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Structural characterization and crystal packing of the isoquinoline derivative

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RESEARCH ARTICLE

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ABSTRACT

We report the crystal and molecular structure of a new isoquinoline-derivative, namely methyl O-[(11*R*, 11a*S*)-4-oxo-1, 3, 4, 6, 11, 11a-hexahydro-2*H*-pyrido[1, 2-b]isoquinolin-11-yl]carbonodithioate (I), $C_{15}H_{17}NO_2S_2$, which crystallizes in the non-centrosymmetric space group $P2_12_12_1$ and its absolute structure was confirmed by anomalous dispersion effects in diffraction measurements on the crystals. Two central six-membered heterocyclic rings adopt a distorted half-chair conformation. The molecules are linked by a combination of weak C—H···O, C—H···S, C—H···π inter- and intra-molecular interactions resulting in a three-dimensional network in the crystal structure. Crystal Data for $C_{15}H_{17}NO_2S_2$ (M =307.41 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 5.2804(5) Å, b = 8.1347(17) Å, c = 35.015(4) Å, V = 1504.1(4) Å^3, Z = 4, T = 298(2) K, μ(MoKα) = 0.354 mm^{-1}, D_{calc} =1.358 g/cm^3, 20270 reflections measured (5.522° ≤ 2Θ ≤ 50.69°), 2757 unique (R_{int} = 0.0346, R_{sigma} = 0.0203) which were used in all calculations. The final R_1 was 0.0389 (I > 2σ(I)) and wR_2 was 0.0965 (all data).

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1. Introduction

The isoquinoline alkaloids and their synthetic derivatives represent a large class of medicinally active compounds with potentially attractive properties, including antispasmodic, antimicrobial, antitumor, antifungal, anti-inflammatory, antiviral, amoebicidal, antioxidant and enzyme-inhibiting activities. The increasing microbial resistance to primary active structures remains alarming and the effort to search for new antibacterial active structures is still of great scientific interest. One of the attractive ways how to find novel active structures consist in derivatization of well-known natural compounds. Quinoline and isoquinoline derivatives are considered as a useful structural motif for displaying chemical functionality in biologically active molecules. Some of these derivatives have appeared to exhibit potent biological activities as antibacterial against some gram-positive and gram-negative bacteria [1,2]. Amino-quinoline derivatives have also been used as inhibitors of human immuno deficiency virus (HIV) [3]. For example, 4-aminoquinoline was applied in treatment of erythrocytic plasmodial infections [4]. Pyrrolizidinylalkyl derivatives of 4-amino-7-chloroquinoline exhibited excellent antimalarial activity [5], through the accumulation in the acidic digestive vacuoles of the malaria parasite. Hence, it inhibits conversion of toxic haematin to b-haematin. Likewise, 8-aminoquinoline constitutes a family of drugs, namely, primaquine, tafenoquine and pamaquine [6] which has been used in the treatment of malaria. Some isoquinolines rendered other activities such as anti-neoplastic [7] and/or have been utilized as cardiovascular agents [8].

Quinolines and their isomers isoquinolines are also found in various natural products, such as quinine (anti-malarial) and quinidine (anti-arrhythmic). Furthermore, many isoquinoline alkaloids, including cepharanthine, berberine and tetrandine, have shown anti-inflammatory effect [9-11]. The binding affinity and the solubility in physiological conditions can be considerably affected by the position of the nitrogen bearing a side chain on the isoquinoline skeleton [12]. Therefore, an

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Table 1. Crystal data and details of the structure refinement for compound **I**.

Parameters	Compound I
Empirical formula	$C_{15}H_{17}NO_2S_2$
Formula weight	307.41
Temperature (K)	298
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a, (Å)	5.2804(5)
b, (Å)	8.1347(2)
c, (Å)	35.015(4)
Volume (Å^3)	1504.1(4)
Z	4
ρ_{calc} (g/cm^3)	1.358
μ (mm^{-1})	0.354
F(000)	648.0
Crystal size (mm^3)	0.15 × 0.20 × 0.45
Radiation	MoK$_\alpha$ (λ = 0.71073)
2Θ range for data collection (°)	5.522 to 50.690
Index ranges	$-6 \le h \le 6$, $-9 \le k \le 9$, $-42 \le l \le 42$
Reflections collected	20270
Independent reflections	2757 [R_{int} = 0.1724, R_{sigma} = 0.1163]
Data/restraints/parameters	2757/0/182
Goodness-of-fit on F^2	1.062
Final R indexes [I≥2σ (I)]	R_1 = 0.0389, wR_2 = 0.0937
Final R indexes [all data]	R_1 = 0.0442, wR_2 = 0.0965
Largest diff. peak/hole (e Å^{-3})	0.16/-0.19
Flack parameter	-0.01(3)

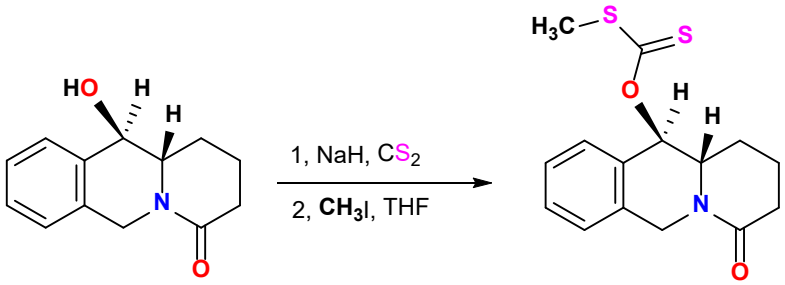

Figure 1. Synthesis of the compound **1**.

enormous effort has been spent in developing novel and effective isoquinoline derivatives.

