organic compounds

A mixed crystal of imperatorin and phellopterin, with C—H···O, C—H···π and π–π interactions

Philip J. Cox,[a]* Marcel Jaspars,[b] Yashodharan Kumarasamy,[a] Lutfun Nahar,[b] Satyajit D. Sarker[a] and Mohammad Shoeb[a]

[a]School of Pharmacy, The Robert Gordon University, Schoolhill, Aberdeen AB10 1FR, Scotland, and [b]Department of Chemistry, Aberdeen University, Meston Walk, Old Aberdeen AB24 3UE, Scotland

Correspondence e-mail: p.j.cox@rgu.ac.uk

The crystal structure of 9-(3-methylbut-2-enyloxy)-7H-furo-[3,2-g]chromen-7-one–4-methoxy-9-(3-methylbut-2-enyloxy)-7H-furo[3,2-g]chromen-7-one (0.926/0.074), $0.926C_{16}H_{14}O_4\cdot 0.074C_{17}H_{16}O_5$, is characterized by two independent imperatorin molecules in the asymmetric unit, which exhibit different side-chain conformations. A small amount of phellopterin overlaps with one of the two imperatorin molecules. The supramolecular structure is supported by C—H···O, C—H···π and π–π interactions.

Comment

In continuation of our studies involving extraction of active molecules from plant species, we have examined the seeds of *Angelica archangelica*. The *n*-hexane extract yielded imperatorin, (I), a furocoumarin that is a known dual inhibitor of cyclooxygenase and lipooxygenase (Abda *et al.*, 2001). The spectroscopic data (UV, IR, ^{1}H NMR and ^{13}C NMR) were

(I)   (II)
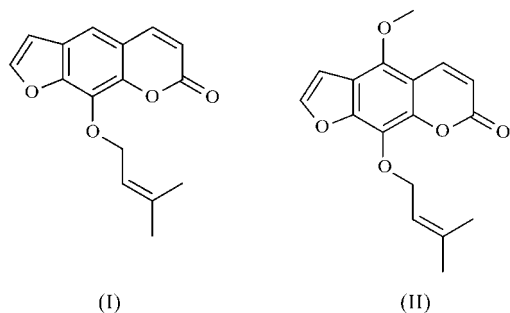
comparable to published data (Masuda *et al.*, 1998), but a minor impurity (< 10%) in the form of phellopterin, (II), was indicated by the NMR data. Phellopterin is a potent inhibitor of the binding of diazepam to the benzodiazepine receptor (Bergendorff *et al.*, 1997).

In the crystal structure, there are two molecules, *viz.* A and B (Figs. 1 and 2), in the asymmetric unit. In molecule A, there is evidence of a methoxy group attached to atom C3A, so that the molecule corresponds to a phellopterin molecule. The refined population parameter of the O and C atoms in this methoxy group was 0.148 (7), indicating an imperatorin/phellopterin ratio of ~93:7.
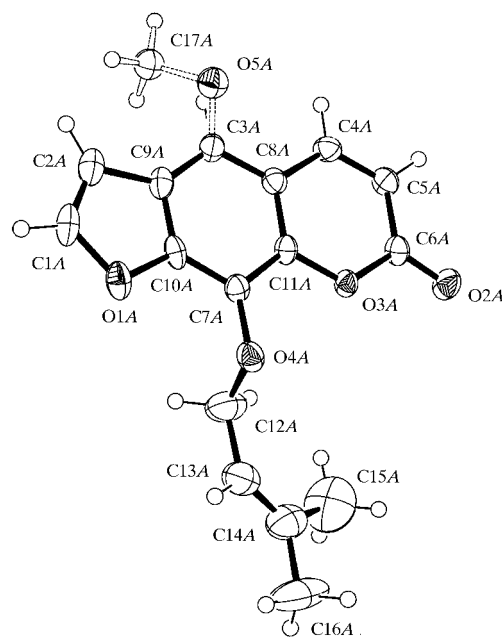

Figure 1
The atomic arrangement in molecule A, showing the additional methoxy group of phellopterin. Displacement ellipsoids are shown at the 50% probability level.

