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Isochroman derivatives and their tendency to crystallize in chiral space groups

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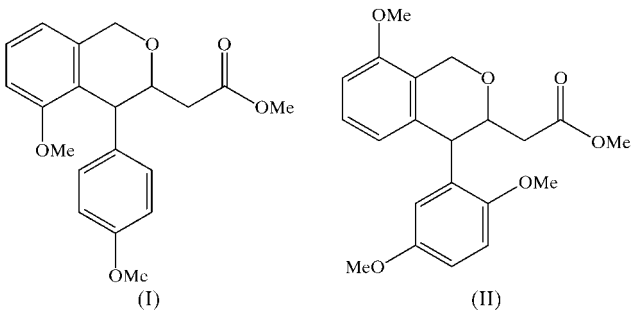
In methyl [5-methoxy-4-(4-methoxyphenyl)isochroman-3-yl]-acetate, $C_{20}H_{22}O_5$, (I), and methyl [4-(2,5-dimethoxyphenyl)-8-methoxyisochroman-3-yl]acetate, $C_{21}H_{24}O_6$, (II), the heterocyclic rings adopt half-chair conformations. The substituents at the 3- and 4-positions are in a *trans* configuration in both (I) and (II), being in an axial conformation in (I) and in an equatorial conformation in (II). The crystal structure of (I) is stabilized by weak C—H···O hydrogen bonding, leading to the formation of an infinite three-dimensional network. Compound (II) crystallizes in a chiral space group. This feature, which was also found in previously investigated isochroman derivatives, is related to the arrangement of substituents attached to the isochroman moiety.

Comment

Some members of the benzo[*c*]pyran family have been found in nature and shown to possess a variety of biological properties (Moore, 1977; Moore & Czerniak, 1981). The title



compounds, (I) and (II), were synthesized while searching for new precursors for antibiotics of this type. The present work forms part of a series of systematic X-ray investigations of isochroman derivatives (Palusiak *et al.*, 2002*a*,*b*; Palusiak, Małecka, Rybarczyk-Pirek *et al.*, 2003; Palusiak, Grabowski *et al.*, 2003).

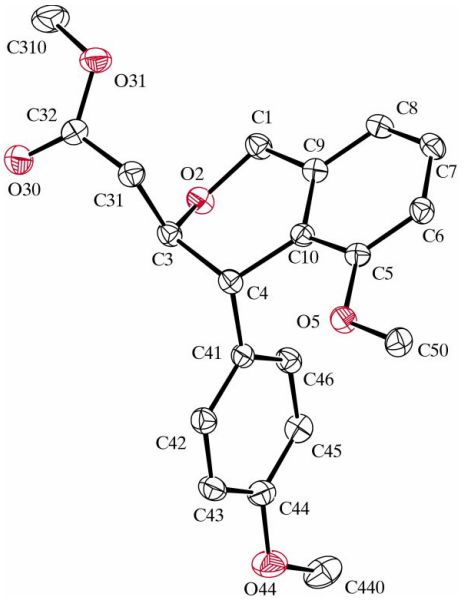


Figure 1
A view of (I) (40% probability displacement ellipsoids). H atoms have been omitted for clarity.

In the molecules of the title compounds (Figs. 1 and 2), the base isochroman moiety is a system of two condensed rings, *viz*. a benzene ring and a heterocyclic ring with an O atom at the 2-position. In both compounds, there is a methoxycarbonylmethyl substituent at the 3-position. The molecules differ from each other in the positions of the methoxy groups attached to the benzene ring of the isochroman moiety and in the substituent at the 4-position. In each case, the heterocyclic ring adopts a half-chair conformation, with a twofold axis passing through the mid-point of the O2—C3 bond. The asymmetry parameter (Nardelli, 1983) Δ_2(O2—C3) is 0.0446 (6) and 0.0124 (7) for (I) and (II), respectively. The puckering parameters (Cremer & Pople, 1975) Q, φ_2 and θ_2 corresponding to the sequence of atoms O2/C3/C4/C10/C9/C1 are 0.487 (2) Å, 17.7 (2)° and 51.9 (2)° for the molecule of (I),

