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

Viktor Vrábel[a], Július Sivý[b], Peter Šafař[c], Jozefína Žúžiová[c]

[a]*Institute of Analytical Chemistry, Faculty of Chemical and Food Technology, Slovak Technical University, Radlinského 9, SK-812 37 Bratislava, Slovak Republic*
[b]*Institute of Mathematics and Physics, Faculty of Mechanical Engineering, Slovak University of Technology, Námestie slobody 17, SK-812 31 Bratislava, Slovak Republic*
[c]*Institute of Organic Chemistry, Catalysis and Petrochemistry, Faculty of Chemical and Food Technology, Slovak Technical University, Radlinského 9, SK-812 37 Bratislava, Slovak Republic*
*viktor.vrabel@stuba.sk*

Abstract: The molecules of the title compound, $C_{11}H_{16}NS \cdot I$, crystallize as single enantiomer with two stereogenic centre, their absolute configuration were confirmed by anomalous dispersion effects in diffraction measurements on the crystals. The conformation of the pyrrolidine ring is close to that of an envelope, with the flap atom N1 displaced by 0.661 (2) Å from the plane of the oder remaining four atoms. The central six-membered ring of the indolizine moiety adopt a half-chair conformation with atom C5 displaced by –0.686 (2) Å from the plane of the oder remaining five atoms. The crystal structure of the title compound is stabilized by C—H···I···H—C 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 pathologies (Gerber-Lemaire, Juillerat-Jeanneret, 2006; Butters, 2002; Compain, Martin, 2001). More importantly, some hybrids of these structures have shown in numerous cases an increase of glycosidase activities as demonstrated by the Pearson's group and others (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 demonstrated that indolizine derivatives show biological activity such as antioxidative (Teklu *et al.*, 2005) and antiherpes (Foster *et al.*, 1995). The other well known pharmacological applications associated with this ring compounds are well documented in the literature (Couture *et al.*, 2000; Jorgensen *et al.*, 2000). Based on these facts and in continuation 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), which crystallizes in the noncentrosymetric orthorhombic space group $P2_12_12_1$ with one crystallographic independent molecule in asymmetric unit.
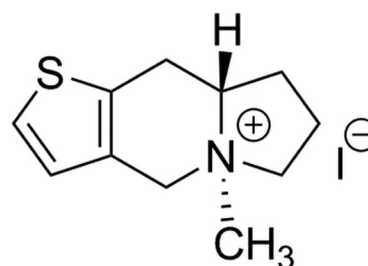
Fig. 1. The molecular structure of the title compound.

Experimental

The title compound (5 *S*,8aS)-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).

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 $F^2 > 2s(F^2)$ is used only for calculating R-factors(gt) *etc.* and is not relevant to the choice of reflections for refinement. R-factors based on F2 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. 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).

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 –0.020 (16) (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 electron structure of the title compound was calculated by the semiempirical quantum chemistry method PM3, (Stewart, 2012). The net charges on the individual atoms and the values of Wiberg bond indices I_w (Wiberg, 1968)

Tab. 1. Experimental details.

Empirical formula	$C_{11}H_{16}NS \cdot I$
Formula weight	$M_r = 321.21$
Temperature	298(2) K
Wavelength	$\lambda = 0.71073$ Å,
	Mo K_α radiation,
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	a = 6.5733 (1) Å
	b = 7.3104 (1) Å
	c = 25.8090 (6) Å
Volume	V = 1240.21 (4) Å³
Z, Calculated density	4, 1.720 Mg/m³
Crystal size	0.45 × 0.25 × 0.20 mm
Reflections collected/unique	19081/2181; 2141 reflections with I > 2σ(I)
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2181/0/127
Goodness-of-fit on F^2	S = 1.03
Absolute structure parameter	–0.020 (13) (Flack, 1983)
Final R indices [I>2sigma(I)]	R1 = 0.013, wR2 = 0.036
Largest diff. peak and hole	0.30 and –0.27 e.A⁻³
Monochromator	Graphite

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

C2—N1	1.515 (3)	C8—C9	1.343 (4)
C2—C3	1.522 (3)	C9—C10	1.427 (3)
C3—C4	1.537 (3)	C7—S1	1.721 (2)
C4—C5	1.515 (3)	C8—S1	1.718 (3)
C5—C6	1.518 (3)	C10—C11	1.496 (3)
C5—N1	1.525 (3)	C11—N1	1.497 (3)
C6—C7	1.494 (3)	C12—N1	1.504 (3)
C7—C10	1.368 (3)		

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

N1—C2—C3	103.7 (2)	C8—C9—C10	113.1 (2)
C4—C5—N1	103.4 (2)	C7—C10—C9	112.0 (2)
C2—C3—C4	105.8 (2)	C7—C10—C11	122.6 (2)
C4—C5—C6	118.9 (2)	C9—C10—C11	125.4 (2)
C5—C4—C3	105.4 (2)	C10—C11—N1	109.4 (2)
C7—C6—C5	109.2 (2)	C11—N1—C12	109.2 (2)
C10—C7—C6	124.4 (2)	C11—N1—C2	113.5 (2)
C6—C5—N1	110.4 (2)	C11—N1—C5	110.7 (2)
C10—C7—S1	111.4 (2)	C12—N1—C5	112.6 (2)
C6—C7—S1	124.1 (2)	C2—N1—C5	101.5 (2)
C9—C8—S1	111.9 (2)	C8—S1—C7	91.6 (1)

are given in Tab. 4. The CCDC deposit number is 863990. The expected stereochemistry of atoms N1 and C5 was confirmed as S, S.

Tab. 4. Values of net charges at individual atoms and Wiberg bonding indices I_w.

