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Crystal and molecular structure of (6S,7R,8R,8aS)-7-bromo-6-(2-bromoethyl)-3-oxooctahydroindolizin-8-yl acetate

Viktor Vrábel[1], Ľubomír Švorc, Peter Šafař[2], Štefan Marchalín[2] , Jozef Kožíšek[3]

[1]Institute of Analytical Chemistry, Faculty of Chemical and Food Technology, Slovak University of Technology, Radlinského 9, SK-812 37 Bratislava, Slovak Republic
[2]Institute of Organic Chemistry, Catalysis and Petrochemistry, Faculty of Chemical and Food Technology, Slovak University of Technology, Radlinského 9, SK-812 37 Bratislava Slovak Republic
[3]Institute of Physical Chemistry and Chemical Physics, Faculty of Chemical and Food Technology, Slovak University of Technology, Radlinského 9, SK-812 37 Bratislava Slovak Republic

lubomir.svorc@stuba.sk

Abstract

The absolute configuration of the title compound, $C_{12}H_{17}Br_2NO_3$, was assigned from the synthesis and confirmed by the structure determination. In the molecular structure, the central six-membered ring of the indolizine moiety adopts a chair conformation, with the deviations from the mean plane of the ring being -0.595 (2)Å for N1 atom and 0.563 (2)Å for C7 atom. The pyrrolidin-2-one ring is distorted towards a flat-envelope conformation, with atom C4 on the flap. Atom C4 is 0.191 (2)Å from the mean plane defined by atoms N1, C2, C3 and C5. The crystal structure is stabilized by van der Waals forces.

Keywords: indolizine, crystal and molecular structure, single-crystal X-ray study, conformation

Introduction

Bridgehead nitrogen heterocycles are important natural products. Among them, indolizines have received much attention in recent years due to their intriguing molecular structures featured with a 10 π-delocalized electrons. They have been found to possess a variety of biological activities such as anti-inflammatory (Malonne et al., 1998), antiviral (Medda et al., 2003), aromatase inhibitory (Sonnet et al., 2000), analgestic (Campagna et al., 1990) and antitumor (Pearson and Guo, 2001) activities. 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). For instance, aminoalkyloxybenzenesulfonylindolizine compounds such as fantofarone and butoprozine have been used for the treatment of hypertension, arrhythmia and angina pectoris (Rosseels et al., 1982). Indolizines are important synthetic targets in view of developing new pharmaceuticals for the treatment of cancer (Liu et al., 2007) and HIV infections (Butters, 2002). Several oxygenated indolizines have been shown to prevent, due to their strong anti-oxidative effects, the initiation of oxidation processes that lead to DNA damage (Oslund et al., 2008; Ostby et al., 2000). More importantly, some hybrids of indolizine have shown in numerous cases an increase of glycosidase activities as demonstrated Pearson´s group and others (Shi et al., 2008; Fujita et al., 2004). Castanospermine (Karanjule et al., 2006), swainsonine (Martin et al., 2005) and lentiginosine (Chaudhari et al., 2006) have shown respective glycosidase and mannosidase inhibitory activities, respectively. Polycyclic indolizine derivatives have been found to have high quantum yield of long-wavelength fluorescence quantum yield (Vlahovici et al., 2002) and use as synthetic dyes (Jaung and Jung, 2003). The synthesis of polycyclic indolizine derivatives has recently attracted much research interest in the search for new opto-electric materials (Mitsumori et al., 2004). Thus, there is a growing interest in the synthesis and study of crystal and molecular structures of indolizine derivatives.

Synthesis, crystal and molecular structure of (6S,7R,8R,8aS)-7-bromo-6-(2-bromoethyl)-3-oxooctahydroindolizin-8-yl acetate (I), (Fig. 1.), are subjects of the present paper.

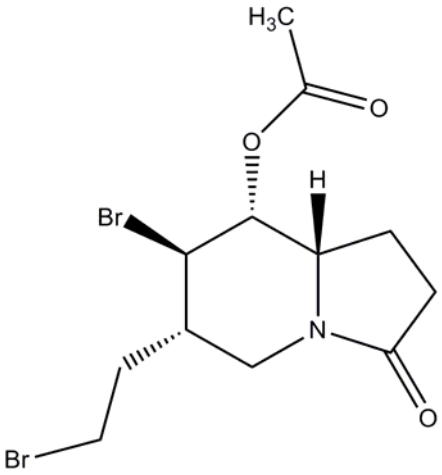

Fig. 1. The molecular structure of the title compound (I)

