

Crystal, molecular and electron structure of (2*R*,3*R*,4*aS*,5*S*,7*R*,10*aS*,10*bS*)-5-ethyl-2,3-dimethoxy-2,3,7-trimethyl-decahydro-2*H*-[1,4]dioxino[2,3-*g*]indolizin-7-ium iodide hydrate

Vrábel Viktor^a, Sivý Július^b, Šafář Peter^c

^aInstitute of Analytical Chemistry, Faculty of Chemical and Food Technology, Slovak Technical University, Radlinského 9, SK-812 37 Bratislava, Slovak Republic

^bInstitute of Mathematics and Physics, Faculty of Mechanical Engineering, Slovak University of Technology, Námetie slobody 17, SK-812 31 Bratislava, Slovak Republic

^cInstitute 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 title compound, C₁₇H₃₂NO₄I·H₂O, is chiral molecule with seven 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 and 1,4-dioxane ring adopt a chair conformation, with two atoms displaced by -0.530(3), 0.712(3) and -0.631(2), 0.602(2) Å, respectively, from the plane of the other four atoms. The conformation of the pyrrolidine ring is close to that of an envelope, with the flap atom displaced by -0.600(3) Å from the plane through the remaining four atoms. The electron structure was calculated by the semiempirical quantum chemistry method PM3. The crystal structure of compound is stabilized by O—H···I and O—H···O hydrogen bonds.

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

Introduction

Heterocycles are involved in a wide range of biologically important chemical reactions in living organisms. One group of heterocycles, indolizines, has received much scientific attention during the recent years. Indolizine derivatives have been found to possess a variety of biological activities such as antibacterial, antiinflammatory, antiviral, (Nash *et al.*, 1988; Molyneux and James, 1982; Medda *et al.*, 2003), anti-HIV (Ruprecht *et al.*, 1989) and antitumor (Pearson and Guo, 2001). 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). As such, indolizines are important synthetic targets in view of developing new pharmaceuticals for the treatment of cardiovascular diseases (Gubin *et al.*, 1992). Due to the diverse properties of indolizine derivatives, the crystal and molecular structure of the title compound (Fig. 1), has been determined as part of our study of the conformational changes caused by different substituents at various positions on the indolizine ring system.

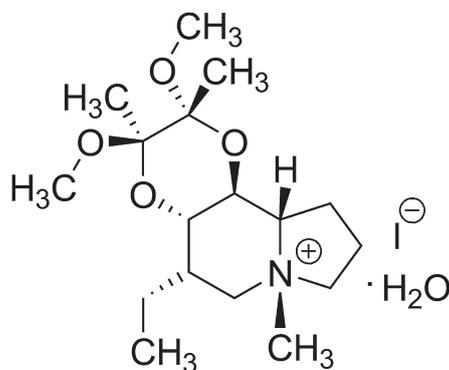


Fig. 1. The molecular structure of the title compound.

Experimental

The title compound (2*R*,3*R*,4*aS*,5*S*,7*R*,10*aS*,10*bS*)-5-ethyl-2,3-dimethoxy-2,3,7-trimethyl-decahydro-2*H*-[1,4]dioxino[2,3-*g*]indolizin-7-ium iodide hydrate 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 riding model with C—H distances are in the range 0.93–0.98 Å and O—H distance 0.85 Å and U_{iso} set at $1.5U_{\text{eq}}$ of the parent atom. The $U_{\text{iso}}(\text{H})$ values were set at $1.2U_{\text{eq}}(\text{C-aromatic})$ or $1.5U_{\text{eq}}(\text{C-methyl})$. An absolute structure was established using anomalous dispersion effects; 1033 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);

Tab. 1. Experimental details.

