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Crystal, molecular and electronic structure of (3aS,4S,9aS,9bR)-4-ethyl-2,2-dimethylhexahydro-[1,3]dioxolo[4,5-g] indolizin-7(3aH)-one

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Abstract: Molecules of the title compound, $C_{13}H_{21}NO_3$, crystallize as single enantiomers with four stereogenic centres, their absolute configuration were confirmed by anomalous dispersion effects determined by diffraction measurements on the crystals. Conformations of the pyrrolidine and 1,3-oxolane rings are close to that of an envelope, with the flap atoms displaced by –0.205 (1) and –0.449 (1) Å, respectively, from the plane of the other remaining four atoms. The central six-membered ring of the indolizine moiety adopts a nearly perfect boat conformation, with two atoms displaced by 0.575 (1) and 0.603 (1) Å from the plane of the other remaining four atoms. Crystal structure of the title compound is stabilized by C—H···O hydrogen interactions.

Keywords: conformation, crystal and electronic structure, hydrogen interactions, indolizine, single-crystal X-ray study.

Introduction

Indolizidines with different degrees of unsaturation are part of the skeleton of numerous natural compounds found in a large number of plants, animals, bacteria, and fungi. They occupy an important and privileged position in modern organic chemistry, because of their wide spectrum of biological activity. For example, polyhydroxylated indolizidine alkaloids represented by the so popular castanospermine and swainsonine are well known for their ability to function as excellent inhibitors of biologically important pathways. These include the binding and processing of glycoproteins, potent glycosidase inhibitory activities (Melo *et al.*, 2006; Michael, 2003; Lillelund *et al.*, 2002), activity against AIDS virus HIV and some carcinogenic cells as well as against other important pathologens (Gerber-Lemaire, Juillerat-Jeanneret, 2006; Butters, 2002; Compain, Martin, 2001). More importantly, some hybrids of these structures have shown an increase of glycosidase activities as demonstrated in (Shi *et al.*, 2008; Fujita *et al.*, 2004). Indolizines have also been tested as antimycobacterial agents against mycobacterial tuberculosis (Gundersen, *et al.*, 2003). Many studies have proved that indolizine derivatives possess biological activities such as antioxidative (Teklu *et al.*, 2005) and antiherpes (Foster *et al.*, 1995). Other well known pharmacological applications associated with this ring compounds are well documented in literature (Couture *et al.*, 2000; Jorgensen *et al.*, 2000). Based on these facts and in continuation of our effort to develop a simple and efficient route for the synthesis of novel indolizine derivatives, we report here the synthesis, molecular and crystal structure of the title compound (Fig. 1), which crystallizes in the noncentrosymetric monoclinic space group $P2_1$ with one crystallographic independent molecule in the asymmetric unit.

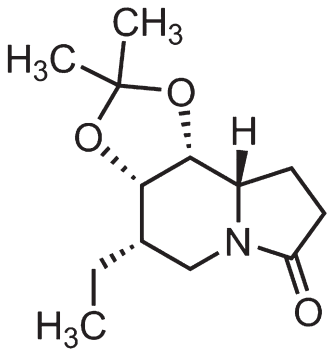

Fig. 1. Molecular structure of the title compound.

Experimental

The title compound, (5*S*,8a*S*)-5-methyl-4,6,7,8,8a,9-hexahydrothieno-[3,2-*f*] indolizinium iodide, was prepared according to a standard protocol described in literature (Šafář *et al.*, 2012).

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Geometry
All estimated standard deviations (esds) (except the esd in the dihedral angle between two l.s. planes) were estimated using the full covariance matrix. The cell esds were taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters were only used when defined by crystal symmetry.

Refinement
Refinement of F^2 against all reflections was done. The weighted *R*-factor, *wR*, and goodness of fit, S, are based on F^2, conventional *R*-factors *R* are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2s(F^2)$ was used only to calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as high as those based on F, and R-factors based on all data will be even higher. All H atoms were positioned with idealized geometry using a constrained riding model with the C—H distances in the range of 0.93—0.98 Å. The U_{iso}(H) values were set to 1.2 U_{eq}(C-aromatic). An absolute structure was established using anomalous dispersion effects; Friedel pairs were not merged.

