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1-(4-Chlorophenyl)-6,7-dimethoxyisochroman

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Key indicators

Single-crystal X-ray study
T = 120 K
Mean σ(C–C) = 0.002 Å
R factor = 0.042
wR factor = 0.115
Data-to-parameter ratio = 18.6

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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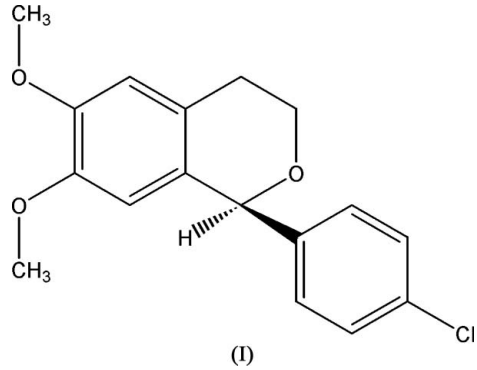
The title compound, $C_{17}H_{17}ClO_3$, is another representative of the rare examples of crystallographically characterized 6,7-dimethoxyisochromans. The packing exhibits intermolecular C(methyl)—H···Cl hydrogen bonds with an infinite zigzag pattern along [010]. Additional intermolecular bonds occur between methoxy groups and the pyran O atoms.

Comment

Various isochroman (3,4-dihydro-1*H*-benzo[*c*]pyran) structures are found in nature or as part of complex natural products. These are also intermediates in the synthesis of pharmaceuticals and drugs. 1-Aryl-6,7-dimethoxyisochromans are an important class of isochromans which exhibit a wide range of biological activities such as analgesic, muscle relaxant, antidepressant, anti-inflammatory, antihistaminic, anticoagulant and antihypertensive (Dobson *et al.*, 1975; Yamato *et al.*, 1985; McCall *et al.*, 1982). 6,7-Dimethoxyisochromans substituted at C-1 *via* a one- to three-carbon chain with arylpiperazines, *p*-fluorophenyl, *etc*., are hypotensives which lower blood pressure, presumably by both peripheral and central α-adrenoreceptor blockade (TenBrink *et al.*, 1996). 1-Phenyl- and 1-(3-methoxy-4-hydroxy)phenyl-6,7-dihydroxyisochromans have been identified in extra virgin olive oil (Malstrom *et al.*, 2000). These natural isochromans or their synthetic derivatives have been shown to exhibit beneficial antioxidant effects (Lorenz *et al.*, 2005). The antiplatelet activity and antioxidant power of these isochromans have also been evaluated and found to be effective free radical scavengers and inhibited platelet aggregation and thromboxane release evoked by agonists (Togna *et al.*, 2003).



(I)

6,7-Dimethoxyisochromans can easily be demethylated to the corresponding 6,7-dihydroxyisochromans. The oxa-Pictet–Spengler reaction is a variation of the Pictet–Spengler reaction in which a phenethyl alcohol reacts with a carbonyl compound to give a 1-substituted isochroman derivative (Guiso *et al.*,

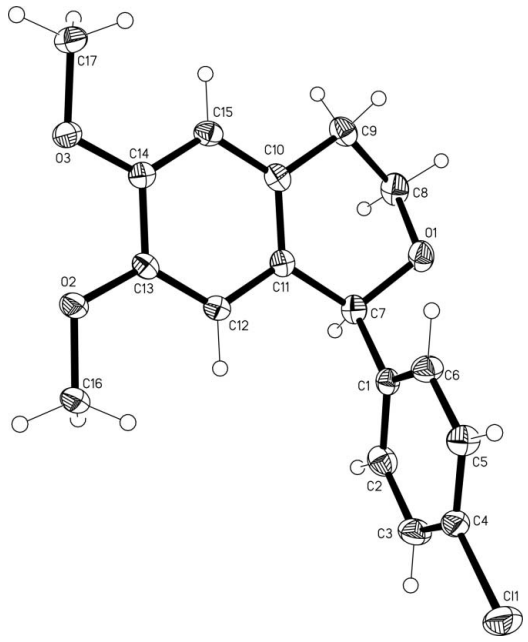


Figure 1
The molecular structure of (I). Displacement ellipsoids are drawn at the 50% probability level.

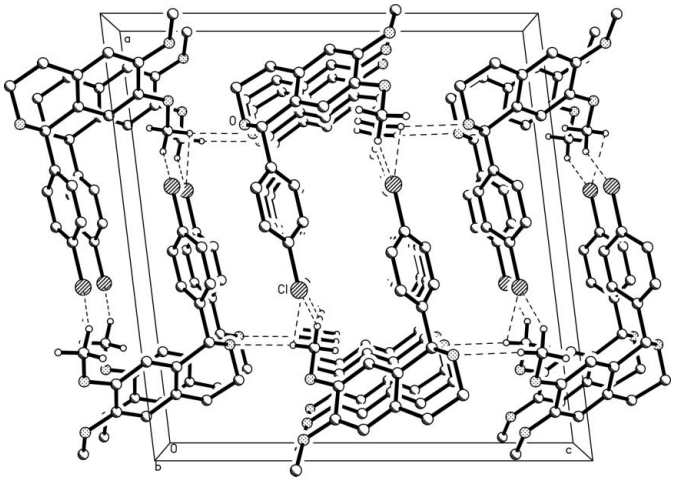


Figure 2
The crystal packing of (I), viewed along [010], with intermolecular hydrogen bonds indicated by dashed lines. H atoms not involved in hydrogen bonding have been omitted.