2. Experimental

2.1. Synthesis

The compound **I** (Figure 1), methyl O-[(11*R*,11a*S*)-4-oxo-1, 3, 4, 6, 11, 11a-hexahydro-2*H*-pyrido[1, 2-b]isoquinolin-11-yl] carbonodithioate was prepared by the reaction of freshly crystallized (11*R*,11a*S*)-11-hydroxy-1,2,3,6,11,11a-hexahydro-4*H*-pyrido[1,2-b]-isoquinolin-4-one with sodium hydride, then carbon disulfide and methyl iodide in dry THF at 60 °C. The recrystallization from n-heptane gave colourless crystals (81 %) as described in literature [13].

2.2. 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 placed in geometrically optimized positions and constrained to ride on their parent atoms, 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) and 1.5 U_{eq}(methyl).

2.3. Data collection

Crystal data and conditions of data collection and refinement are reported in Table 1. CrysAlis CCD [14]; cell refinement: CrysAlis RED [14]; data reduction: CrysAlis RED [14]; program(s) used to solve structure: SHELXS97 [15]; program(s) used to refine structure: SHELXL97 [15]; molecular graphics: DIAMOND [16]; software used to prepare material for publication: enCIFer [17], PLATON [18] and WinGX [19].

2.4. Instrument

X-ray single crystal diffraction was carried out on a four-circle diffractometer, device type Xcalibur, Ruby, Gemini, enhance (Mo) X-ray source, radiation monochromator type graphite, CCD plate detector type Ruby, detector area resolution 5.2170 pixels/mm, analytical numeric absorption correction using a multifaceted crystal model based on expressions derived by R.C. Clark & J.S. Reid [20], empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.

3. Results and discussion

The molecular geometry and the atom numbering scheme of the compound **I** is shown in Figure 2. The crystal packing of compound **I** is depicted in Figure 3. The geometric parameters are listed in Tables 2 and 3.

Table 2. Bond lengths for compound **I**.

Atoms	Length [Å]	Atoms	Length [Å]
C1—C2	1.511 (5)	C7—C12	1.394 (4)
C1—C5	1.512 (4)	C8—C9	1.372 (5)
C2—C3	1.510 (5)	C9—C10	1.365 (5)
C3—C4	1.500 (5)	C10—C13	1.385 (5)
C4—O1	1.229 (4)	C11—N1	1.451 (4)
C4—N1	1.353 (4)	C11—C13	1.497 (5)
C5—N1	1.465 (4)	C12—C13	1.392 (4)
C5—C6	1.531 (4)	C14—O2	1.337 (4)
C6—O2	1.460 (3)	C14—S1	1.617 (4)
C6—C12	1.506 (4)	C14—S2	1.742 (3)
C7—C8	1.381 (5)	C15—S2	1.786 (5)

Table 3. Bond angles for compound **I**.

Atoms	Angle [°]	Atoms	Angle [°]
C2—C1—C5	111.1 (3)	N1—C11—C13	111.6 (3)
C3—C2—C1	108.8 (3)	C13—C12—C7	118.8 (3)
C4—C3—C2	115.6 (3)	C13—C12—C6	121.1 (3)
O1—C4—N1	121.0 (3)	C7—C12—C6	120.0 (3)
O1—C4—C3	120.7 (3)	C10—C13—C12	119.8 (3)
N1—C4—C3	118.3 (3)	C10—C13—C11	119.6 (3)
N1—C5—C1	112.3 (3)	C12—C13—C11	120.6 (3)
N1—C5—C6	106.7 (2)	O2—C14—S1	127.7 (3)
C1—C5—C6	113.8 (3)	O2—C14—S2	104.7 (2)
O2—C6—C12	107.5 (2)	S1—C14—S2	127.5 (2)
O2—C6—C5	107.2 (2)	C4—N1—C11	120.9 (3)
C12—C6—C5	112.6 (2)	C4—N1—C5	125.5 (3)
C8—C7—C12	120.1 (3)	C11—N1—C5	113.4 (2)
C9—C8—C7	120.6 (3)	C14—O2—C6	121.2 (2)
C10—C9—C8	119.8 (3)	C14—S2—C15	102.7 (2)

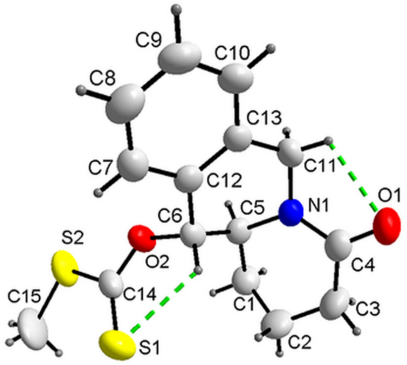

Figure 2. Molecular structure of the compound **I** showing the atom labelling scheme. Displacement ellipsoids are drawn at the 50% probability level. The intramolecular hydrogen interaction is shown as a green dashed line.