Experimental

The title compound (6S,7R,8R,8aS)-7-bromo-6-(2-bromoethyl)-3-oxooctahydroindolizin-8-yl (I) acetate was prepared according literature procedures of Šafář et al. (2010). In a 25 ml ace pressure tube are placed (3aS,8aS,9R,9aS)-9-hydroxyoctahydrofuro[3,2-f]indolizin-6(7H)-one (0.987 g) and hydrogen bromide solution (33 % in acetic acid, 10 ml). The ace pressure tube was closed and heated at 75 ºC for 48 h. The reaction mixture in the tube was cooled to 0 ºC, diluted with water (15 ml), neutralized with potassium carbonate solution (50%), and extracted with CH_2Cl_2 (3 x 30 ml). The combined organic layer was dried with Na_2SO_4. Evaporation of the solution afforded a crude oil, which was purified by chromatography (CH_2Cl_2/acetone 20:1) on silica gel column to provide a colorless crystalline solid (1.50 g, 78%). Recrystallization from n-hexane gave an analytical sample of (6S,7R,8R,8aS)-7-bromo-6-(2-bromoethyl)-3-oxooctahydroindolizin-8-yl, mp 114–115 ºC.

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 has been accomplished. 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 $F^2 > 2\text{sigma}(F^2)$ 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 placed in geometrically calculated positions and allowed to ride on their parent atoms, with C—H distances of 0.93 Å and U_{iso} set at $1.2U_{eq}$ of the parent atom.

Data collection

CrysAlis CCD (Oxford Diffraction, 2006); cell refinement: CrysAlis RED (Oxford Diffraction, 2006); data reduction: CrysAlis RED (Oxford Diffraction, 2006); 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).

Crystal data and structure refinement

Empirical formula	$C_{12}H_{17}Br_2NO_3$
Formula weight	M_r = 383.09
Temperature	298(2) K
Wavelength	λ = 0.71073 Å , Mo K_α radiation,
Crystal system, space group	Tetragonal, $P4_3$
Hall symbol	P 4cw
Unit cell dimensions	a = 15.635(4) Å
	b = 15.635(3) Å
	c = 12.2472(8)Å
Volume	V = 2993.9 (11) $Å^3$
Z, Calculated density	4, 1.700 Mg/m^3
F(000)	1520
Crystal size	0.57 × 0.11 × 0.08 mm
Theta range for data collection	3.33 to 29.32^o
Limiting indices	-19<=h<=21, -21<=k<=21, -16<=l<=16
Reflections collected/unique	65508 / 7601; 3596 reflections with I > 2σ(I)
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7601 / 1 / 328
Goodness-of-fit on F^2	S = 0.972
Absolute structure parameter	0.01(1) (Flack, 1983)
Final R indices [I>2sigma(I)]	R1 = 0.0230, wR2 = 0.0698
Largest diff. peak and hole	0.481 and -0.261 $e.A^{-3}$
	$(\Delta/\sigma)_{max}$ < 0.001
Monochromator	graphite

Table 1.Atomic coordinates (. 10^4) and equivalent isotropic displacement parameters U(eq) ($Å^2$. 10^3).

atom	x	y	z	U(eq)
C(2)	4185(2)	7423(2)	9272(3)	59(1)
C(3)	4074(2)	6479(2)	9072(3)	84(1)
C(4)	4259(2)	6339(2)	7880(3)	93(1)
C(5)	4283(2)	7234(2)	7364(2)	63(1)
C(6)	3554(2)	7474(2)	6592(2)	61(1)
C(7)	3509(2)	8437(2)	6384(2)	51(1)
C(8)	3576(2)	8992(2)	7399(2)	48(1)
C(9)	4322(2)	8714(2)	8110(2)	49(1)
C(10)	2757(2)	8997(2)	8090(2)	54(1)
C(11)	1960(2)	9289(2)	7476(2)	67(1)
C(12)	2257(2)	6632(2)	6612(3)	66(1)
C(13)	1416(2)	6548(2)	7189(3)	104(1)
N(1)	4275(1)	7806(2)	8304(2)	51(1)
O(1)	4188(1)	7774(1)	10161(2)	86(1)
O(2)	2746(1)	7239(1)	7102(1)	58(1)
O(3)	2492(2)	6223(1)	5832(2)	88(1)
Br(1)	4422(1)	8724(1)	5339(1)	83(1)
Br(2)	978(1)	9300(1)	8457(1)	82(1)

Table 2. The geometric parameters: bond lengths [Å] and angles [°]

