Crystal, molecular and electronic structure of (5*S*,11*R*,11a*S*)-11-hydroxy-5-methyl-1,2,3,4,5,6,11,11a-octahydropyrido[1,2-b]isoquinolin-5-ium iodide

Július Sivý[a], Peter Šafář[b], Jozefína Žúžiová[b]

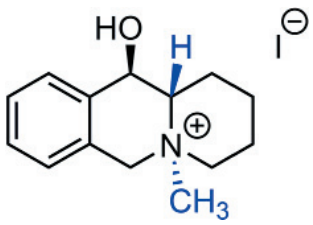
[a]*Faculty of Mechanical Engineering, Slovak University of Technology, Námestie slobody 17, SK-812 31 Bratislava, Slovak Republic*
[b]*Institute of Organic Chemistry, Catalysis and Petrochemistry, Faculty of Chemical and Food Technology, Slovak Technical University, Radlinského 9, SK-812 37 Bratislava,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

Abstract: The title compound, $C_{14}H_{20}INO$, is a molecule with three stereogenic centres. It absolute configuration was derived from the synthesis and confirmed by structure determination (AD, Flack (Parsons') parameter: 0.031 (8)). The expected stereochemistry of atoms N1 was confirmed to be *S*, C5 was confirmed to *S*, C6 was confirmed to *R*. The central *N*-heterocyclic ring is not planar and adopts a half-chair conformation. A calculation of least-squares planes showed that these rings are puckered in such a manner that the five atoms: C5, C6, C7, C12 and C13 (the second ring: C1, C2, C3, C4, C5 and N1) are planar, while atom N1 is displaced from these plane with the out-of-plane displacement of –0.694 (4) and –0.670 (5) Å in the second ring, respectively. Dihedral angle between the planes of the central N-heterocyclic rings is 23.4 (2)°. Crystal structure is also stabilized by C—H···O hydrogen interactions.

Keywords: crystal structure, DFT calculation, hydrogen interactions, isoquinoline, single-crystal X-ray study

Introduction

Alkaloids are the configurationally and conformationally various group of natural products with a wide range of biological and human effects. Many naturally occurring plant alkaloid derivatives have shown wide spectra of biological properties, as determined by in vivo pharmacological screening and research investigation. The attempts to expansion the activity of alkaloids by chemical modifications has been successful. Interesting biological activity has been achieved in compound where the isoquinolines were used as pharmacophore. Artificially prepared derivatives of natural lead structures possess biological effects as well antimicrobial activity. The attempts to increase the antimicrobial activity of alkaloids by chemical paths of modifications were successful (Renner et al., 2009; Fattorusso et al., 2008). Hydroisoquinoline (benzoisoquinolinium) derivatives play role to attract the attention of medicinal chemists because of their potential application as pharmaceutical drugs for the treatment of DM (Kubo et al., 2000). Some of them are used in clinical treatment and they act as inhibitors of testosterone-5α-reductase, which is of great importance for treatment of various skin diseases, for example, acne treatment, as well as excessive hair loss treatment (Vrábel et al., 2016). Benzoisoquinoline derivatives are interesting as selective non-steroidal inhibitors of steroid 5α-reductase-1 (Guarna et al., 2001). Selective inhibition of 5α-reductase-1 is currently investigated as a potential therapeutic tool for the treatment of dihydrotestosterone-related skin disorders, such as acne, alopecia, male baldness and hirsutism (Harris & Kozarich, 1997). Hydroisoquinoline derivatives, e. g. *tylophorine* or *tylophorinine*, are important in a wide range of biological activities and they possesse anticoagulant and anti-inflammatory activities. Tylophorine derivatives are known as bioactive compounds with weak toxic, anti-carcinogenic, anticoagulant and antibiotic activities. In this work, epi-benzoanalogue of bioactive phenanthroquinolidine alkaloid was prepared by synthesis and X-ray investigation was performed, and also DFT/B3LYP (Becke, 1988; Becke, 1993; Lee et al., 1988)/LanL2MB/ Auto calculation. The absolute configuration of the product was controlled by anomalous dispersion. We report here the crystal structure of the



Scheme 1: View of molecular structure of the title compound.

title compound (Scheme 1) as a novel quinolizine derivatives, which crystallizes in the noncentrosymetric orthorhombic space group $P2_12_12_1$ with one crystallographically independent molecule in asymmetric unit of the basic cell.