Atom	Charge, q	Bond	I_w
I1	– 0.994	N1 – C2	0.957
C2	– 0.149	C2 – C3	0.991
C3	– 0.087	C3 – C4	0.983
C4	– 0.082	C4 – C5	0.983
C5	– 0.159	C5 – C6	0.979
C6	0.026	C6 – C7	0.986
C7	– 0.324	C7 – C10	1.610
C8	– 0.239	C8 – C9	1.691
C9	– 0.055	C9 – C10	1.200
C10	– 0.135	C10 – C11	0.987
C11	– 0.079	N1 – C11	0.958
C12	– 0.147	N1 – C12	0.974
N1	0.566	N1 – C5	0.938
S1	0.389	S1 – C7	1.142
		S1 – C8	1.154

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

D—H···A	D—H	H···A	D···A	D—H···A
C11—H11A···I1[i]	0.97 (2)	3.19 (2)	4.158 (2)	173.0 (2)
C12—H12B···I1[ii]	0.96 (2)	3.00 (2)	3.930 (2)	162.5 (3)

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

The central six-membered piperidine ring of the indolizine moiety and the pyrrolidine ring are not planar and adopt a half-chair and an envelope conformation with ring-puckering parameters (Cremer, Pople, 1975) calculated for the atom sequence N1-C5-C6-C7-C10-C11 of Q = 0.515 (2) Å, θ = 46.8 (2)° and φ = 267.0 (4)° for the piperidine ring and for the atom sequence N1-C2-C3-C4-C5 of Q = 0.436 (2) Å and φ = 357.4 (3)° for the pyrrolidine ring. A calculation of least-squares planes shows that these rings are puckered in such a manner that the five atoms N1, C6, C7, C10, C11of the piperidine ring and the four atoms C2, C3, C4, C5 of the pyrrolidine ring are coplanar, while atom C5 is displaced by –0.686 (2) Å and atom N1 is displaced by 0.661 (2) Å, respectively. On the other hand, the thiophene ring is essentially planar with a maximum deviation from the mean plane of the five ring atoms of 0.004 (3) Å for atom C8. The dihedral angles between the plane of the five atoms C6, C7, C10, C11 and N1 of piperidine ring and the plane of the thiophene ring is 12.8 (1)°.

The crystal structure of the salt can be described as a donor-acceptor adduct, in which the independent components are connected through a hydrogen-bonding network. A detailed examination of the molecular packing reveals that the cation and anion are connected alternately by means of two the intramolecular C11—H11A···I1 and the inter-molecular C12—H12B···I1 hydrogen interactions as H-atoms donor, link the molecules into infinite C(4) (Bernstein et al., 1995) zigzag chains along the b axis (Fig. 3 and Tab. 4) and help to stabilize the crystal structure.

Calculation of the electronic structure of a compound provides several indices which characterize the distribution of electron density in the molecule and the multiplicity of 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 one to estimate the
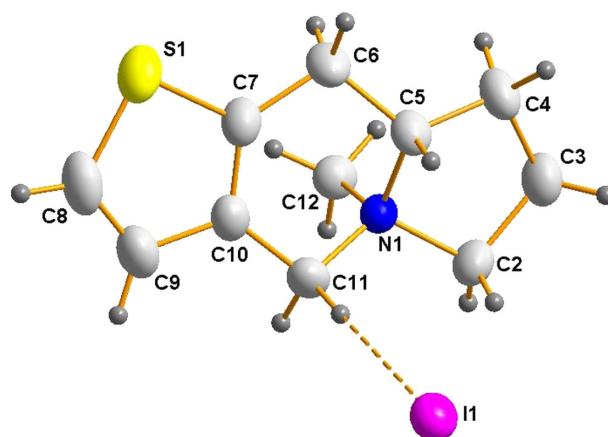
Fig. 2. Molecular structure of the title compound showing the atom labelling scheme. Displacement ellipsoids are drawn at the 50 % probability level (Brandenburg, 2001). The intramolecular hydrogen interaction is shown as a dashed line.
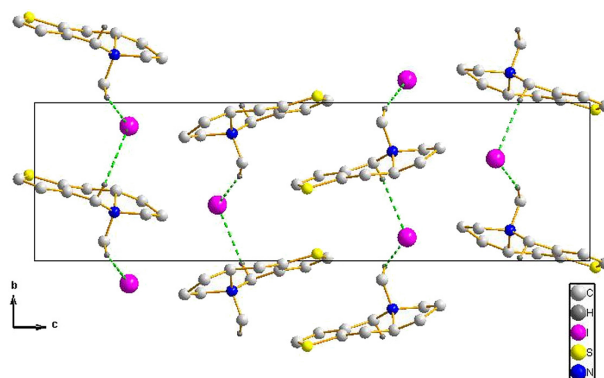
Fig. 3. Packing view of the title compound. Hydrogen interactions C—H···I are shown by green dashed lines. H atoms not involved in hydrogen bonding have been omitted.

multiplicity of individual atomic bonds. The net charge distribution in the molecule indicates that the large positive charges are localized at the atoms N1 (0.566) and S1 (0.389), whereas the negative net charge is located on atom I1 (–0.994). 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. It follows from the Wiberg index values for the bonds C7—C10 (I_w = 1.610) and C8—C9 (I_w = 1.691) is not a pure double bond, but that π-electrons are delocalized in the region of the thiophene ring. The values of the Wiberg indices for the bonds S1—C7 (I_w = 1.142) and S1—C8 (I_w = 1.154), indicate the character of partial single or conjugated bonds. The other bonds of the central six-membered and pyrrolidine ring have the character of single bonds (Tab. 4.). The results of these calculations are in good agreement with the experimental values of the bond lengths found by the X-ray structure analyses.

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