Crystal and molecular structure of (5*S*,8aS,9*S*)-9-hydroxy-5-methyl-4,6,7,8,8a,9-hexahydrothieno-[3,2-*f*] indolizin-5-ium iodide

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Abstract: The title compound, $C_{11}H_{16}NOS \cdot I$, is chiral molecule with three stereogenic centres. The absolute configuration was assigned from the synthesis and confirmed by the structure determination. The central six-membered ring of the indolizine moiety adopts a half-chair conformation with atom displaced by 0.655 (2) Å from the plane of the oder remaining five atoms. The pyrrolidine ring adopts an envelope conformation, with the greatest deviation from the mean plane of the ring being 0.646 (2) Å for the bridgehead N atom. The crystal structure of the title compound is stabilized by O—H···I and C—H···O hydrogen bonds.

Keywords: conformation, crystal structure, hydrogen bonds, indolizine, single-crystal X-ray study.

Introduction

Indolizines are electron-rich heterocycles with very low oxidation potential. Functionalized indolizines are common substructures found in biologically important natural products and synthetic pharmaceuticals. Due to the various biological functions associated with this skeleton, it has been frequently employed as a key scaffold in the drug industry (Gundersen *et al.*, 2007). Indolizine alkaloids are excellent inhibitors of biologically important pathways. These include the binding and processing of glycoproteins, potent glycosidase inhibitory activities (Pyne, 2005), activity against AIDS virus HIV and some carcinogenic cells (Mikael, 1999). They have also shown to be calcium entry blockers (Gupta *et al.*, 2003) and potent antioxidants inhibiting lipid peroxidation *in vitro* (Teklu *et al.*, 2005).

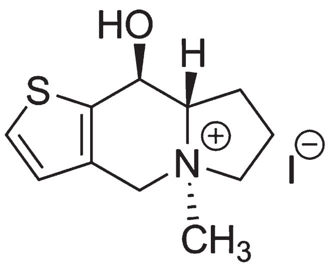

Fig. 1. The molecular structure of the title compound.

As such, indolizines are important synthetic targets in view of developing new pharmaceuticals for the treatment of cardiovascular diseases (Gubin *et al.*, 1992). Based on these facts and in contitutation of our interest in developing 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).

Experimental

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

Geometry

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

Refinement

Refinement of F^2 against all reflections. 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 $F^2 > 2\sigma(F^2)$ is used only for 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 large as those based on F, and R-factors based on all data will be even larger. All H atoms were positioned with idealized geometry using a constrained riding model with C—H distances in the range of 0.93–0.98 Å and and O—H distance 0.85 Å and U_{iso} set at $1.5U_{eq}$ of the parent atom. The U_{iso}(H) values were set at 1.2 U_{eq}(C-aromatic) or 1.5 U_{eq}(*C*-methyl). 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, 1999).

Tab. 1. Experimental details.

Empirical formula	$C_{11}H_{16}NOS \cdot I$
Formula weight	$M_r = 337.21$
Temperature	298(2) K
Wavelength	$\lambda = 0.71073$ Å, Mo K_α radiation,
Crystal system, space group	Monoclinic, $P2_1$
Unit cell dimensions	$a = 6.6835$ (2) Å
	$b = 13.1301$ (4) Å
	$c = 7.4499$ (2) Å
	$\beta = 92.415$ (3) (°)
Volume	$V = 653.19$ (3) Å^3
Z, Calculated density	2, 1.715 Mg/m^3
Crystal size	0.45 × 0.33 × 0.21 mm
Reflections collected/unique	10003/2528; 2669 reflections with $I > 2\sigma(I)$
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2528/2/139
Goodness-of-fit on F^2	$S = 1.02$
Absolute structure parameter	–0.004 (13) (Flack, 1983)
Final R indices $[I > 2\sigma(I)]$	$R1 = 0.016$, $wR2 = 0.033$
Largest diff. peak and hole	0.26 and –0.23 e.A^{-3}
Monochromator	graphite

Tab. 2. Geometric parameters: bond lengths [Å].

C2–N1	1.507 (3)	C7–C10	1.357 (3)
C2–C3	1.531 (3)	C7–S1	1.733 (2)
C3–C4	1.540 (4)	C8–C9	1.349 (4)
C4–C5	1.513 (3)	C8–S1	1.713 (3)
C5–C6	1.520 (3)	C9–C10	1.427 (3)
C5–N1	1.524 (3)	C10–C11	1.496 (3)
C6–O1	1.416 (3)	C11–N1	1.498 (3)
C6–C7	1.490 (4)	C12–N1	1.501 (3)

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

N1–C2–C3	104.7 (2)	C7–C10–C11	122.1 (2)
C2–C3–C4	105.5 (2)	C8–C9–C10	112.2 (3)
C4–C5–N1	103.1 (2)	C9–C8–S1	112.2 (2)
C4–C5–C6	119.6 (2)	C9–C10–C11	124.6 (2)
C5–C4–C3	105.0 (2)	C10–C7–S1	110.6 (2)
O1–C6–C7	114.0 (2)	C10–C11–N1	109.5 (2)
O1–C6–C5	110.0 (2)	C11–N1–C12	109.9 (2)
C7–C6–C5	108.6 (2)	C11–N1–C2	112.8 (2)
C10–C7–C6	125.9 (2)	C11–N1–C5	110.4 (2)
C6–C5–N1	112.1 (2)	C12–N1–C5	112.4 (2)
C6–C7–S1	123.5 (2)	C2–N1–C5	101.7 (2)
C7–C10–C9	113.3 (2)	C8–S1–C7	91.8 (1)

Tab. 4. Hydrogen-bond geometry (Å, º).