Experimental

The title compound, (5*S*,11*R*,11a*S*)-11-hydroxy-5-methyl-1,2,3,4,5,6,11,11a-octahydro-pyrido[1,2-b]isoquinolin-5-ium iodide, was prepared according to a standard protocol described in literature (Pagáč et al., 2018).

Geometry

All estimated standard deviations (esds) (except for 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 the cell parameters were only used when defined by crystal symmetry.

Refinement

Refinement of F^2 against all reflections. The weighted *R*-factor, *wR*, and the 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 $F^2 > 2\sigma(F^2)$ was used only to calculate the *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 are 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 O—H distance 0.82 Å. The U_{iso}(H) values were set to 1.2 U_{eq} (C-aromatic) and 1.5 U_{eq} (C-methyl), respectively.

Data collection

Crystal data and conditions of data collection and refinement are reported in Table 1. Data collection: CrysAlis CCD (Oxford Diffraction, 2009); cell refinement: CrysAlis CCD; data reduction: CrysAlis RED (Oxford Diffraction, 2009); program(s) used to solve structure: SHELXS (Sheldrick, 2015), Sir2014 (Burla et al., 2015); program(s) used to refine structure: SHELXL (Sheldrick, 2015); molecular graphics: Diamond (Brandenburg, 1999), Ortep-3 (Farrugia, 2012); software used to prepare material for publication: Gaussian09 (Frisch et al., 2013), Olex2 (Dolomanov et al., 2009), PLATON (Spek, 2009) SHELXL (Sheldrick, 2015), ShelXle (Hübschle et al., 2011).

Tab. 1. Experimental details.

Empirical formula	$C_{14}H_{20}INO$
Formula weight	M_r = 345.21
Temperature	298.0(2) K
Wavelength	λ = 0.71073 Å, Mo Kα radiation
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	*a* = 9.8884(6) Å
	b = 10.6201(5) Å
	c = 13.9265(8) Å
	α, β, γ = 90(4) °
Volume	*V* = 1462.50(14) Å^3
Z, Calculated density	4, 1.568 Mg/^{m}3
Crystal size	0.5072 × 0.3915 × 0.1974
Temp	298.0(2) K
F(000)	688.0
2Θ range for data collection	4.824 to 50.694 /^{o}
Index ranges	–11 ≤ h ≤ 11, –12 ≤ k ≤ 12,
	–16 ≤ l ≤ 16
Reflections collected	22007
Independent reflections	2679 [R_{int} = 0.0240,
	R_{sigma} = 0.0111]
Data/restraints/parameters	2679/0/155
Goodness-of-fit on F^2	1.057
Final *R* indexes [$I >= 2\sigma(I)$]	R_1 = 0.0185, wR_2 = 0.0462
Final *R* indexes [all data]	R_1 = 0.0198, wR_2 = 0.0470
Largest diff. peak/hole	0.38/–0.56 eÅ^{-3}
Flack parameter	0.031(8)

Tab. 2. Selected geometric parameters: bond lengths (Å).