Empirical formula $\text{C}_{17}\text{H}_{32}\text{NO}_4 \cdot \text{I} \cdot \text{H}_2\text{O}$
Formula weight $M_r = 459.35$
Temperature 298(2) K
Wavelength $\lambda = 0.71073 \text{ \AA}$, Mo K_{α} radiation,
Crystal system, space group Orthorhombic, $P2_12_12_1$
Hall symbol P 2ac 2ab
Unit cell dimensions $a = 9.152(2) \text{ \AA}$
$b = 9.526(2) \text{ \AA}$
$c = 22.770(5) \text{ \AA}$
Volume $V = 1985.3(7) \text{ \AA}^3$
Z , Calculated density 4, 1.537 Mg/m ³
Crystal size $0.35 \times 0.30 \times 0.25 \text{ mm}$
Reflections collected/unique 38675/ 4525; 3621 reflections with $I > 2\sigma(I)$
Refinement method Full-matrix least-squares on F^2
Data/restraints/parameters 4525/2/229
Goodness-of-fit on $F^2 S = 1.01$
Absolute structure parameter $-0.03(4)$ (Flack, 1983)
Final R indices [$I > 2\sigma(I)$] $R1 = 0.030$, $wR2 = 0.040$
Largest diff. peak and hole 1.18 and -0.69 e.\AA^{-3}
Monochromator graphite

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 $-0.03(4)$ (Flack, 1983)]. The molecular geometry and the atom-numbering scheme of the title compound is shown in Fig. 2. 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) are given in Tab. 5. The expected stereochemistry of atoms N1, C5, C6, C7, C8, C12 and C13 was confirmed as R, S, S, S, S, S, S ,

Tab. 2. Geometric parameters: bond lengths [\AA].

C2—C3	1.515 (5)	C11—H11B	0.9600
C2—N1	1.521 (4)	C11—H11C	0.9600
C2—H2A	0.9700	C12—O1	1.427 (4)
C2—H2B	0.9700	C12—O2	1.431 (3)
C3—C4	1.556 (5)	C12—C14	1.504 (4)
C3—H3A	0.9700	C12—C13	1.543 (4)
C3—H3B	0.9700	C13—O3	1.426 (3)
C4—C5	1.530 (4)	C13—O4	1.440 (4)
C4—H4A	0.9700	C13—C16	1.505 (4)
C4—H4B	0.9700	C14—H14A	0.9600
C5—N1	1.512 (4)	C14—H14B	0.9600
C5—C6	1.522 (4)	C14—H14C	0.9600
C5—H5	0.9800	C15—O2	1.433 (3)
C6—O1	1.430 (4)	C15—H15A	0.9600
C6—C7	1.500 (4)	C15—H15B	0.9600
C6—H6	0.9800	C15—H15C	0.9600
C7—O4	1.434 (4)	C16—H16A	0.9600
C7—C8	1.525 (4)	C16—H16B	0.9600
C7—H7	0.9800	C16—H16C	0.9600
C8—C9	1.531 (4)	C17—O3	1.434 (4)
C8—C10	1.536 (4)	C17—H17A	0.9600
C8—H8	0.9800	C17—H17B	0.9600
C9—N1	1.518 (4)	C17—H17C	0.9600
C9—H9A	0.9700	C18—N1	1.500 (4)
C9—H9B	0.9700	C18—H18A	0.9600
C10—C11	1.527 (5)	C18—H18B	0.9600
C10—H10A	0.9700	C18—H18C	0.9600
C10—H10B	0.9700	O5—H55A	0.926 (19)
C11—H11A	0.9600	O5—H55B	0.919 (18)