The very low occupancy of the methoxy group is associated with some uncertainty in the positions of atoms C17A and O5A; nevertheless, these assignments are supported by the NMR data. Other overlapping atom positions could not be resolved, but the displacement parameters of atoms in the side chain are higher in molecule A than in molecule B, especially for the methyl C atoms.
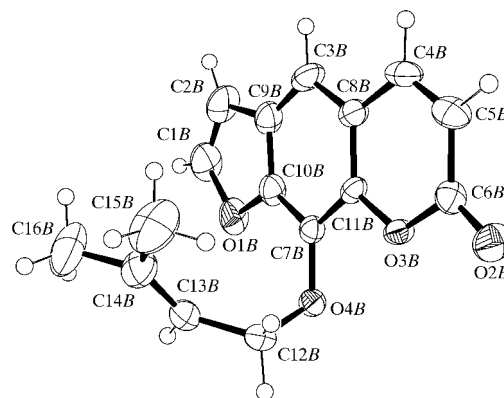

Figure 2
The atomic arrangement in molecule B. Displacement ellipsoids are shown at the 50% probability level.

The two molecules differ in the conformation of the prenyloxy side chain at atom C7, as shown by the C7—O4—C12—C13 torsion angle, which is −179.0 (3)° in molecule A and 63.3 (3)° in molecule B (Table 1). The atoms in the side chain of molecule B deviate more from the mean plane of the tricyclic ring system than atoms in the side chain of molecule A. In the related isoimperatorin molecule (Rajnikant *et al.*, 1996), where the prenyloxy side chain is at position C3, the corresponding torsion angle is −174.3 (2)°, which is similar to that in molecule A.
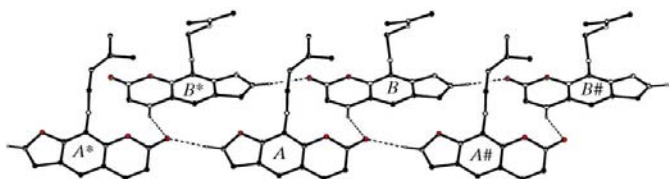

Figure 3
C—H···O hydrogen bonding between molecules A and B. Only the major (imperatorin) disordered component is shown. Molecules marked with an asterisk (*) or a hash (#) are at positions (1 + x, y, z) and (−1 + x, y, z), respectively.

The imperatorin molecules are linked by three intermolecular C—H···O bonds (Table 2 and Fig. 3). One of these bonds joins the A molecules into a continuous chain running parallel to the *a* axis, and another C—H···O bond joins the B molecules into a continuous chain running in the same direction. The third bond links the two chains, thus forming $R_4^3(23)$ rings involving two A and two B molecules. C—H···O bonds are a common feature of furocoumarin ring systems (Delettré *et al.*, 1986; Wolska *et al.*, 1990; Magotra *et al.*, 1995). The supramolecular structure is also supported by edge-to-face π···H interactions (Table 2 and Fig. 4).

Finally, there are π–π interactions (Table 3 and Fig. 5) between rings of the planar tricyclic systems that pack in near parallel arrangements across centres of symmetry. Stacking interactions are also found in the furocoumarin bergaptol (Ginderow, 1991).
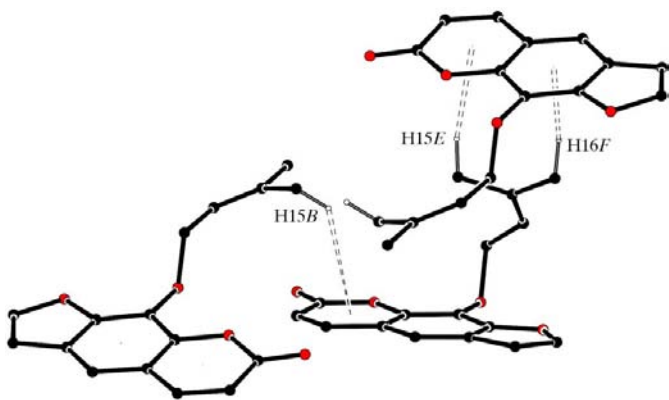

Figure 4
C—H···π interactions between molecules A and B, shown as dashed lines. Only the major (imperatorin) disordered component is shown.
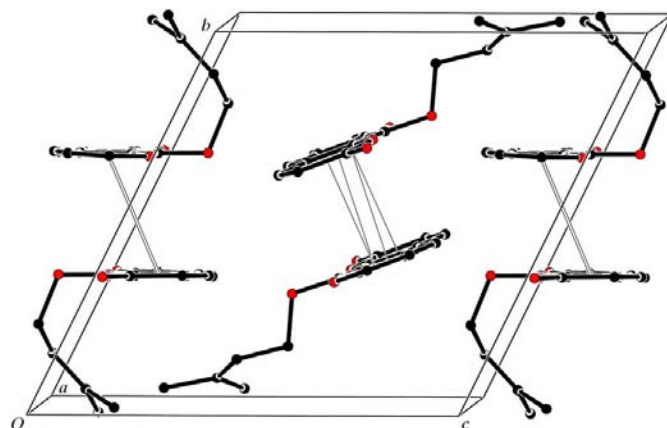