C1—C2	1.511(7)	C7—C8	1.392(6)
C1—N1	1.526(5)	C7—C12	1.394(5)
C2—C3	1.509(7)	C8—C9	1.375(7)
C3—C4	1.520(6)	C9—C10	1.379(8)
C4—C5	1.520(5)	C10—C11	1.377(8)
C5—N1	1.524(4)	C13—N1	1.502(5)
C6—C7	1.509(5)	C12—C13	1.495(6)
C6—O1	1.426(4)	C14—N1	1.508(4)
C11—C12	1.382(6)		

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

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1···I1	0.82	2.60	3.415(3)	172.2
C1—H1A···O1^{i}	0.97	2.33	3.253(5)	158.3
C1—H1B···I1^{ii}	0.97	3.02	3.965(4)	165.0

Symmetry codes: (**i**) 2 – x, –1/2 + y, 1/2 – z; (**ii**) 3/2 – x, 1 – y, 1/2 + z.

Tab. 3. Selected geometric parameters: bond and torsion angles (deg.).

C2—C1—N1	112.7(4)	C5—N1—C1	109.0(3)
C3—C2—C1	110.5(4)	C13—N1—C1	107.7(3)
C2—C3—C4	110.7(4)	C13—N1—C5	108.2(3)
C3—C4—C5	113.0(4)	C13—N1—C14	109.2(3)
C4—C5—C6	112.6(3)	C14—N1—C1	110.0(3)
C4—C5—N1	112.2(3)	C14—N1—C5	112.5(3)
C6—C5—N1	110.5(3)	C8—C7—C6	119.7(3)
C7—C6—C5	114.5(3)	C8—C7—C12	119.0(4)
O1—C6—C5	104.3(3)	C12—C7—C6	121.2(4)
O1—C6—C7	111.9(3)	C2—C1—N1	112.7(4)
C4—C5—C6—O1	–70.9(4)	N1—C1—C2—C3	58.7(5)
N1—C5—C6—O1	162.8(3)	C11—C12—C13—N1	154.0(4)
N1—C5—C6—C7	40.1(4)	C4—C5—N1—C1	53.1(4)
C4—C5—N1—C13	170.0(3)	C4—C5—N1—C14	–69.2(4)
C12—C13—N1—C1	174.1(3)	C12—C13—N1—C5	56.4(4)
C12—C13—N1—C14	–66.4(4)	C6—C5—N1—C1	179.7(3)
C6—C5—N1—C13	–63.4(4)	C6—C5—N1—C14	57.4(4)

Results and Discussion

The absolute configuration is known from the synthesis and it was confirmed by the structure determination. The stereochemistry of atoms N1 was confirmed to be *S*, C7 was confirmed to *S*, C6 was confirmed to *R*. Molecular geometry and the atom numbering scheme of the title compound is shown in Fig. 1. Crystal packing of the title compound is shown in Fig. 2 and selected geometric parameters are listed in Tabs. 2, 3. Central *N*-heterocyclic rings are not planar and adopt a half-chair and chair conformation with atom N1 and N1, C3 above the plane [–0.715 (5) and –0.670 (5), 0.650 (0.7) Å, respectively]. 6-membered ring N1, C5, C6, C7, C12, C13 is confirmed by the ring-puckering parameters (Cremer, Pople, 1975): Q = 0.516(4) Å, θ = 49.1(4)° and φ = 13.0(6)(4)°, Cremer-Pople puckering amplitudes for second ring N1, C1, C2, C3, C4, C5: Q = 0.561(5) Å, θ = 3.8(5)° and φ = 76(8)°. Dihedral angle between the planes of the central N-heterocyclic rings is 24.7 (2)°. Atom N1 is sp^3-hybridized, as evidenced by the net charge on it. The crystal structure is also stabilized by one intramolecular O1—H1···I1 and the intermolecular C1—H1A···O1, C1—H1B···I1 hydrogen interactions as H-atom donor (Tab. 4). Bond length of the couple atoms group C6—O1 is 1.426 (4) Å and it is not a strange bond (strange C—O—H geometry with C—O > 1.45 Å, IUCr checkCIF procedure), this may be due to atom O1 participating in weak intra- and inter-molecular hydrogen interactions.