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

C6—C5—C4	112.8 (3)	O1—C12—C14	106.4 (2)
O1—C6—C7	110.6 (2)	O2—C12—C14	113.3 (2)
O1—C6—C5	105.6 (3)	O1—C12—C13	110.0 (2)
C7—C6—C5	111.2 (3)	O2—C12—C13	103.5 (2)
O4—C7—C6	111.4 (2)	C14—C12—C13	114.0 (3)
O4—C7—C8	109.9 (2)	O3—C13—O4	109.7 (2)
C6—C7—C8	110.8 (3)	O3—C13—C16	112.5 (2)
C7—C8—C9	107.2 (3)	O4—C13—C16	106.4 (3)
C7—C8—C10	114.7 (3)	O3—C13—C12	104.4 (3)
C9—C8—C10	117.5 (3)	O4—C13—C12	110.1 (2)
N1—C9—C8	117.3 (3)	C16—C13—C12	113.7 (2)
N1—C5—C6	110.3 (3)	O1—C12—O2	109.6 (2)
C2—C3—C4	106.5 (2)	C3—C2—N1	104.8 (3)
C18—N1—C5	109.5 (2)	C9—N1—C2	115.1 (2)
C18—N1—C9	107.4 (2)	C12—O1—C6	112.2 (2)
C5—N1—C9	114.1 (2)	C12—O2—C15	115.3 (2)
C18—N1—C2	107.4 (3)	C13—O3—C17	114.9 (3)
C5—N1—C2	103.2 (2)	C7—O4—C13	112.9 (2)
C11—C10—C8	113.4 (3)	C13—O3—C17	114.9 (3)
C7—O4—C13	112.9 (2)		

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

D—H...A	D—H	H...A	D...A	D—H...A
O5—H55A...O3 ⁱ	0.93 (2)	2.04 (2)	2.916 (3)	157 (4)
O5—H55B...I1	0.92 (2)	2.69 (2)	3.605 (3)	173 (3)

Symmetry code: (i) $x, y-1, z$.

R and R , respectively (Fig. 2). The central piperidine and 1,4-dioxane rings are not planar and adopt a chair conformation with a Cremer-Pople puckering amplitude (Q) of 0.550(3) Å and 0.544(3) Å, respectively; orientation angles θ , φ of 14.5(3) and 158.9(4)° for piperidine ring, 3.1(3) and 346.0(5)° for 1,4-dioxane rings, respectively (Cremer, Pople, 1975). A calculation of least-squares planes shows that these rings are puckered in such a manner that the four atoms C5, C6, C8, C9 and C6, C7, C12, C13 are coplanar to within 0.022(2) Å, while atoms N1, C7 and O1, O4 are displaced from this plane on opposite sides, with out-of-plane displacements of -0.530(3), 0.712(2) and -0.631(2), 0.602(2) Å, respectively. The pyrrolidine ring attached to the indolizine ring system has envelope conformation, with atom N1 on the flap. The maximum deviation from planarity for N1 is -0.600 (3) Å. The dihedral angles between the plane of the four atoms C2, C3, C4 and C5 of pyrrolidine ring and the planes of the four atoms C5, C6, C8, C9 of piperidine ring and C6, C7, C12, C13 of 1,4-dioxane ring are 71.4(1)

Tab. 5. Net charges on the individual atoms and Wiberg bond indices I_w .

Atom	Net charge	Bond	I_w
N1	0.553428	N1—C2	0.9024
C2	-0.150819	N1—C5	0.8898
C3	-0.095297	N1—C9	0.9143
C4	-0.078385	N1—C18	0.9534
C5	-0.157585	C2—C3	1.0043
C6	0.035755	C4—C5	0.9950
C7	0.046188	C5—C6	0.9731
C8	-0.081554	C6—O1	0.9776
C9	-0.149852	C7—H7	0.9634
C10	-0.087396	C7—C8	0.9696
C11	-0.067782	C7—O4	0.9801
C12	0.202381	C8—H8	0.9656
C13	0.198633	C8—C9	0.9862
C14	-0.088054	C8—C10	0.9942
C15	0.100141	C10—C11	1.0081
C16	-0.089254	O1—C12	0.9349
C17	0.108032	C12—O2	0.9868
C18	-0.142951	C12—C14	0.9765
O1	-0.258186	C12—C13	0.9169
O2	-0.279294	C13—O4	0.9413
O3	-0.290481	C13—C16	0.9782
O4	-0.241685	C13—O3	0.9716
I1	-0.965581	O3—C17	0.9917