Figure 5
The π–π interactions (thin lines) between molecules related by a centre of symmetry. Only the major (imperatorin) disordered component is shown.

Experimental

Seeds of *Angelica archangelica* were purchased from B&T World Seeds Sarl, Paguignan, 34210 Olonzac, France. A voucher specimen (PH020503) has been deposited in the herbarium of the Plant and Soil Science Department, University of Aberdeen, Scotland (ABD). The seeds (80 g) were ground using a coffee grinder and extracted sequentially with *n*-hexane, dichloromethane and methanol using a Soxhlet apparatus. The *n*-hexane extract was cooled to room temperature, and the crystals were separated by filtration and dried on filter paper.

Crystal data

$0.926C_{16}H_{14}O_4 \cdot 0.074C_{17}H_{16}O_5$	$Z = 4$
$M_r = 272.69$	$D_x = 1.317$ Mg m^{-3}
Triclinic, $P\bar{1}$	Mo $K\alpha$ radiation
$a = 11.0551$ (4) Å	Cell parameters from 18 828
$b = 11.7236$ (4) Å	reflections
$c = 11.8718$ (5) Å	$\theta = 2.9–27.5°$
$\alpha = 64.1855$ (18)°	$\mu = 0.10$ mm^{-1}
$\beta = 89.6613$ (16)°	$T = 120$ (2) K
$\gamma = 83.484$ (2)°	Needle, colourless
$V = 1374.53$ (9) Å^3	$0.28 \times 0.04 \times 0.03$ mm

Data collection

Nonius KappaCCD area-detector diffractometer	6279 independent reflections
	3538 reflections with $I > 2\sigma(I)$
φ and ω scans to fill Ewald sphere	$R_{int} = 0.115$
Absorption correction: multi-scan	$\theta_{max} = 27.5°$
(*SORTAV*; Blessing, 1995, 1997)	$h = -14 \rightarrow 14$
$T_{min} = 0.977$, $T_{max} = 1.000$	$k = -15 \rightarrow 15$
24 271 measured reflections	$l = -15 \rightarrow 15$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0419P)^2$
$R[F^2 > 2\sigma(F^2)] = 0.084$	$+ 1.433P]$
$wR(F^2) = 0.181$	where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.05$	$(\Delta/\sigma)_{max} = 0.001$
6279 reflections	$\Delta\rho_{max} = 0.33$ e Å^{-3}
380 parameters	$\Delta\rho_{min} = -0.31$ e Å^{-3}
H atoms treated by a mixture of independent and constrained refinement	Extinction correction: *SHELXL*97
	Extinction coefficient: 0.018 (3)

organic compounds

Table 1
Selected geometric parameters (Å, °).

O4A—C12A	1.446 (4)	O4B—C12B	1.466 (4)
C14A—C16A	1.489 (6)	C14B—C16B	1.512 (6)
C3A—C9A—C2A	135.9 (3)	C3B—C9B—C2B	136.1 (3)
O4A—C12A—C13A	109.3 (3)	O4B—C12B—C13B	111.0 (3)
C7A—O4A—C12A—C13A	−179.0 (3)	C7B—O4B—C12B—C13B	63.3 (3)

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

Cg represents the centre of gravity of the following rings: $Cg2$ furan (molecule B), $Cg3$ pyrone (molecule A) and $Cg4$ pyrone (molecule B).

D—H···A	D—H	H···A	D···A	D—H···A
C1A—H1A···O2A[i]	0.95	2.29	3.232 (4)	172
C1B—H1B···O2B[ii]	0.95	2.40	3.323 (4)	164
C4B—H4B···O2A	0.95	2.59	3.482 (4)	156
C15A—H15B···Cg4	0.98	3.35	4.072 (7)	132
C15B—H15E···Cg3[iii]	0.98	2.92	3.773 (6)	145
C16B—H16F···Cg2[iii]	0.98	2.90	3.597 (5)	129

Symmetry codes: (i) $1 + x, y, z$; (ii) $x − 1, y, z$; (iii) $1 − x, 2 − y, 1 − z$.