C(2)-O(1)	1.220(3)
C(2)-N(1)	1.335(4)
C(2)-C(3)	1.505(4)
C(3)-C(4)	1.504(4)
C(4)-C(5)	1.536(4)
C(5)-N(1)	1.459(3)
C(5)-C(6)	1.528(3)
C(6)-O(2)	1.456(3)
C(6)-C(7)	1.529(3)
C(7)-C(8)	1.520(3)
C(7)-Br(1)	1.969(2)
C(8)-C(9)	1.520(3)
C(8)-C(10)	1.535(3)
C(9)-N(1)	1.441(3)
C(10)-C(11)	1.525(3)
C(11)-Br(2)	1.949(2)
C(12)-O(3)	1.208(3)
C(12)-O(2)	1.359(3)
C(12)-C(13)	1.498(4)
O(1)-C(2)-N(1)	126.2(3)
O(1)-C(2)-C(3)	125.9(4)
N(1)-C(2)-C(3)	107.9(3)

C(4)-C(3)-C(2)	106.2(3)
C(3)-C(4)-C(5)	105.7(3)
N(1)-C(5)-C(6)	109.3(2)
N(1)-C(5)-C(4)	103.5(2)
C(6)-C(5)-C(4)	117.4(3)
O(2)-C(6)-C(5)	108.7(2)
O(2)-C(6)-C(7)	106.2(2)
C(5)-C(6)-C(7)	112.3(3)
C(8)-C(7)-C(6)	115.1(2)
C(8)-C(7)-Br(1)	110.6(2)
C(6)-C(7)-Br(1)	107.4(2)
C(7)-C(8)-C(9)	110.9(2)
C(7)-C(8)-C(10)	113.3(2)
C(9)-C(8)-C(10)	109.0(2)
N(1)-C(9)-C(8)	109.7(2)
C(11)-C(10)-C(8)	114.3(2)
C(10)-C(11)-Br(2)	110.1(3)
O(3)-C(12)-O(2)	123.2(3)
O(3)-C(12)-C(13)	126.5(3)
O(2)-C(12)-C(13)	110.3(3)

Table 3. The geometric parameters: torsion angles [°]

O(1)-C(2)-C(3)-C(4)	-170.9(3)
N(1)-C(2)-C(3)-C(4)	9.3(3)
C(2)-C(3)-C(4)-C(5)	-11.9(3)
C(3)-C(4)-C(5)-N(1)	10.2(3)
C(3)-C(4)-C(5)-C(6)	-110.3(3)
N(1)-C(5)-C(6)-O(2)	-70.5(3)
C(4)-C(5)-C(6)-O(2)	46.9(4)
N(1)-C(5)-C(6)-C(7)	46.7(3)
C(4)-C(5)-C(6)-C(7)	164.1(3)
O(2)-C(6)-C(7)-C(8)	72.2(3)
C(5)-C(6)-C(7)-C(8)	-46.4(3)
O(2)-C(6)-C(7)-Br(1)	-164.2(2)
C(5)-C(6)-C(7)-Br(1)	77.2(2)
C(6)-C(7)-C(8)-C(9)	48.1(3)
Br(1)-C(7)-C(8)-C(9)	-73.8(2)
C(6)-C(7)-C(8)-C(10)	-74.9(3)
Br(1)-C(7)-C(8)-C(10)	163.2(2)
C(7)-C(8)-C(9)-N(1)	-51.1(3)
C(10)-C(8)-C(9)-N(1)	74.4(3)
C(7)-C(8)-C(10)-C(11)	-57.4(3)
C(9)-C(8)-C(10)-C(11)	178.5(2)
C(8)-C(10)-C(11)-Br(2)	-178.2(2)
O(1)-C(2)-N(1)-C(9)	-5.6(5)
C(3)-C(2)-N(1)-C(9)	174.2(2)
O(1)-C(2)-N(1)-C(5)	177.5(3)
C(3)-C(2)-N(1)-C(5)	-2.7(3)
C(8)-C(9)-N(1)-C(2)	-118.0(3)
C(8)-C(9)-N(1)-C(5)	58.8(3)
C(6)-C(5)-N(1)-C(2)	121.0(3)
C(4)-C(5)-N(1)-C(2)	-4.8(3)
C(6)-C(5)-N(1)-C(9)	-56.2(3)
C(4)-C(5)-N(1)-C(9)	178.0(2)
O(3)-C(12)-O(2)-C(6)	6.9(4)
C(13)-C(12)-O(2)-C(6)	-173.9(3)
C(5)-C(6)-O(2)-C(12)	-116.3(2)
C(7)-C(6)-O(2)-C(12)	122.7(2)