and 35.0(2)°, respectively. Bond lengths and angles in the indolizine ring system are in good agreement with values from the literature (Vrábel *et al.*, 2011). The crystal packing of the title compound is shown in Fig. 3. The crystal structure is stabilized by two intermolecular hydrogen bonds. The molecules are connected through O—H...O hydrogen bonds between coordinated water molecule and methoxy oxygen atom of neighboring molecule. The hydrogen bonds are also supplemented by O—H...I hydrogen bonding interactions (Tab. 4).

The calculation of the electron structure provided several indices which characterize the distribution of electron density in the molecule and the multiplicity of bonds. The net charges give a picture of distribution of electron density in the molecule and the values of Wiberg bond indices enable to estimate the multiplicity of individual bonds.

The most negative net charges except iodine atom are at O1, O2, O3 and O4 atoms. The most positive charge is at N1 atom. The Wiberg bond indices indicate that all bonds in the molecule are single bonds. The charge distribution in the cation $[C_{17}H_{32}NO_4]^+$ shows that the positive charge is localized not only at the nitrogen atom N1, but part of charge is

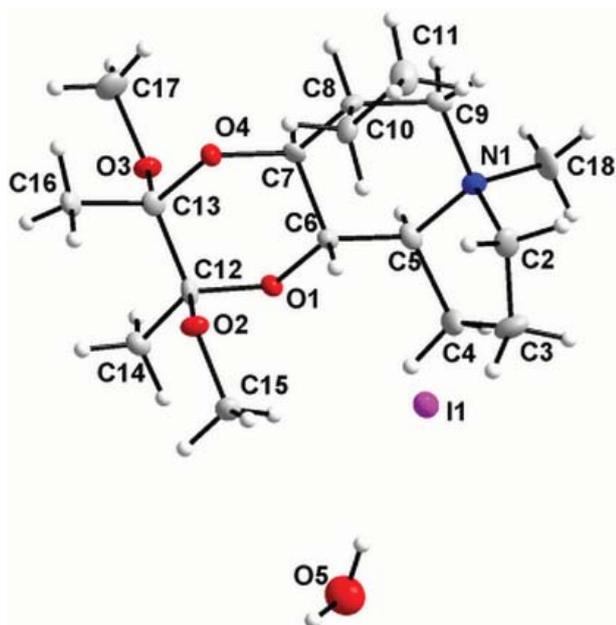


Fig. 2. Molecular structure of the title compound showing the atom labelling scheme. Displacement ellipsoids are drawn at the 50 % probability level (Brandenburg, 2001).

distributed over the whole molecule. These results of PM3 calculations are in a good agreement with the experimental values of bond lengths found by X-ray structure analysis (Tab. 5).

Acknowledgement

The authors thank the Grant Agency of the Ministry of Education of the Slovak Republic, (grant Nos. 1/0429/11, 1/0679/11), and Structural Funds, Interreg IIIA, for financial support in purchasing the diffractometer and this work was supported by the Slovak Research and Development Agency under the contract Nos. APVV-0797-11, APVV-0204-10 and Structural Funds, Interreg IIIA, for financial support in purchasing the diffractometer. This contribution is also the result of the project: Research Center for Industrial Synthesis of Drugs, ITMS 26240220061, supported by the Research & Development Operational Programme funded by the ERDF.

