

5,8-Dimethoxy-3-methylisochroman

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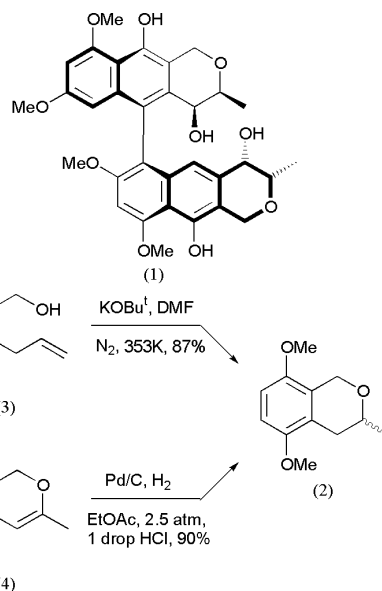
Key indicators

Single-crystal X-ray study
T = 293 K
Mean $\sigma(\text{C}-\text{C}) = 0.003 \text{ \AA}$
R factor = 0.056
wR factor = 0.179
Data-to-parameter ratio = 15.9For details of how these key indicators were automatically derived from the article, see <http://journals.iucr.org/e>.

The crystal structure of the title compound, $\text{C}_{12}\text{H}_{16}\text{O}_3$, an analogue of the naturally occurring 1,3-dimethylisochromans or the related naphtho[2,3-*c*]pyrans, confirms that the C-3 methyl substituent adopts an equatorial position in the solid state.

Comment

The synthesis of substituted 1,3-dimethylisochromans or the related naphtho[2,3-*c*]pyrans is important as a result of the biological activities of both these classes of compounds (Thomson, 1987). For example, the recently isolated bioanthracenes, such as compound (1), show promising antimalarial activity (Isaka *et al.*, 2001). A large number of these types of compounds have been synthesized by several research groups but only a few X-ray crystallographic studies have been carried out (Cook *et al.*, 2002; Zhang *et al.*, 1997; Giles *et al.*, 1988; Zhengxiong *et al.*, 1986; Egert *et al.*, 1983; Cooke *et al.*, 1980; Cameron *et al.*, 1977). From these X-ray crystallographic studies, it is clear that the C-1 methyl group of the fused pyran ring adopts a pseudo-axial position, while the C-3 methyl substituent adopts an equatorial position.



As part of our ongoing research programme on the syntheses of substituted isochromans, we needed to synthesize compounds lacking the C-1 methyl substituent. The synthesis of 3-methylisochroman, (2), was therefore pursued. This was achieved by reacting the benzylic alcohol (3) with potassium *t*-butoxide in DMF, as previously described (Green *et al.*,

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1995), or by the reduction of the corresponding isochromene (4), as detailed in the *Experimental* and shown in the Scheme. A single-crystal X-ray structure determination on the product, (2), confirmed that the heterocyclic ring adopts a half-chair conformation, with the C-3 methyl substituent in an equatorial position (Figs. 1 and 2).

Experimental

10% Pd/C (24 mg) and 1 drop of concentrated hydrochloric acid were added to ethyl acetate (6.3 ml) in a two-necked 50 ml flask. The system was purged for 15 min by exposing the suspension to hydrogen gas before isochromene (4) (99.8 mg) was introduced. The reaction mixture was then stirred under a hydrogen gas pressure of 2.5 atm for 24 h. The reaction mixture was filtered through a silica gel plug, followed by removal of solvent *in vacuo*. The crude material was purified by silica-gel column chromatography (20% ethyl acetate/hexane) to afford (±)-5,8-dimethoxy-3-methylisochroman, (2) (90.7 mg), in 90% yield. The compound was recrystallized from CH₂Cl₂ by slow evaporation, to afford colourless block-like crystals [m.p. 346–347 K, literature 347–348 K (Green *et al.*, 1995)].

Crystal data

C ₁₂ H ₁₆ O ₃	$D_x = 1.220 \text{ Mg m}^{-3}$
$M_r = 208.25$	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 701 reflections
$a = 13.2543 (15) \text{ \AA}$	$\theta = 3.1\text{--}23.2^\circ$
$b = 5.9923 (7) \text{ \AA}$	$\mu = 0.09 \text{ mm}^{-1}$
$c = 14.5744 (17) \text{ \AA}$	$T = 293 (2) \text{ K}$
$\beta = 101.633 (2)^\circ$	Block, colourless
$V = 1133.8 (2) \text{ \AA}^3$	$0.30 \times 0.26 \times 0.17 \text{ mm}$
$Z = 4$	

Data collection

Bruker SMART CCD area-detector diffractometer	2219 independent reflections
φ and ω scans	1431 reflections with $I > 2\sigma(I)$
Absorption correction: multi-scan (SADABS; Bruker, 1999)	$R_{\text{int}} = 0.049$
$T_{\text{min}} = 0.975$, $T_{\text{max}} = 0.985$	$\theta_{\text{max}} = 26.0^\circ$
6472 measured reflections	$h = -16 \rightarrow 16$
	$k = -7 \rightarrow 7$
	$l = -17 \rightarrow 15$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.1085P)^2]$
$R[F^2 > 2\sigma(F^2)] = 0.056$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.179$	$(\Delta/\sigma)_{\text{max}} = 0.001$
$S = 1.03$	$\Delta\rho_{\text{max}} = 0.17 \text{ e \AA}^{-3}$
2219 reflections	$\Delta\rho_{\text{min}} = -0.21 \text{ e \AA}^{-3}$
140 parameters	Extinction correction: SHELXL97
H-atom parameters constrained	Extinction coefficient: 0.028 (7)

H atoms were positioned geometrically and allowed to ride on their respective parent atoms, with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$ [$1.5U_{\text{eq}}(\text{C})$ for methyl groups].

Data collection: SMART-NT (Bruker, 1998); cell refinement: SAINT (Bruker, 1999); data reduction: SAINT; program(s) used to solve structure: SHELXTL (Bruker, 1999); program(s) used to refine structure: SHELXTL; molecular graphics: PLATON (Spek, 1990); software used to prepare material for publication: SHELXTL.

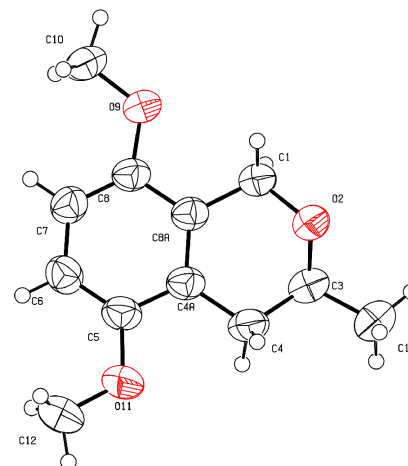


Figure 1

A view of (2), with the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

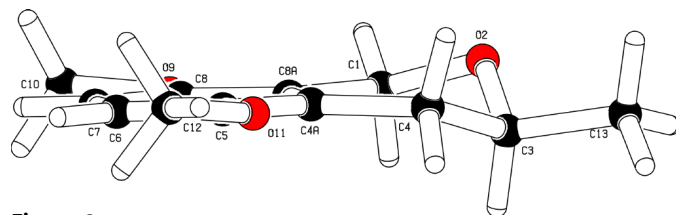


Figure 2

A side view of (2), showing the equatorial C-3 methyl group.

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