The NBO analyse of theoretical calculations in vacuum and for polarities (but this does not actually add any polarization functions) at *ab initio* DFT/B3LYP level using LanL2MB basis set model (single point geometry, net charges) is shown for selected atoms in Fig. 3 and also I_w (Wiberg bond index; Wiberg, 1966; Gaussian09 rev.: D.01, 2013).

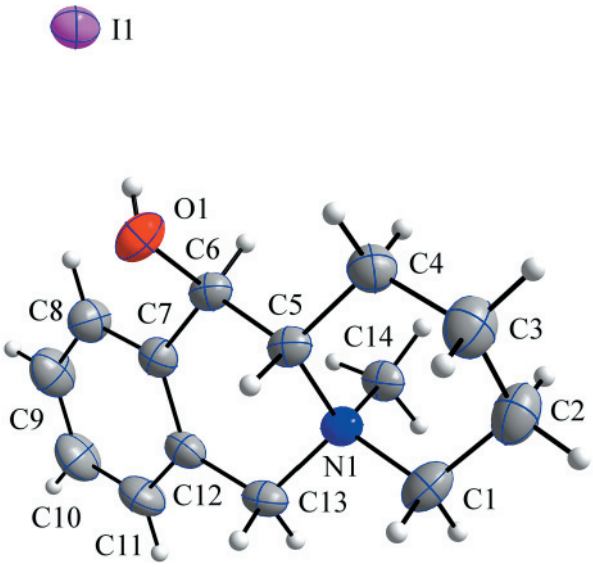


Fig. 1. Molecular structure of the title compound with the atom labelling scheme. Displacement ellipsoids are drawn at the 30 % probability level (Diamond, 1999).

Acknowledgement

This work was supported by the Slovak Research and Development Agency under the contract no. APVV-17-0513. This contribution is also the result of the project: Research Center for Industrial Synthesis of Drugs, ITMS

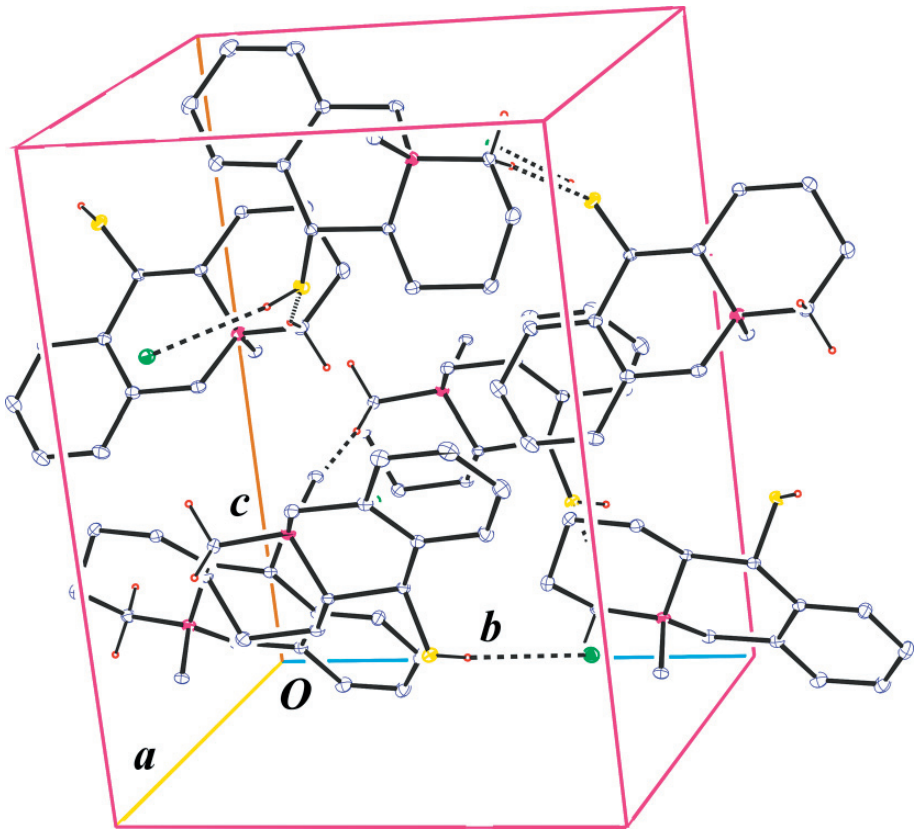


Fig. 2. Part of the crystal structure of the title compound, showing the formation of the intra- and inter-molecular hydrogen interactions.
Dashed lines indicate hydrogen bonds.
H atoms not involved in the motif have been omitted (Ortep-3, 2012).