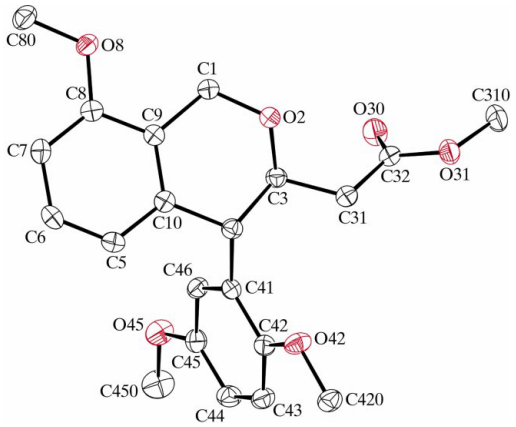


Figure 2
A view of (II) (40% probability displacement ellipsoids). H atoms have been omitted for clarity.

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and 0.506 (2) Å, 32.64 (3)° and 50.6 (2)° for the molecule of (II). As in the previously investigated isochromans, the substituents at the 3- and 4-positions are in *trans* configurations, being in an axial conformation in (I) and in an equatorial conformation in (II). Torsion angles describing these features are presented in Tables 1 and 3.

Molecules of both (I) and (II) have two chiral centres, at atoms C3 and C4. In the case of (I), which crystallizes in a centrosymmetric space group, the relative stereochemistry is 3*S*,4*R* and the crystals contain a racemic mixture. In the case of (II), which is in a chiral space group, the absolute configuration of the molecules is 3*S*,4*S* or its enantiomorph 3*R*,4*R*. The absence of a strong anomalous scatterer in the crystal does not allow unequivocal determination of the absolute configuration.

In both (I) and (II), the phenyl substituent at atom C4 and the aromatic ring of the isochroman moiety are oriented almost perpendicular to each other. The dihedral angles between the planes of these rings are 84.45 (3) and 75.21 (5)° for (I) and (II), respectively. The non-H atoms of the methoxy groups do not deviate significantly from the planes of the rings to which they are attached, the maximum deviation being 0.215 (2) Å for atom C440 in (I) and 0.026 (4) Å for atom O45 in (II). As expected, the methoxycarbonylmethyl substituents are planar. In the molecule of (I), the C31/C32/O30/O31/C310 plane makes a dihedral angle of 16.95 (3)° with the flat fragment of the isochroman moiety (C5–C10/C1/C4); in the molecule of (II), this angle is 60.06 (5)°.

There is no typical H-atom donor system in the molecules of the title compounds, and therefore typical inter- or intramolecular hydrogen bonds cannot form. Only C—H···*X* interactions, usually defined as weak, can be found in the crystal structures of (I) and (II). Analysis of the packing suggests the presence of such interactions in the crystal of (I). There are two weak interactions in which aromatic C atoms act as H-atom donors, with O atoms acting as acceptors (Table 2). In one of these bonds, C7—H7···O2($1-x$, $\frac{1}{2}+y$, $\frac{1}{2}-z$), the linked molecules, related *via* a 2_1 symmetry operation, form chains. This topological motif corresponds to the first-level graph-set descriptor *C*(6) (Bernstein *et al.*, 1995). In the second interaction, C46—H46···O5($-1+x$, y, z), *C*(7) chains, generated from a translation operation along the [100] direction, are formed by adjacent molecules. The crystal structure is therefore stabilized by an infinite three-dimensional network of weak hydrogen bonds. In (II), the number of short contacts (less than 4 Å) is greater than it is in (I). Nevertheless, none of these interactions can be recognized as hydrogen bonds.