Data collection
Crystal data and conditions of data collection and refinement are reported in Tab. 1. CrysAlis CCD (Oxford Diffraction, 2009); cell refinement: CrysAlis RED (Oxford Diffraction, 2009); data reduction: CrysAlis RED (Oxford Diffraction, 2009); program(s) used to solve structure: SHELXS97 (Sheldrick, 2008); program(s) used to refine structure: SHELXL97 (Sheldrick, 2008); molecular graphics: DIAMOND (Brandenburg, 2001); software used to prepare material for publication: enCIFer (Allen *et al.*, 2004) and PLATON (Spek, 2009), WinGX (Farrugia, 2012).

Tab. 1. Experimental details.

Empirical formula	$C_{13}H_{21}NO_3$
Formula weight	M_r = 321.21
Temperature	298(2) K
Wavelength	λ = 1.54184 Å , Cu K_α radiation,
Crystal system, space group	Monoclinic, $P2_1$
Unit cell dimensions	a = 6.4383 (4) Å
	b = 8.9886 (5) Å
	c = 11.8645 (8) Å
Volume	V = 665.53 (7) $Å^3$
Z, Calculated density	2, 1.1942 Mg/m^3
Crystal size	0.25 × 0.35 × 0.40 mm
Reflections collected/unique	15442 / 1137; 13923 reflections with I > 2σ(I)
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1137 / 1 / 156
Goodness-of-fit on F^2	S = 1.05
Absolute structure parameter	–0.01 (13) (Flack, 1983)
Final R indices [I > 2sigma(I)]	R1 = 0.037, wR2 = 0.042
Largest diff. peak and hole	0.11 and -0.10 $e.A^{-3}$
Monochromator	Graphite

Tab. 2. Selected geometric parameters: bond lengths [Å].

C2—N1	1.334 (1)	C8—C9	1.516 (1)
C2—O1	1.226 (1)	C8—C10	1.514 (1)
C2—C3	1.490 (2)	C9—N1	1.446 (1)
C3—C4	1.501 (2)	C6—O2	1.421 (1)
C4—C5	1.524 (1)	C12—O2	1.412 (1)
C5—C6	1.510 (1)	C10—C11	1.503 (1)
C5—N1	1.456 (1)	C12—O3	1.414 (1)
C6—C7	1.531 (1)	C12—C13	1.502 (1)
C7—C8	1.514 (1)	C12—C14	1.498 (1)
C7—O3	1.433 (1)		

Tab. 3. Selected geometric parameters: bond angles [°].

N1—C2—O1	124.3 (1)	C9—C8—C10	110.4 (1)
N1—C2—C3	108.8 (1)	C8—C9—N1	111.2 (1)
C3—C2—O1	126.9 (1)	C8—C10—C11	114.9 (1)
C2—C3—C4	105.9 (1)	O2—C12—C13	110.9 (1)
C3—C4—C5	105.7 (1)	O2—C12—C14	109.2 (1)
C4—C5—C6	115.7 (1)	O2—C12—O3	104.7 (1)
C4—C5—N1	103.5 (1)	C13—C12—C14	112.3 (1)
C5—C6—C7	112.7 (1)	O3—C12—C13	111.2 (1)
C5—C6—O2	108.8 (1)	O3—C12—C14	108.4 (1)
C7—C6—O2	104.7 (1)	C2—N1—C5	114.0 (1)
C6—C7—C8	114.6 (1)	C2—N1—C9	123.3 (1)
C6—C7—O3	103.8 (1)	C5—N1—C9	120.7 (1)
C8—C7—O3	109.0 (1)	C6—C5—N1	109.4 (1)
C7—C8—C9	110.3 (1)	C6—O2—C12	108.6 (1)
C7—C8—C10	113.4 (1)	C7—O3—C12	107.4 (1)

Tab. 4. Net charges at individual atoms and Wiberg bonding indices I_w.

