimental

Compound (I) was obtained by purification of the hydroethanolic extract of the leaves of *C. guianensis*, using dichloromethane extraction and a silica-gel chromatographic column. Single crystals were obtained by evaporation from a chloroform solution. ^{1}H NMR ($CDCl_3$, 500.14 MHz): δ 7.483–7.357 (*m*, 5H, Ar), 5.382 (*dd*, *J* = 13.1 and 2.8 Hz, 1H, –CH), 5.339 (*s*, 1H, –OH), 3.810 (*s*, 3H, $-OCH_3$), 2.968 (*dd*, *J* = 16.6 and 13.1 Hz, 1H, –CHH), 2.829 (*dd*, *J* = 16.6 and 2.8 Hz, 1H, –CHH), 2.139 (*s*, 3H, $-CH_3$), 2.135 (*s*, 3H, $-CH_3$). ^{13}C NMR ($CDCl_3$, 125.77 MHz): δ 189.7 (C=O), 159.6 (C—OH), 158.8 (C—O), 157.7 (C—O), 139.2 (C), 128.7 (2 × CH, Ar), 128.4 (CH, Ar), 125.8 (2 × CH, Ar), 111.2 (C), 109.1 (C—Me), 106.9 (C—Me), 78.6 (O—CH), 61.3 ($-OCH_3$), 45.7 (CH_2), 8.1 ($-CH_3$), 7.9 ($-CH_3$). EI/MS: *m*/*e* 298 (M^+, 21).

Crystal data

$C_{18}H_{18}O_4$
M_r = 298.32
Monoclinic, $P2_1/c$
a = 12.6503 (5) Å
b = 17.1770 (5) Å
c = 7.1379 (3) Å
β = 105.009 (2)°
V = 1498.11 (10) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 100 (2) K
0.14 × 0.11 × 0.02 mm

Table 1
Selected bond angles (°).

C9—O1—C2	115.6 (2)	O1—C2*B*—C3*B*	109.1 (9)
C9—O1—C2*B*	115.0 (4)	C4—C3*B*—C2*B*	106.5 (10)
O1—C2—C3	107.8 (4)	C10—C4—C3	114.8 (3)
C2—C3—C4	110.7 (4)	O1—C9—C8	114.3 (2)

Table 2
Hydrogen-bond geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O21—H21···O17^{i}	0.87 (4)	1.96 (4)	2.784 (3)	158 (4)

Symmetry code: (i) $-x, y-\frac{1}{2}, -z+\frac{1}{2}$.

Table 3
Geometry of weak intermolecular π–π interactions (Å, °).

CgI···*CgJ*^{a}	α^b	β^c	$CgI_{Perp}{}^d$
4.1717 (16)^{ii}	0.03	31.86	3.543
3.5952 (16)^{iii}	0.03	14.72	3.477

Notes: (*a*) the distance between the ring centroids of aromatic rings *I* and *J* of the chroman-4-one groups; (*b*) the dihedral angle between stacking planes; (*c*) the angle between *CgI*···*CgJ* and the normal to plane *I*; (*d*) the perpendicular distance of *CgI* on ring *J*. [Symmetry codes: (ii) $-x, -y, -z$; (iii) $-x, -y, -z+1$.]

Data collection

Bruker APEXII CCD diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 2001)
T_{min} = 0.809, T_{max} = 0.998
30663 measured reflections
3189 independent reflections
1994 reflections with $I > 2\sigma(I)$
R_{int} = 0.091

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.066
$wR(F^2)$ = 0.170
S = 1.07
3076 reflections
230 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.24 e Å^{-3}
$\Delta\rho_{min}$ = −0.22 e Å^{-3}

The hydroxy atom H21 was located in a difference map and refined isotropically. All other H atoms were positioned geometrically and included as riding atoms, with C—H distances in the range 0.95–1.00 Å and U_{iso}(H) values of 1.2 or 1.5 times U_{eq}(C). It was necessary to include a disordered model with three orientations, designated *A*, *B* and *C*, at occupancies of 43, 30 and 27%, respectively.

Data collection: *APEX2* (Bruker, 2007); cell refinement: *APEX2*; data reduction: *APEX2*; program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997) and *Mercury* (Macrae *et al.*, 2006); software used to prepare material for publication: *WinGX* (Farrugia, 1999); geometric calculations: *PLATON* (Spek, 2003).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SQ3134). Services for accessing these data are described at the back of the journal.

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