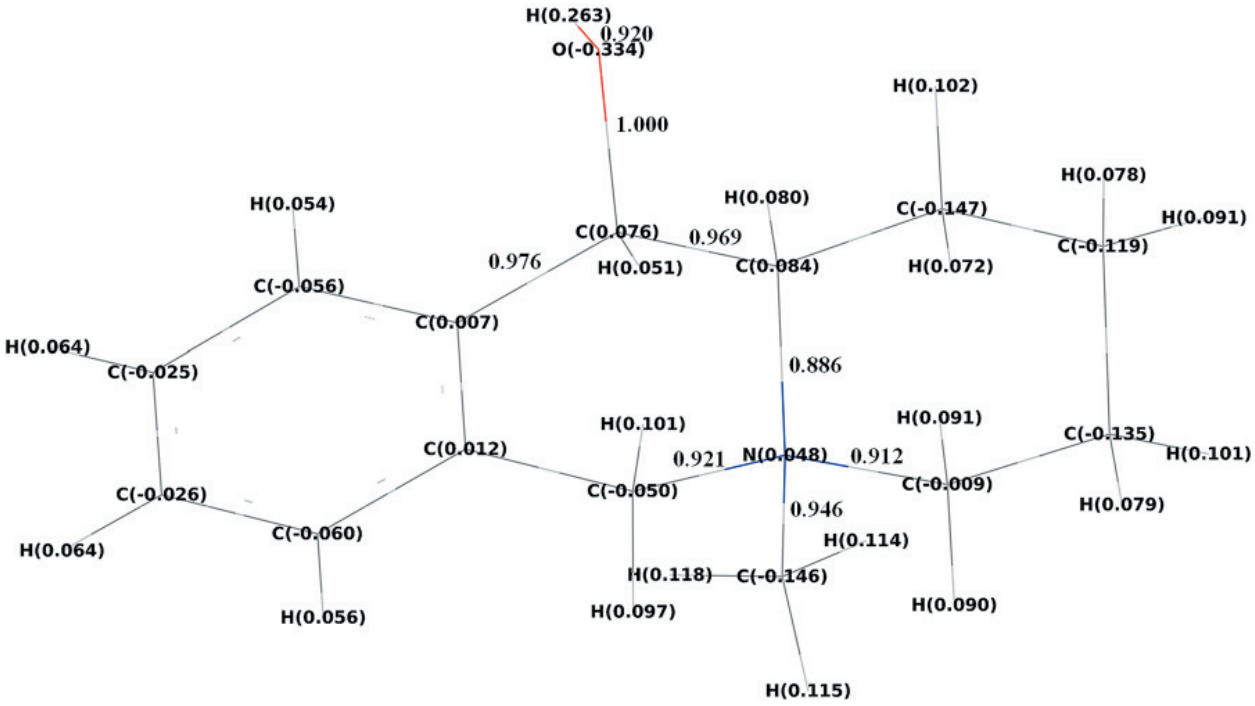


Fig. 3. Molecular structure of the title compound with the selected charge-atoms and I_w (Wiberg bond index).

26240220061, supported by the Research & Development Operational Programme funded by the ERDF.
We are grateful to the HPC center at the Slovak University of Technology in Bratislava, which is a part of the Slovak Infrastructure of High Performance Computing (SIVVP project, ITMS code 26230120002, funded by the European region development funds, ERDF), for the computational time and resources made available.