D—H···A	D—H	H···A	D···A	D—H···A
C11—H11*A*···O1^{i}	0.97	2.59	3.140 (3)	116
O1—H1···I1^{ii}	0.86 (2)	2.65 (2)	3.4992 (17)	171 (3)

Symmetry codes: (i) $x + 1, y, z$; (ii) $x, y, z + 1$.

Results and Discussion

The absolute configuration is known from the synthesis and has been established without ambiguity from the anomalous dispersion of the I atom [absolute structure parameter –0.004 (13) (Flack, 1983)]. The molecular geometry and the atom-numbering scheme of the title compound is shown in Fig. 2. The crystal packing of the title compound is shown in Fig. 3. The geometric parameters are in Tab. 2 and Tab. 3. The CCDC deposit number is 863991.

The expected stereochemistry of atoms N1, C5 and C6 was confirmed as S, S, S (Fig. 2). The central six-membered ring of the indolizine moiety and the pyrrolidine ring are not planar and adopt a half-chair and an envelope conformation with a Cremer-Pople puckering amplitude (Q) of 0.365 (2) and –0.342 (2) Å, orientation angles θ, φ of 133.2 (2) and 141.2 (2)º for the piperidine ring,

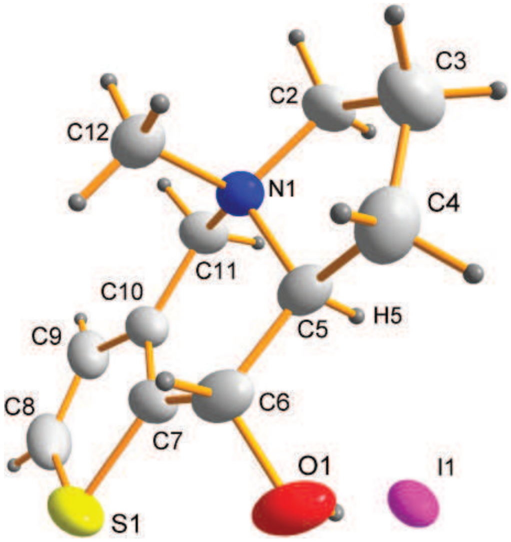

Fig. 2. Molecular structure of the title compound showing the atom labelling scheme. Displacement ellipsoids are drawn at the 50 % probability level (Brandenburg, 2001).

0.432(2) Å and 133.6 (3)° for the pyrrolidine ring, respectively (Cremer, Pople, 1975). A calculation of least-squares planes shows that these rings are puckered in such a manner that the five atoms C5, C6, C7, C10, C11 of the piperidine ring and the four atoms C2, C3, C4, C5 of the pyrrolidine ring are coplanar, while atom N1 is displaced by 0.655 (2) and 0.646 (2) Å, respectively. The dihedral angles between the plane of the four atoms C2, C3, C4 and C5 of pyrrolidine ring and the plane of the five atoms C5, C6, C7, C10 and C11 of piperidine ring is 16.5 (1). The fused thiophene ring is planar (mean deviation 0.003 (2) Å. Two Intermolecular O—H···I and C—H···O hydrogen bonds link the title molecules into extended chains, which run parallel to the b axis (Fig. 3 and Tab. 4) and help to stabilize the crystal structure.

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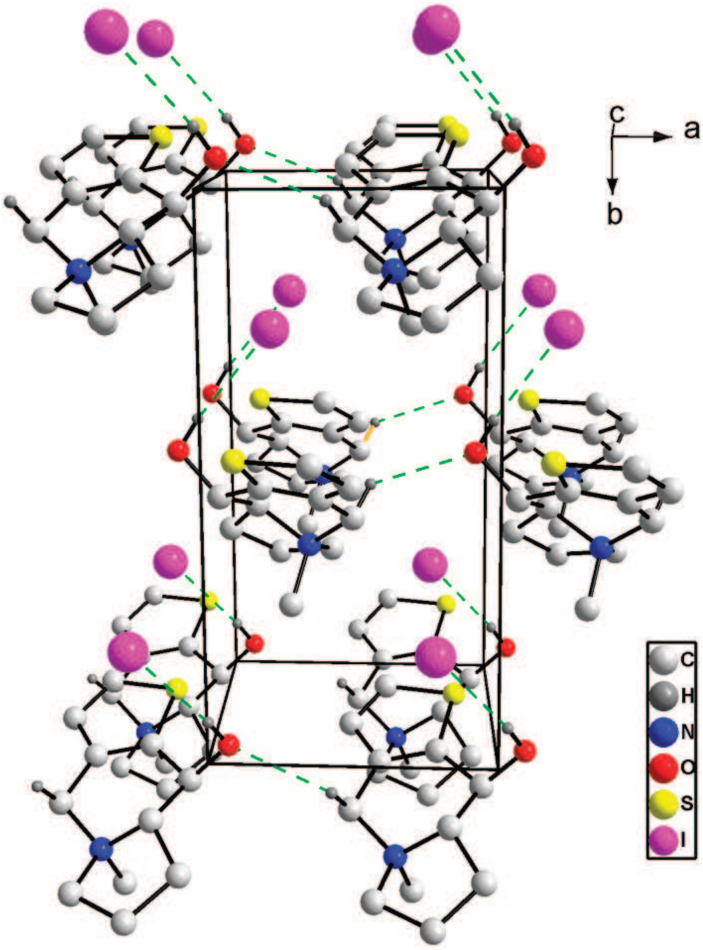

Fig. 3. Packing view of the title compound. Hydrogen bonds O—H···O and O—H···I, are shown by green dashed lines. H atoms not involved in hydrogen bonding have been omitted.

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