Atom	Charge, q	Bond	I_w
C2	0.246	N1—C2	1.166
C3	–0.112	C2—C3	0.937
C4	–0.077	C3—C4	0.996
C5	–0.049	C4—C5	0.979
C6	0.040	C5—C6	0.961
C7	0.055	C6—C7	0.958
C8	–0.094	C7—C8	0.972
C9	–0.022	C8—C9	0.982
C10	–0.082	C8—C10	0.984
C11	–0.072	C10—C11	1.004
C12	0.214	C9—N1	0.962
C13	–0.119	C12—C13	0.938
C14	–0.081	C12—C14	0.973
N1	–0.003	N1—C5	0.962
O1	–0.399	O2—C6	0.972
O2	–0.269	O2—C12	0.948
O3	–0.263	O3—C7	0.969
		O3—C12	0.970

Tab. 5. Hydrogen-bond geometry (Å, º).

D—H···A	D—H	H···A	D···A	D—H···A
C5—H5*A*···O1^{i}	0.98	2.51	3.376 (1)	141.6 (1)
C8—H8A···O1^{i}	0.98	2.55	3.378 (1)	147.8 (1)
C10—H10B···O3	0.97	2.57	2.933 (1)	102.4 (1)

Symmetry codes: (i) 1 + *x*, *y*, *z*

Results and Discussion

Absolute configuration is known from the synthesis and has been established without ambiguity from the anomalous dispersion [absolute structure parameter –0.010 (13) (Flack, 1983)]. Molecular geometry and the atom numbering scheme of the title compound is shown in Fig. 2. Crystal packing of the title compound is shown in Fig. 3. Geometric parameters are presented in Tab. 2 and Tab. 3. Electron structure of the title compound was calculated by the semiempirical quantum chemistry method PM3, (Stewart, 2012). Net charges on the individual atoms and values of the Wiberg bond indices I_w (Wiberg, 1968) are given in Tab. 4. The CCDC deposit number is 863989. The expected stereochemistry of atoms C6, C7, C8 was confirmed as S, S, S and of atom C5 as R.

The central six-membered ring of the indolizine moiety has a nearly perfect boat conformation, with atoms C5 and C8 above the plane [0.575 (1) and 0.603 (1) Å, respectively] formed by the other remaining four atoms: N1, C6, C7 and C9, as confirmed by the ring-puckering parameters (Cromer,

Pople, 1975): Q = 0.677 (1) Å, θ = 91.3 (1)° and φ = 55.6 (1)°. Conformations of the pyrrolidine and 1,3-oxolane rings are close to that of an envelope with the Cremer-Pople puckering amplitude Q of 0.142 (1) and 0.296 (1) Å, orientation angle φ of 124.3 (4) and 133.5 (2)°, respectively. Calculation of the least-squares planes showed that these rings are puckered so that the four atoms N1, C2, C3, C4 of the pyrrolidine ring and the four atoms O2, C6, C7, O3 of the oxolane ring are coplanar, while atoms C5 and C12 are displaced by –0.205 (1) and –0.449 (1) Å, respectively. Atom N1 is sp^2-hybridized, as evidenced by the sum of the valence angles around it (358.0 °). Dihedral angles between the plane of the central N-heterocyclic ring and the plane of the pyrrolidine and 1,3-oxolane rings are 50.1 (1) and 44.2(1) °, respectively.

The crystal structure is stabilized by the intramolecular C10—H10B···O3 and two intermolecular C5—H5A···O1, C8—H8A···O1 hydrogen interactions as the H-atoms donor, which link the molecules into infinite C(4) (Bernstein et al., 1995) zigzag chains along the a axis (Figs. 2, 3 and Tab. 5). Moreover, these hydrogen interactions result in the formation of a seven-membered ring with an $R^2_2(7)$ motif, generating a sheet. Bond length of the carbonyl group C2═O1 is 1.226 (1) Å, which is somewhat longer than typical carbonyl bonds. This may be caused by the fact that atom O1 participates in the intermolecular hydrogen interactions.