2001). The title compound, (I), was prepared by condensation of 2-(3,4-dimethoxyphenyl)ethanol with 4-chlorobenzaldehyde in the presence of a catalytic amount of *p*-toluenesulfonic acid under microwave irradiation. The compound was characterized by a 1H singlet at δ 5.54 for H-1 in the ^{1}H NMR spectrum. The non-planar nature of the tetrahydropyran ring was indicated by separate 2H multiplets at δ 3.84 and 4.0 and at δ 2.56 and 2.94 for the C-3 and C-4 methylene protons, respectively.

The pyran ring is puckered with O1 and C8 lying −0.429 (1) and 0.342 (2)Å, respectively, below and above the isochroman plane. The C atom of the O3/C17 methoxy group is slightly bent out of this plane [C17 0.325 (2), with Å below the plane], whereas the second methoxy group is almost coplanar [deviation for C16 of 0.066 (2)Å]. The angle formed by the two aromatic isochroman (C10–C15) and benzene (C1–C6) planes is 84.30 (4)°.

The packing shows stacking of the molecules along [010]. Intermolecular C—H···Cl hydrogen bonds (see Table) form a zigzag pattern with each of the two methyl donors linked to one chlorine acceptor. These infinite centrosymmetric double chains (Fig. 2) are then connected to each other by C(methyl)—H···O(pyran) bridges. The shortest intermolecular H···O(methoxy) distances are about 2.7Å and there are no π–π interactions between the molecules. There are short C—H···π contacts between C3—H3 and X1($-x+1$, $y+\frac{1}{2}$, $-z+\frac{1}{2}$), the mid-point of the C1–C6 *p*-chlorophenyl ring, and between C16—H16*A* and X2(x, $y+1$, z), the mid-point of the C10–C15 dimethoxyisochroman unit.

Experimental

To a mixture of 2-(3,4-dimethoxyphenyl)ethanol (0.182 g, 1 mmol) and 4-chlorobenzaldehyde (0.136 g, 0.12 ml, 1 mmol), a catalytic amount of *p*-toluenesulfonic acid monohydrate was added. The reaction mixture was homogenized and irradiated for 90 s. On completion of the reaction, as monitored by thin-layer chromatography (TLC, every 30 s) using petroleum ether and ethyl acetate (7:2), the reaction mixture was purified by thick-layer chromatography. The product obtained was recrystallized from ethyl acetate (0.29 g, 0.98 mmol, 98%; 357–358 K). TLC (R_f): 0.38; ^{1}H NMR ($CDCl_3$): δ 6.59 (1H, *s*, H-5), 6.20 (1H, *s*, H-8), 5.54 (1H, *s*, H-1), 3.84 and 4.0 (2H, *m*, 2 × H-3), 3.79 (6H, *s*, 2 × OCH_3), 2.56 and 2.94 (2H, *m*, 2 × H-4); chlorophenyl group: 7.23 (2H, *d*, J = 8.4 Hz, C-3′ and C-5′), 7.20 (2H, *d*, J = 8.4 Hz, C-2′ and C-6′). Analysis calculated for $C_{17}H_{17}ClO_3$: C 67.00, H 5.62%; found: C 67.3, H 5.58%.

Crystal data

$C_{17}H_{17}ClO_3$
M_r = 304.76
Monoclinic, $P2_1/c$
a = 16.877 (1) Å
b = 5.3142 (3) Å
c = 16.3985 (9) Å
β = 96.964 (1)°
V = 1459.89 (14) Å^3
Z = 4
D_x = 1.387 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.27 mm^{-1}
T = 120 (2) K
Block, colourless
0.42 × 0.26 × 0.25 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Bruker, 2002)
T_{min} = 0.895, T_{max} = 0.936
13531 measured reflections
3531 independent reflections
3050 reflections with $I > 2\sigma(I)$
R_{int} = 0.025
θ_{max} = 28.1°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.042
$wR(F^2)$ = 0.115
S = 1.04
3531 reflections
190 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0609P)^2 + 0.562P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.39 e Å^{-3}
$\Delta\rho_{min}$ = −0.37 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

Cl1—C4	1.7427 (15)	O1—C7	1.4302 (18)
O1—C8	1.4294 (17)	C1—C7	1.5102 (19)
C8—O1—C7	110.94 (11)	O1—C7—C11	110.98 (12)
O1—C7—C1	106.73 (11)	C1—C7—C11	113.34 (11)
C2—C1—C7—C11	117.11 (15)	C17—O3—C14—C13	167.44 (12)
C16—O2—C13—C14	177.65 (12)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C16—H16*B*···O1^{i}	0.98	2.59	3.5375 (19)	164
C16—H16*B*···Cl1^{ii}	0.98	2.88	3.3115 (14)	108
C16—H16*C*···Cl1^{iii}	0.98	2.89	3.7440 (17)	146

Symmetry codes: (i) $x, -y+\frac{3}{2}, z+\frac{1}{2}$; (ii) $-x+1, -y+2, -z+1$; (iii) $-x+1, -y+1, -z+1$.

H atoms were placed at idealized positions (C–H = 0.95–0.99Å) and refined as riding, with U_{iso}(H) = 1.2U_{eq}(C) and 1.5U_{eq}(methyl C).

Data collection: *SMART* (Bruker, 2002); cell refinement: *SAINT* (Bruker, 2002); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Bruker, 2002); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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