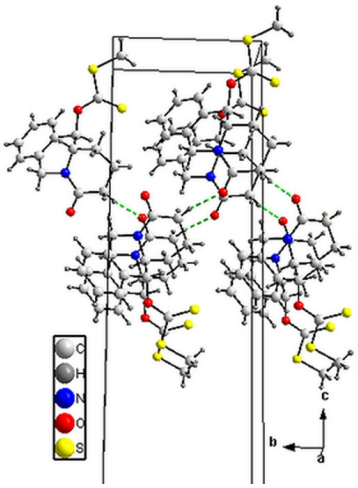

Figure 3. Stereo view of part crystal structure of the compound **I**, showing the formation of a hydrogen bonded C(8) chain parallel to [010]. Green dashed lines indicate hydrogen bonds.

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C6—H6A···S1	0.98(3)	2.576(1)	3.083(3)	112.3(2)
C11—H11A···O1	0.97(3)	2.311(3)	2.739(4)	105.7(2)
C3—H3B···O1^{i}	0.97(3)	2.527(3)	3.483(5)	168.3(2)
C5—H5A···*Cg*1^{ii}	0.97(3)	2.620	3.583	168.0

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

The absolute configuration was unambiguously established by the structure determination. The expected stereochemistry of atoms C5, C6 was confirmed to be *S, R*.

The results indicated that two six-membered rings in the quinolizine moiety of the structure are not planar and yield a half-chair conformation with atoms C2 and C5 above the plane [0.624 (4) and 0.667 (3) Å, respectively] formed by the remaining five atoms N1, C5, C1, C3 and C4 (second ring: C6, C12, C13, C11 and N1,), as approved by the ring-packering parameters [21]: Q = 0.479 (4) Å, θ = 132.9 (5)° and φ = 33.1 (4)° (Cremer-Pople puckering amplitude for second ring: Q = 0.509 (3) Å, θ = 48.6 (3)° and φ = 31.3 (5)°, respectively). Dihedral angle between the two six-membered rings in the quinolizine moiety is 44.7 (1)°. Atom N1 is sp^2-hybridized, as shown by the sum of the valence angles around it (359.8°). These data are consistent with the conjugation of the lone-pair electrons on N1 with an adjacent carbonyl.

Additionally, there is a number of weak intra and intermolecular hydrogen bonds, together with C—H···π contacts, within the crystal structure of (**I**) (geometric parameters are given in Table 4). Two intramolecular hydrogen bonds with graph-set motif S(5) [21], are generated by C6—H6A···S1 and C11—H11A···O1 contacts. Intermolecular C3—H3B···O1 hydrogen bonds, involving O atoms of the carbonyl group link the molecules into infinite C(8) [22] zigzag chains of molecules along the *b* axis (Figure 3). Finally, there are further intermolecular C5—H5A···*Cg*1 (*Cg*1 is the centroid of the C7 – C12 benzene ring) hydrogen bonds in compound **I**. The molecules are linked into an extensive network in which every molecule acts as both a hydrogen-bond donor and acceptor, and the supramolecular assembly takes the form of infinite three-dimensional network.

Bond length of the carbonyl group C4=O1 is 1.229 (4) Å which somewhat longer than typical carbonyl bonds. This may be due to atom O1 participating in intra- and intermolecular hydrogen interactions.

4. Conclusion

The isoquinoline-derivatives are a large class of medicinally active compounds with potentially attractive properties, including antispasmodic, antimicrobial, anti-tumour, antifungal and anti-inflammatory activities. In this study, a new isoquinoline-derivative namely, methyl O-[(11*R*, 11a*S*)-4-oxo-1, 3, 4, 6, 11, 11a-hexahydro-2*H*-pyrido[1, 2-b] isoquinolin-11-yl] carbonodithioate (**I**), was synthesized and structurally characterized by single-crystal X-ray diffraction technique. The crystal structure allowed elucidating the absolute configuration of two stereo centers. According to the results of determination by single crystal X-ray diffraction it was established that the crystal structure of compound **1** is stabilized by intramolecular hydrogen bonds of the C—H···O, C—H···S, C-H···S type. In addition, C-H···O and C—H···π intermolecular interactions play a crucial role for the formation of supramolecular architectures in the structure of the studied compound.

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Supporting information

CCDC-1815853 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
Author contributions: All authors contributed equally to this work.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Samples of the compounds are available from the author.

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