Calculation of the electronic structure of a compound provides several indices characterizing the distribution of electron density in the molecule and the multiplicity of the atomic bonds. The net charges give a picture of the distribution of electron density in the molecule and the values of the Wiberg bond indices enable estimation of the multiplicity of individual atomic bonds. The net charge distribution in the molecule indicates that the large positive charges are localized at atoms C2 (0.246) and C12 (0.214), whereas the negative net charges are located on oxide atoms O1 (–0.399), O2 (–0.269) and O3 (–0.263). This charge distribution and the spatial arrangement (geometry) of the molecule govern its biological activity and are important for the overall stabilization of the crystal structure. From the Wiberg index value follows that bond N1—C2 (I_w = 1.166) is not a pure single bond, but it indicates the character of partial single or conjugated bonds as π-electrons are delocalized in the region of the O1, C2, N1 atoms. The other bonds of the molecule have the character of single bonds (Tab. 4.). Results of these calculations are in good agreement with the experimental values of the bond lengths found by the X-ray structure analysis.

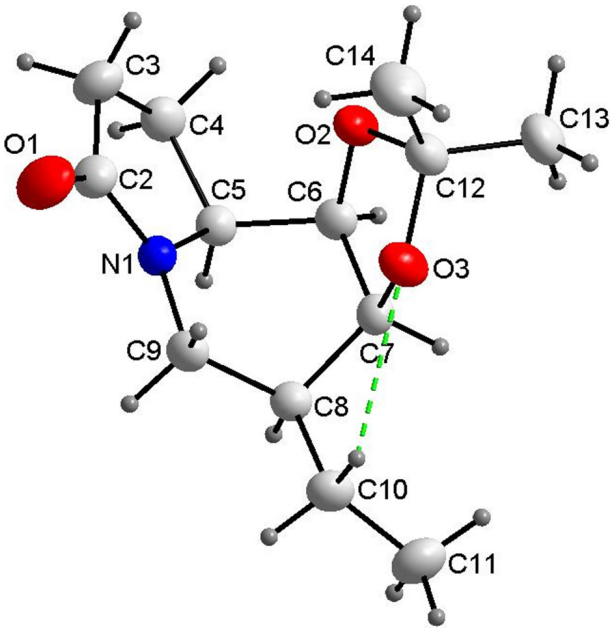

Fig. 2. Molecular structure of the title compound, the atom labelling scheme. Displacement ellipsoids are drawn at the 30 % probability level (Brandenburg, 2001). Intramolecular hydrogen interaction is shown as a dashed line.

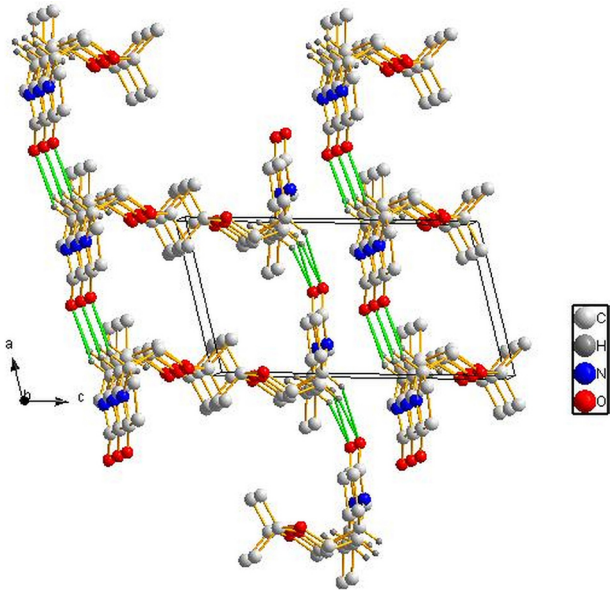

Fig. 3. Part of the crystal structure of the title compound, showing the formation of an intermolecular hydrogen interactions C(7) chain parallel to [100]. Green lines indicate hydrogen bonds. H atoms not involved in the motif have been omitted.

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