References

Allen FH, Johnson O, Shields GP, Smith BR, Towler M (2004) J. Appl. Cryst. 37: 335—338.
Antonov KL, Hohla KL (1983) Appl. Phys. B32: 9—14.
Becke AD (1988) Phys. Rev. A38: 3098—3100.
Becke AD (1993) J. Chem. Phys. 98: 5648—5652.
Brandenburg K (1999) Diamond. Crystal Impact GbR, Bonn, Germany.
Burla MC, Caliandro R, Carrozzini B, Cascarano GL, Cuocci C, Giacovazzo C, Mallamo M, Mazzone A, Polidori G (2015) J. Appl. Cryst. 48: 306—309.
Cremer D, Pople JA (1975) J. Am. Chem. Soc. 97: 1354—1362.
Dolomanov OV, Bourhis LJ, Gildea RJ, Howard JAK, Puschmann H (2009) J. Appl. Cryst. 42: 339—341.
Farrugia LJ (2012) J. Appl. Cryst. 45: 849—854.
Fattorusso E, Taglialatela-Scafati O (2008) Wiley-VCH, Weinheim.
Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Scalmani G, Barone V, Mennucci B, Petersson GA, Nakatsuji H, Caricato M, Li X, Hratchian HP, Izmaylov AF, Bloino J, Zheng G, Sonnenberg JL, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Montgomery JA Jr., Peralta JE, Ogliaro F, Bearpark M, Heyd JJ, Brothers E, Kudin KN, Staroverov VN, Kobayashi R, Normand J, Raghavachari K, Rendell A, Burant JC, Iyengar SS, Tomasi J, Cossi M, Rega N, Millam JM, Klene M, Knox JE, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Martin RL, Morokuma K, Zakrzewski VG, Voth GA, Salvador P, Dannenberg JJ, Dapprich S, Daniels AD, Farkas Ö, Foresman JB, Ortiz JV, Cioslowski J, Fox DJ (2013) Gaussian09, Revision D.01, Gaussian, Inc., Wallingford CT.
Guarna A, Occhiato EG, Machetti F, Trabocchi A, Scarpi D, Danza G, Mancina R, Comerci A, Serio M (2001) Bioorg. Med. Chem. 9: 1385—1393.
Harris GS, Kozarich JW (1997) Curr. Opin. Chem. Biol. 1: 254—259.
Hübschle ChB, Sheldrick GM, Dittrich B (2011) J. App. Cryst. 44: 1281—1284.
Kubo H, Kobayashi J, Higashiyama K, Kamel J, Fujii Y, Ohmiya S (2000) Biol. Pharm. Bull. 23: 1114—1117.
Lee C, Yang W, Parr RG (1988) Phys. Rev. B37: 785—789.
Oxford Diffraction (2009). CrysAlisPro. Oxford Diffraction Ltd, Abingdon, Oxfordshire, England.
Pagáč T, Šafář P, Marchalín Š, Ježíková Z, Balónová B, Šupolíková M, Nováková E, Kubíčková J, Šoral M, Sivý J, Olejníková P (2018) Monatshefte für Chemie — Chemical Monthly 149: 1865—1876, CCDC1815854.
Renner S, van Otterlo WAL, Seoane MD, Möcklinghoff S, Hofmann B, Wetzel S, Schuffenhauer A, Ertl P, Steinhilber D, Brunsveld L, Rauh D, Waldmann H (2009) Nat. Chem. Biol. 5: 585.
Sheldrick GM (2015) Acta Cryst. C71: 3—8.
Spek AL (2009) Acta Cryst. D65: 148—155.
Šafář P, Marchalín Š, Prónayová N, Vrábel V, Lawson AM, Othman M, Daich A (2016) Tetrahedron 72: 3221—3231.
Vrábel V, Sivý J, Šafář P, Marchalín Š (2016) Acta Chimica Slovaca 9: 180—183.
Wiberg KB (1966) Tetrahedron 24: 1083—1096.