References

- Allen FH, Johnson O, Shields GP, Smith BR, Towler M (2004) *J. Appl. Cryst.* 37: 335–338.
 Brandenburg K (2001) DIAMOND Version 2.1e. Crystal Impact GbR, Bonn, Germany.
 Cremer D, Pople JA (1975) *J. Am. Chem. Soc.* 97: 1354–1362.
 Farrugia LJ (1999) *J. Appl. Cryst.* 30: 565.
 Flack HD (1983) *Acta Cryst.* A39: 876–881.
 Gubin J, Lucchetti J, Mahaux J, Nisato D, Rosseels G, Clinet M, Polster P, Chatelain P (1992) *J. Med. Chem.* 35: 981–988.

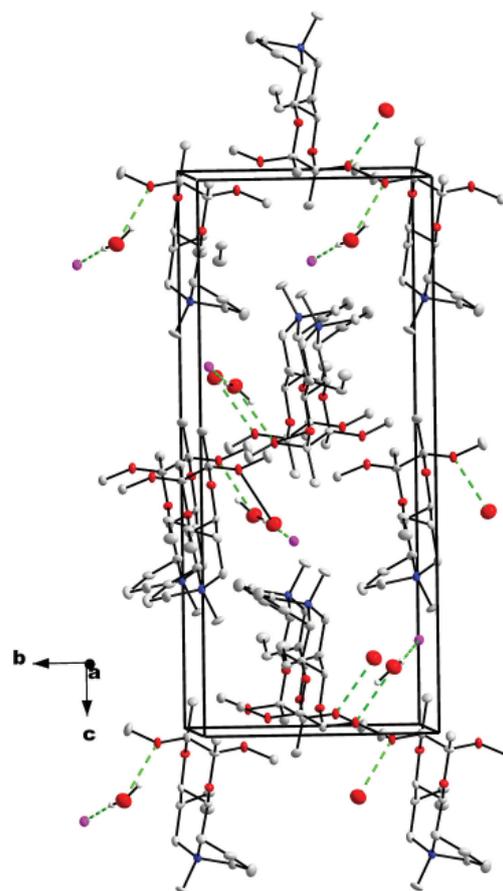


Fig. 3. Packing view of the title compound. Hydrogen bonds O—H...O and O—H...I, are shown by green dashed lines. H atoms not involved in hydrogen bonding have been omitted.

- Gupta SP, Mathur AN, Nagappa AN, Kumar D, Kumaran S (2003) *Eur. J. Med. Chem.* 38: 867–873.
 Medda S, Jaisankar P, Manna RK, Pal B, Giri VS, Basu MK (2003) *J. Drug Target.* 11: 123–128.
 Molyneux RJ, James LF (1982) *Science* 216: 190–191.
 Nash RJ, Fellows LE, Dring JV, Stirton CH, Carter D, Hegarty MP, Bell EA (1988) *Phytochemistry* 27: 1403–1406.
 Oxford Diffraction (2009). CrysAlisPro. Oxford Diffraction Ltd, Abingdon, Oxfordshire, England.
 Pearson WH, Guo L (2001) *Tetrahedron Lett.* 42: 8267–8271.
 Ruprecht RM, Mullaney S, Andersen J, Bronson R (1989) *J. Acquir. Immune Defic. Syndr.* 2: 149–157.
 Sheldrick GM (2008) *Acta Cryst.* A64: 112–122.
 Spek AL (2009) *Acta Cryst.* D65: 148–155.
 Stewart JJP (2012) MOPAC2012–DG3. Stewart Computational Chemistry, Colorado Springs, CO, USA.
 Šafář P, Žužiová, J, Marchalín Š, Prónayová N, Švorc L, Vrabel V, Šesták S, Rendič D, Tognetti V, Joubert L, Daich A (2012) *Eur. J. Org. Chem.* 5498–5514.
 Teklu S, Gundersen LL, Larsen T, Malterud KE, Rise F (2005) *Med. Chem.* 13: 3127–3139.
 Vrabel V, Sivý J, Švorc L, Šafář P, Žužiová J (2011) *Acta Cryst.* E67: o3520–o3521.
 Wiberg KB (1968) *Tetrahedron*, 24(3): 1083–1096.