Results and Discussion

As part of our recent efforts to synthesize novel polycyclic indolizine derivative, we report here the synthesis, crystal and molecular structure of the title compound, (I) (Fig. 1). The absolute configuration is known from the synthesis and is depicted in the scheme and figure and has been established without ambiguity from the anomalous dispersion of the Br atoms [absolute structure parameter 0.01(1) (Flack, 1983)]. The molecular geometry and the atom-numbering scheme of the title compound is shown in Fig. 2. The atomic coordinates and equivalent isotropic displacement parameters of (I) are in Table 1, the geometric parameters are in Table 2 and Table 3.

The expected stereochemistry of atoms C5, C6, C7 and C8 was confirmed as S, R, R and S, respectively. The central six-membered N-heterocyclic ring is not planar and adopts a chair conformation (Cremer and Pople, 1975). A calculation of least-squares planes shows that this ring is puckered in such a manner that the four atoms C5, C6, C8 and C9 are coplanar to within 0.010 (2)Å, while atoms N1 and C7 are displaced from this plane on opposite sides, with out-of-plane displacements of -0.595 (2) and 0.563 (2)Å, respectively. The pyrrolidin-2-one ring is distorted towards a flat-envelope conformation, with atom C4 on the flap. Atom

C4 is 0.191 (2)Å from the mean plane defined by atoms N1, C2, C3 and C5. Dihedral angle between plane defined by atoms C5, C6, C8 and C9 and plane defined by atoms N1, C2, C3 and C5 is 125.5 (1)°. As shown in Table 2, the N1-C5 and N1-C9 bonds are approximately equivalent and both are much longer than the N1-C2 bond. Moreover, the N1 atom is sp^2 hybridized, as evidenced by the sum of the valence angles around it [359.9 (2)°]. These data are consistent with conjugation of the lone-pair electrons on N1 with the adjacent carbonyl and agree with literature values for simple amides (Brown and Corbridge, 1954; Pedersen, 1967). The bond length of the carbonyl group C2=O1 is 1.220 (3)Å, respectively, is somewhat longer than typical carbonyl bonds. This may be due to the fact that atom O1 participates in weak intermolecular interactions.

In the crystal structure, neighboring molecules are linked and stabilized through weak van der Waals forces [shortest intramolecular contacts are C4...O2 (x, y, z-1), 2.913 (2)Å and C7...N1 (y, 1-x, -3/4+z), 2.817 (3)Å]. All the interactions demonstrated were found by PLATON (Spek, 2009). The geometric parameters of the title compounds agree well with reported similar structures (Vrábel et al., 2004, Švorc et al., 2009).

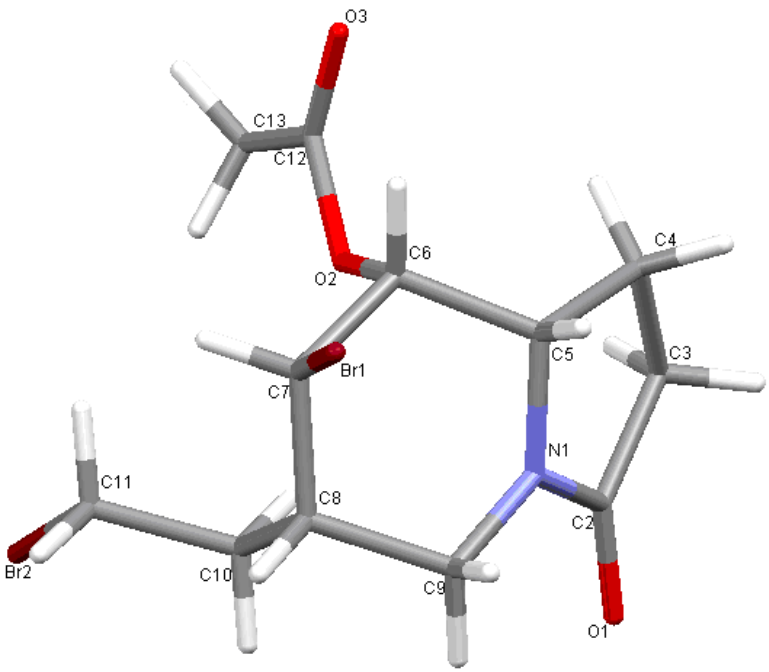

Fig. 2. The molecular structure of the title compound, with the atomic numbering scheme.

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