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Supramolecular structure of racemic 5-hydroxy-4-(4-methoxyphenyl)-10-oxa-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one

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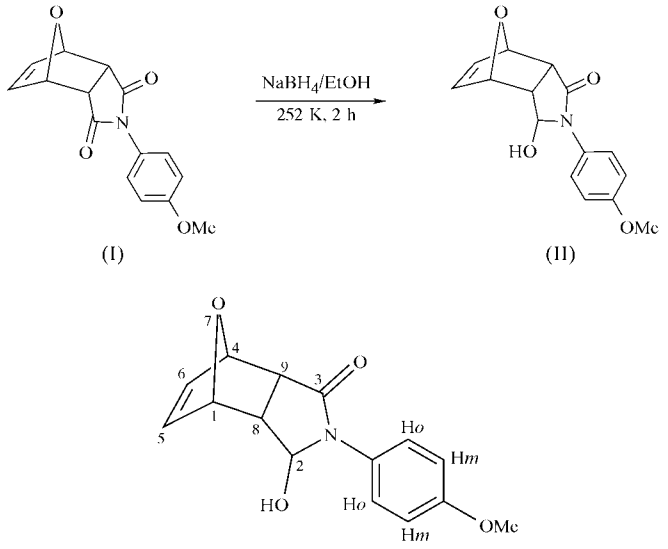
The structure of the title compound, $C_{15}H_{15}NO_4$, comprises a racemic mixture of chiral molecules containing five stereogenic centres. The cyclohexane ring tends towards a boat conformation and the two tetrahydrofuran rings adopt envelope conformations. Molecules are linked into sheets parallel to (100) by a combination of O—H···O, C—H···O and C—H···π hydrogen bonds, leading to a two-dimensional supramolecular structure.

Comment

The derivatives of *exo*-5,6-dehydronorcantharidin are of great pharmacological interest and have attracted considerable attention (Abel *et al.*, 1996; Deng *et al.*, 2005). Furthermore, molecules of this type containing nitrogen have become a hot topic in heterocyclic chemistry because of their antitumour, antiviral, analgesic, sedative and fungicidal activities (Salvati *et al.*, 2005). We therefore became interested in the synthesis of the title compound, the cantharidin analogue (II), with the possibility that biological activity is modified in the bicyclic imide systems. We report here the synthesis and crystal structure of (II) (Fig. 1), which is generated from (I) in a single synthetic reduction using $Na(BH_4)$.

The regiochemistry of (II) was established by ^{1}H and C NMR spectroscopy, and the diagnostic spin–spin interactions were identified with the aid of HH COSY experiments. The structure determination of (II) confirmed this connectivity and also established the stereochemistry (*exo*). The molecules of (II) are chiral, with five stereogenic centres at atoms C1, C2, C3, C6 and C7. Compound (II) crystallizes as a racemic mixture in the space group $P2_1/c$. The reference molecule was selected to have *S*, *S*, *R*, *S* and *R* configurations at atoms C1, C2, C3, C6 and C7, respectively. Hence, the racemic mixture consists of molecules whose configurations are 1*S*,2*S*,3*R*,6*S*,7*R* and 1*R*,2*R*,3*S*,6*R*,7*S*. The inter-bridgehead angles O3—C6—C7 and O3—C3—C2 of 100.44 (17) and 101.04 (16)°, respectively, are contracted with respect to the tetrahedral value, as



is the C6—O3—C3 angle of 95.59 (15)°. The cyclohexane ring (C2–C7) adopts a boat conformation. The tetrahydrofuran rings (O3/C3/C2/C7/C6 and O3/C3/C4/C5/C6) each have an envelope conformation with atom O3 as the flap atom and with puckering parameters (Cremer & Pople, 1975) of Q = 0.590 (2) Å and φ = 180.5 (2)°, and Q = 0.508 (2) Å and φ = 359.4 (3)°, respectively. The maximum deviations of atom O3 from the planes defined by the remaining four atoms are 0.840 (1) and 0.755 (1) Å, respectively. The dihedral angle between the benzene and imide rings is 29.28 (12)°. The methoxy substituent is approximately coplanar with the attached benzene ring. The N—C_{aryl} bond length is 1.428 (3) Å and is comparable to those found in previously reported structures (Trujillo-Ferrara *et al.*, 2004; Miller *et al.*, 2000; Ellis & Spek, 2001).

