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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, C20H22O5, (I), and methyl [4-(2,5-dimethoxyphenyl)-8-methoxyisochroman-3-yl]acetate, C21H24O6, (II), the carbonylmethyl 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) Δ2(O2—C3) is 0.0446 (6) and 0.0124 (7) for (I) and (II), respectively. The puckering parameters (Cremer & Pople, 1975) Q, q2 and θ2 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 1
A view of (I) (40% probability displacement ellipsoids). H atoms have been omitted for clarity.

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

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., 2002a,b; Palusiak, Malecka, Rybarczyk-Pirek et al., 2003; Palusiak, Grabowski et al., 2003).

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 methoxy-carbonylmethyl 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) Δ2(O2—C3) is 0.0446 (6) and 0.0124 (7) for (I) and (II), respectively. The puckering parameters (Cremer & Pople, 1975) Q, q2 and θ2 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),
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 S,R,4S or its enantiomorph S,R,4R. 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, 1/2 + y, 1/2 − z), the linked molecules, related via a 21 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., 2002a; 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).

### 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**

\( \text{C}_{20}\text{H}_{22}\text{O}_{5} \)

\( M_r = 342.38 \)

Monoclinic, \( P2_1/c \)

\( a = 5.6432(3) \) Å

\( b = 14.5521(8) \) Å

\( c = 20.9417(12) \) Å

\( \beta = 96.799(7) \)

\( V = 1707.65(16) \) Å³

\( Z = 4 \)

**Data collection**

Stoe IPDS diffractometer

\( 17 \) 008 measured reflections

3267 independent reflections

2607 reflections with \( I > 2\sigma(I) \)

\( R_{\text{int}} = 0.057 \)

\( \theta_{\text{max}} = 25.9^\circ \)

\( k = -17 \rightarrow 17 \)

\( l = -25 \rightarrow 25 \)
Refinement

Refinement on \( F^2 \)
\[ R[F^2 > 2\sigma(F^2)] = 0.033 \]
\[ wR^2(F^2) = 0.088 \]
\[ S = 1.03 \]
3267 reflections
229 parameters
H-atom parameters constrained

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

<table>
<thead>
<tr>
<th>Bond/Angle</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C32–O30</td>
<td>1.2034 (16)</td>
</tr>
<tr>
<td>O2–C1</td>
<td>1.4309 (14)</td>
</tr>
<tr>
<td>C22–O31</td>
<td>1.3377 (15)</td>
</tr>
<tr>
<td>O2–C3</td>
<td>1.4385 (13)</td>
</tr>
<tr>
<td>C31–C3–C4</td>
<td>110.18 (13)</td>
</tr>
<tr>
<td>C41–C4–C10</td>
<td>70.87 (17)</td>
</tr>
<tr>
<td>C9–C10–C4</td>
<td>173 (2)</td>
</tr>
<tr>
<td>C110–C111</td>
<td>102.73 (2)</td>
</tr>
<tr>
<td>C112–C111</td>
<td>102.73 (2)</td>
</tr>
<tr>
<td>C113–C111</td>
<td>102.73 (2)</td>
</tr>
<tr>
<td>C115–C111</td>
<td>102.73 (2)</td>
</tr>
</tbody>
</table>

Other geometric parameters:

- \( \theta = 2.8-25.9^\circ \)
- \( \mu = 0.10 \) mm\(^{-1} \)
- \( T = 173 (2) \) K
- Cut block, colourless
- \( 0.3 \times 0.2 \times 0.1 \) mm

Data collection

Stoe IPDS diffractometer
\( \phi \) scans
13 101 measured reflections
2076 independent reflections
1862 reflections with \( I > 2\sigma(I) \)

Refinement

Refinement on \( F^2 \)
\[ R[F^2 > 2\sigma(F^2)] = 0.028 \]
\[ wR^2(F^2) = 0.068 \]
\[ S = 1.03 \]
2076 reflections
256 parameters
H-atom parameters constrained

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

<table>
<thead>
<tr>
<th>Bond/Angle</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1–O2</td>
<td>1.424 (2)</td>
</tr>
<tr>
<td>C3–O2</td>
<td>1.433 (2)</td>
</tr>
<tr>
<td>C2–O30</td>
<td>1.205 (2)</td>
</tr>
<tr>
<td>C2–O2</td>
<td>1.25 (2)</td>
</tr>
<tr>
<td>O2–C3</td>
<td>1.4309 (14)</td>
</tr>
<tr>
<td>O30–C3–O2</td>
<td>110.18 (13)</td>
</tr>
<tr>
<td>C1–O2–C3</td>
<td>70.87 (17)</td>
</tr>
<tr>
<td>C41–C4–C10</td>
<td>173 (2)</td>
</tr>
<tr>
<td>C9–C10–C4</td>
<td>102.73 (2)</td>
</tr>
<tr>
<td>C110–C111</td>
<td>102.73 (2)</td>
</tr>
<tr>
<td>C112–C111</td>
<td>102.73 (2)</td>
</tr>
<tr>
<td>C113–C111</td>
<td>102.73 (2)</td>
</tr>
<tr>
<td>C115–C111</td>
<td>102.73 (2)</td>
</tr>
</tbody>
</table>

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, \( U_{eq}(H) \) values were taken to be 1.5\( U_{eq}(C) \); for all other H atoms, \( U_{eq}(H) \) values were set at 1.2\( U_{eq}(C) \).

For both compounds, data collection: IPDS Software; cell refinement: IPDS Software; data reduction: IPDS Software; program(s) used to solve structure: SHELXS97; program(s) used to refine structure: SHELXL97; molecular graphics: PLATON; software used to prepare material for publication: PARST.

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.

References