Compound (II) crystallizes in a chiral space group, in spite of its non-stereospecific synthesis in which both *trans* stereoisomers were obtained (Epsztajn *et al.*, 2001). A similar situation has been found in the cases of two previously examined crystal structures of isochroman derivatives crystallizing in chiral space groups (Palusiak *et al.*, 2002*a*; Palusiak, Grabowski *et al.*, 2003). The scheme in Fig. 3 shows the correlation between the arrangement of substituents attached to the isochroman moiety and the space group for previously investigated isochroman derivatives. Analysis of the arrangement of the substituents in comparison with their space group suggests that isochroman molecules in which a methoxy group is attached at the 8-position have a tendency to crystallize in a chiral space group. As shown, this effect exists for derivatives containing a hydroxy group at the 3-position, and our results now demonstrate that this group can be replaced by a methoxycarbonylmethyl substituent. It is thus possible to speculate that these observations must be related to advantageous packing of molecules in a chiral space group. In addition, the melting points of both compounds were determined by differential scanning calorimetry measurements. Interestingly, the melting point is considerably higher in the case of (II), being 426.01 K for (II) and 361.63 K for (I). Such a large difference cannot be explained solely on the basis of a difference in molecular mass and may, in part, be related to the close C—H···O interactions observed in (II).

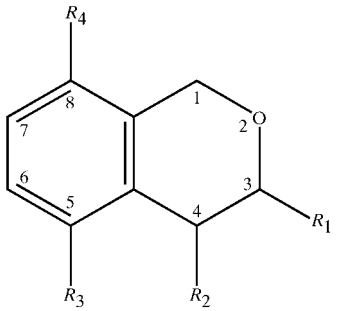

Figure 3
The molecular schemes of previously investigated isochroman derivatives (space groups are also given): (1) R_1 = OH, R_2 = 4-methoxyphenyl, R_3 = OMe and R_4 = H ($P\overline{1}$; Palusiak, Małecka, Rybarczyk-Pirek *et al.*, 2003); (2) R_1 = OH, R_2 = 2,5-dimethoxyphenyl, R_3 = H and R_4 = OMe ($P2_12_12_1$; Palusiak *et al.*, 2002*a*); (3) R_1 = OH, R_2 = 4-methoxyphenyl, R_3 = H and R_4 = OMe ($P2_1$; Palusiak, Grabowski *et al.*, 2003); (4) R_1 = CH_2COOCH_3, R_2 = 3-methoxyphenyl, R_3 = OMe and R_4 = H ($P\overline{1}$; Palusiak *et al.*, 2002*b*).

Experimental

The syntheses of (I) and (II) were described by Epsztajn *et al.* (2001). Single crystals were obtained by slow evaporation from methanol solutions at room temperature.

Compound (I)

Crystal data

$C_{20}H_{22}O_5$
M_r = 342.38
Monoclinic, $P2_1/c$
a = 5.6432 (3) Å
b = 14.5521 (8) Å
c = 20.9417 (12) Å
β = 96.799 (7)°
V = 1707.65 (16) Å^3
Z = 4
D_x = 1.332 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 8000 reflections
θ = 2.4–25.9°
μ = 0.10 mm^{-1}
T = 173 (2) K
Prism, colourless
0.5 × 0.5 × 0.4 mm

Data collection

Stoe IDPS diffractometer
φ scans
17 008 measured reflections
3267 independent reflections
2607 reflections with $I > 2\sigma(I)$
R_{int} = 0.057
θ_{max} = 25.9°
$h = -6 \rightarrow 6$
$k = -17 \rightarrow 17$
$l = -25 \rightarrow 25$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.051P)^2 + 0.1166P]$ where $P = (F_o^2 + 2F_c^2)/3'$
$R[F^2 > 2\sigma(F^2)] = 0.033$	$(\Delta/\sigma)_{max} = 0.001$
$wR(F^2) = 0.088$	$\Delta\rho_{max} = 0.26$ e Å^{-3}
$S = 1.03$	$\Delta\rho_{min} = -0.13$ e Å^{-3}
3267 reflections	
229 parameters	
H-atom parameters constrained	

Table 1
Selected geometric parameters (Å, °) for (I).