The supramolecular structure of (II) is composed of sheets generated by a combination of O—H···O, C—H···O and C—H···π hydrogen bonds (Table 1). The formation of the sheet is analysed in terms of two different low-dimensional substructures. The first substructure is built using the O—H···O and C—H···π hydrogen bonds, where atoms O1 and C7 in the molecule at (x, y, z) act as hydrogen-bond donors, respectively, to atom O2 and the C9–C14 ring, both in the molecule at ($-x+1$, $y+\frac{1}{2}$, $-z+\frac{3}{2}$), so forming $C(6)$ (Bernstein *et al.*, 1995)

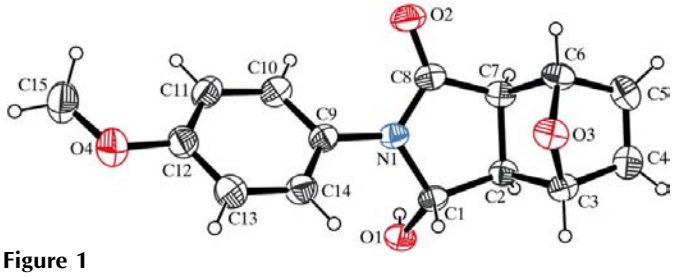


Figure 1
The molecular structure of (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

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chains running parallel to the [010] direction (Fig. 2). The chains include only the molecules of 1*S*,2*S*,3*R*,6*S*,7*R* configuration. In the second substructure, atom C1 in the molecule at (x, y, z) (configuration 1*S*,2*S*,3*R*,6*S*,7*R*) acts as a hydrogen-bond donor to atom O3 in the molecule at ($-x+1$, $-y+1$, $-z+1$) (configuration 1*R*,2*R*,3*S*,6*R*,7*S*), leading to a centrosymmetric $R_2^2(10)$ dimer centred at ($\frac{1}{2}$, $\frac{1}{2}$, $\frac{1}{2}$) (Fig. 3). The combination of these interactions generates a sheet parallel to (100). There are no direction-specific interactions between the sheets, so the supramolecular structure of the title compound is two-dimensional (Fig. 4).

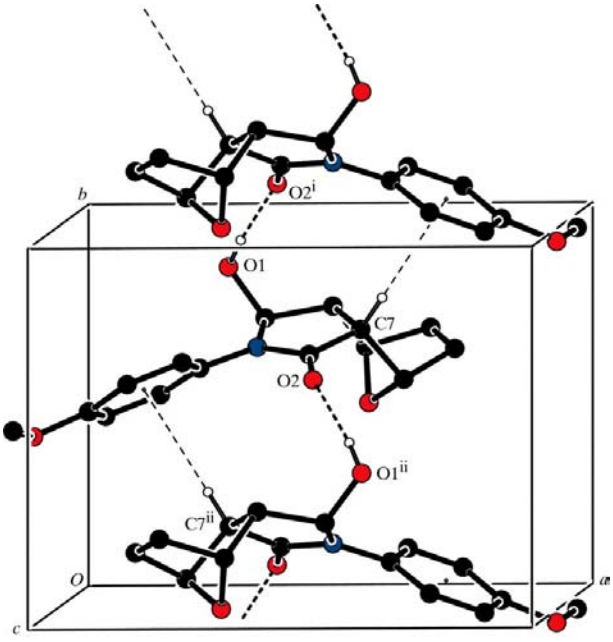

Figure 2
Part of the crystal structure of (II), showing the formation of $C(6)$ chains running parallel to [010]. For the sake of clarity, H atoms not involved in the motifs shown have been omitted. [Symmetry codes: (i) $-x+1$, $y+\frac{1}{2}$, $-z+\frac{3}{2}$; (ii) $-x+1$, $y-\frac{1}{2}$, $-z+\frac{3}{2}$.]

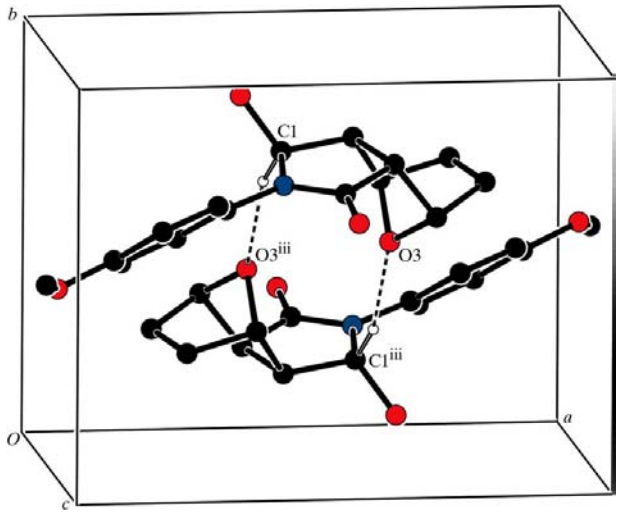

Figure 3
Part of the crystal structure of (II), showing the formation of an $R_2^2(10)$ dimer centred at ($\frac{1}{2}$, $\frac{1}{2}$, $\frac{1}{2}$). For the sake of clarity, H atoms not involved in the motifs shown have been omitted. [Symmetry code: (iii) $-x+1$, $-y+1$, $-z+1$.]