Table 3
π–π interactions (Å, °).

Cg represents the centre of gravity of the following rings: $Cg1$ furan (molecule A), $Cg2$ furan (molecule B), $Cg3$ pyrone (molecule A), $Cg4$ pyrone (molecule B), $Cg5$ benzene (molecule A) and $Cg6$ benzene (molecule B).

CgI	CgJ	Symmetry code	Cg···Cg	Dihedral angle	Interplanar distance	Offset
1	3	$2 − x, 1 − y, 1 − z$	3.560 (2)	3.3	3.326 (3)	1.27
1	5	$2 − x, 1 − y, 1 − z$	3.550 (2)	1.9	3.375 (3)	1.10
4	6	$1 − x, 1 − y, 2 − z$	3.682 (2)	1.7	3.371 (3)	1.48
5	5	$2 − x, 1 − y, 1 − z$	3.534 (2)	0.0	3.390 (3)	1.00

All non-H atoms, except atoms O5A and C17A, were refined with anisotropic displacement parameters. Because of their low occupancy, atoms O5A and C17A were refined with isotropic displacement parameters. H atoms were initially placed in calculated positions and thereafter were allowed to ride on their attached atoms, with C—H distances of 0.95–0.99 Å and U_{iso} values of 1.2 times (non-methyl) or 1.3 times (methyl) the U_{eq} values of the attached atom. In the final cycles of refinement, the coordinates of atom H3 were refined, but the C3A—H3A distance was restrained to be 0.95 (1) Å. The final R values are higher than normal, possibly because overlapping atom positions in molecule A were not resolved. There

appears to be a physically unreasonable short intermolecular contact between a partially-occupied atom (C17A from phellopterin) and a fully occuped site (O1B in a formally imperatorin-only molecule). We believe that this artefact arises from two factors: (i) uncertainty in the position of C17A due to its very low occupancy, and (ii) although O1B is formally fully occupied, its position (as well as that of the rest of the ordered part of the structure) is a compromise between imperatorin and phellopterin, biased towards the former major component.

References

Abda, M. J., de las Heras, B., Silvan, A. M., Pascual, R., Bermejo, P., Rodriguez, B. & Villar, A. M. (2001). *J. Pharm. Pharmacol.* **53**, 1163–1168.
Altomare, A., Burla, M. C., Camalli, M., Cascarano, G. L., Giacovazzo, C., Guagliardi, A., Moliterni, A. G. G., Polidori, G. & Spagna, R. (1999). *J. Appl. Cryst.* **32**, 115–119.
Bergendorff, O., Dekermendjian, K., Nielsen, M., Shan, R., Witt, R., Ai, J. & Sterner, O. (1997). *Phytochemistry*, **44**, 1121–1124.
Blessing, R. H. (1995). *Acta Cryst.* A**51**, 33–38.
Blessing, R. H. (1997). *J. Appl. Cryst.* **30**, 421–426.
Delettré, P. J., Delaitre, M.-E., Vigny, P. & Bisagni, E. (1986). *Acta Cryst.* C**42**, 1849–1851.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Fletcher, D. A., McMeeking, R. F. & Parkin, D. (1996). *J. Chem. Inf. Comput. Sci.* **36**, 746–749.
Ginderow, P. D. (1991). *Acta Cryst.* C**47**, 2144–2146.
Hooft, R. (1998). *COLLECT.* Nonius BV, Delft, The Netherlands.
Magotra, D. K., Gupta, V. K., Rajnikant & Goswami, K. N. (1995). *Acta Cryst.* C**51**, 2196–2198.
Masuda, T., Takasugi, M. & Anetai, M. (1998). *Phytochemistry*, **47**, 13–16.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
Rajnikant, Gupta, V. K., Singh, A., Lal, M., Gupta, B. D. & Banjeree, S. K. (1996). *Mol. Cryst. Liq. Cryst. Sect. C Mol. Mater.* **6**, 199–203.
Sheldrick, G. M. (1997). *SHELXL*97. Release 97–2. University of Göttingen, Germany.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
Wolska, I., Borowiak, T. & Gawron, M. (1990). *Acta Cryst.* C**46**, 2146–2148.