C32—O30	1.2034 (16)	O2—C1	1.4309 (14)
C32—O31	1.3377 (15)	O2—C3	1.4385 (13)
O2—C3—C4	110.34 (9)	C1—O2—C3	113.60 (8)
O2—C3—C4—C10	50.63 (12)	O30—C32—O31—C310	−5.8 (2)
C31—C3—C4—C41	158.56 (9)	C1—O2—C3—C4	−65.25 (12)
C10—C9—C1—O2	−9.41 (16)	C440—O44—C44—C45	3.04 (18)
C9—C10—C4—C41	104.65 (12)	C50—O5—C5—C6	−0.24 (16)
C9—C10—C4—C3	−18.99 (14)		

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

D—H···A	D—H	H···A	D···A	D—H···A
C7—H7···O2^{i}	0.95	2.46	3.354 (1)	156
C46—H46···O5^{ii}	0.95	2.45	3.320 (1)	152

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

Compound (II)

Crystal data

$C_{21}H_{24}O_6$	Mo $K\alpha$ radiation
$M_r = 372.4$	Cell parameters from 8000 reflections
Orthorhombic, $P2_12_12_1$	$\theta = 2.8$–$25.9°$
$a = 6.4796$ (4) Å	$\mu = 0.10$ mm^{-1}
$b = 17.9680$ (9) Å	$T = 173$ (2) K
$c = 16.0587$ (9) Å	Cut block, colourless
$V = 1869.64$ (18) Å^3	0.3 × 0.2 × 0.2 mm
$Z = 4$	
$D_x = 1.323$ Mg m^{-3}	

Data collection

Stoe IPDS diffractometer	$R_{int} = 0.031$
φ scans	$\theta_{max} = 25.9°$
13 101 measured reflections	$h = -7 \rightarrow 7$
2076 independent reflections	$k = -20 \rightarrow 21$
1862 reflections with $I > 2\sigma(I)$	$l = -19 \rightarrow 19$

Refinement

Refinement on F^2	H-atom parameters constrained
$R[F^2 > 2\sigma(F^2)] = 0.028$	$w = 1/[\sigma^2(F_o^2 + (0.0497P)^2]$ where $P = (F_o^2 + 2F_c^2)/3'$
$wR(F^2) = 0.068$	$(\Delta/\sigma)_{max} < 0.001$
$S = 1.03$	$\Delta\rho_{max} = 0.20$ e Å^{-3}
2076 reflections	$\Delta\rho_{min} = -0.11$ e Å^{-3}
256 parameters	

Table 3
Selected geometric parameters (Å, °) for (II).

C1—O2	1.424 (2)	C32—O30	1.205 (2)
C3—O2	1.433 (2)	C32—O31	1.348 (2)
O2—C3—C4	110.18 (13)	C1—O2—C3	111.50 (12)
O2—C1—C9—C10	−18.2 (2)	C3—C4—C10—C9	−13.6 (2)
C4—C3—O2—C1	−69.08 (17)	C7—C8—O8—C80	−3.2 (2)
O2—C3—C4—C10	46.65 (18)	O30—C32—O31—C310	−2.1 (3)
C31—C3—C4—C41	−70.87 (17)	C43—C42—O42—C420	−3.1 (2)
C41—C4—C10—C9	−136.37 (15)	C44—C45—O45—C450	−3.1 (3)

All H atoms were placed in idealized positions and constrained to ride on their parent atoms, with C—H distances in the range 0.93–0.98 Å. For methoxy H atoms, U_{iso}(H) values were taken to be $1.5U_{eq}$(C); for all other H atoms, U_{iso}(H) values were set at $1.2U_{eq}$(C). In the refinement of (II), data were merged using MERG4 in *SHELXL*97, according to the standard procedure for X-ray Mo $K\alpha$ measurements of chemical compounds without heavy atoms.

For both compounds, data collection: *IPDS Software* (Stoe & Cie, 1998); cell refinement: *IPDS Software*; data reduction: *IPDS Software*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 1990); software used to prepare material for publication: *PARST* (Nardelli, 1996).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1129). Services for accessing these data are described at the back of the journal.

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