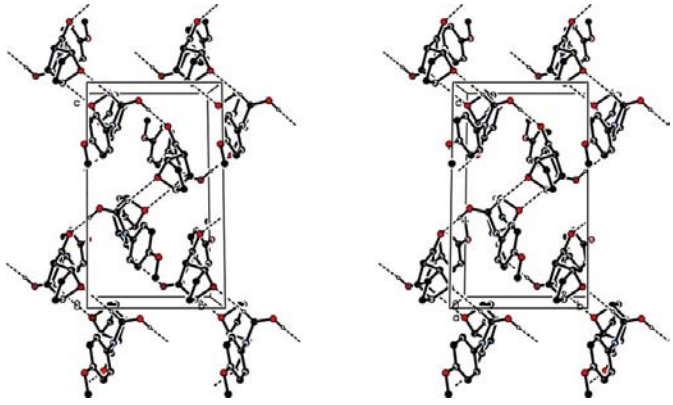

Figure 4
A stereoview of part of the crystal structure of (II), showing the formation of a hydrogen-bonded sheet parallel to (100). For the sake of clarity, H atoms not involved in the motifs shown have been omitted.

Experimental

The general synthetic procedure has been described by Hubert *et al.* (1975). *N*-(4-Methoxyphenyl)-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide, (I) (0.77 g, 2.84 mmol), prepared from furan and *N*-(4-methoxyphenyl)maleimide, was reduced in ethanol solution (250 ml) with 0.94 g of $Na(BH_4)$ added in small portions at 252 K over a period of 2 h. The excess of $Na(BH_4)$ was destroyed in 15–30 min at 278 K by adding aqueous HCl (2 mol dm^{-3}) until the pH reached 3.0. The mixture was stirred for an additional 45–60 min at the same temperature and poured into water. After extraction with dichloromethane, the organic layer was separated, dried over $Na_2(SO_4)$ and filtered; the solvent was removed under reduced pressure to give a white solid that was purified by column chromatography [silica gel, *n*-hexane/ethyl acetate (1:2 *v*/*v*)] to give colourless crystals in 84% yield. NMR (DMSO): δ(H) 2.11–2.13 (d, J = 7.02 Hz, 1H, H_2), 2.73–2.75 (d, J = 7.02 Hz, 1H, H_6), 3.72 (s, 3H, OCH_3), 4.97 (s, 1H, H_1), 5.10 (s, 1H, H_7), 5.25–5.27 (d, J = 7.8 Hz, 1H, H_5), 6.36–6.38 (d, J = 7.8 Hz, 1H, OH exchange with D_2O), 6.44–6.48 (m, 2H, H_8 and H_9), 6.90–6.92 (d, J = 9.36 Hz, 2H, aromatic), 7.36–7.39 (d, J = 9.36 Hz, 2H, aromatic); δ(C) 47.42 (C_6), 49.38 (C_2), 55.72 (OCH_3), 81.35 (C_7), 82.56 (C_1), 88.21 (C_5), 114.84 (C_{ar}), 127.08 (C_{ar}), 136.80 (C_8 and C_9), 137.01 (Cq—N). FT–IR (KBr): ν 3347 (OH), 3074, 3021, 2954, 2934 and 2833, 1672 (C═O), 1609 and 1513 (aromatic, C═C), 1445, 1414, 1306, 1252 (C–OCH_3), 1182 (C—O stretching), 1036 (C—N), 829 cm^{-1}.

Crystal data

$C_{15}H_{15}NO_4$
M_r = 273.28
Monoclinic, $P2_1/c$
a = 11.2076 (11) Å
b = 8.4910 (7) Å
c = 14.1867 (15) Å
β = 99.457 (8)°
V = 1331.7 (2) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.10 mm^{-1}
T = 293 (2) K
0.60 × 0.32 × 0.05 mm

Data collection

Stoe IPDSII diffractometer
Absorption correction: integration (*X-RED32*; Stoe & Cie, 2002)
T_{min} = 0.952, T_{max} = 0.993
9348 measured reflections
2600 independent reflections
1497 reflections with $I > 2\sigma(I)$
R_{int} = 0.070

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.046$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.105$	$\Delta\rho_{max} = 0.14$ e Å^{-3}
$S = 0.95$	$\Delta\rho_{min} = -0.16$ e Å^{-3}
2600 reflections	
185 parameters	

Table 1
Intermolecular hydrogen-bond interactions (Å, °).

Cg is the centroid of the C9–C14 ring.

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1A···O2^{i}	0.89 (3)	1.85 (3)	2.735 (2)	172 (3)
C1—H1···O3^{iii}	0.98	2.52	3.480 (2)	165.5
C7—H7···Cg^{i}	0.98	2.72	3.676 (2)	166

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

All H atoms bonded to C atoms were treated as riding atoms, with C—H distances in the range 0.93–0.98 Å and with U_{iso}(H) = kU_{eq}(C), where k = 1.5 for the methyl group and k = 1.2 for all other H atoms. The position of the hydroxy H atom was obtained from a difference map and its parameters were refined freely.

Data collection: *X-AREA* (Stoe & Cie, 2002); cell refinement: *X-AREA*; data reduction: *X-RED32* (Stoe & Cie, 2002); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEPIII* (Burnett & Johnson, 1996) and *PLATON* (Spek, 2003); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD3181). Services for accessing these data are described at the back of the journal.

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