Synthesis and crystal structure
of 2-[(2,3-dihydro-2-oxo-3-benzoxazolyl)methyl]benzoic acid

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The synthesis, IR, NMR and X-ray structure of 2-[(2,3-dihydro-2-oxo-3-benzoxazolyl)methyl]benzoic acid – a potential new drug scaffold are reported. The compound crystallizes in the triclinic *P*-1 space group with unit cell parameters: $a = 6.716(3)$, $b = 7.828(4)$, $c = 13.283(5)$ Å, $\alpha = 78.029(12)$, $\beta = 81.360(17)$, $\gamma = 65.7100(10)$ °, $V = 621.0(4)$ Å^3, $M_w = 269.25$ and $Z = 2$. In the three-dimensional arrangement of the molecules only one classical hydrogen bond (O-H…O) is observed. Weak and C–H…O and π…π interactions are responsible for the additional stabilization and packing of the molecules in the crystal structure.

Key words: 2(3*H*)-benzoxazolone, benzoic acid, X-ray

INTRODUCTION

Benzoxazole represents an important heterocyclic scaffold, as several of its derivatives are shown to display a range of promising pharmaceutical properties such as anticonvulsant, anti-inflammatory, analgesic, antiulcer, antineoplastic, antibacterial and antifungal activities [1-3]. A number of substituted (2,3-dihydro-2-oxo-3-benzoxazolyl)alkanoic acid derivatives have been recognized as therapeutically useful cyclooxygenase inhibitors (Non-Steroidal Anti-Inflammatory Drugs, NSAIDs).

The analgesic activity of substituted 2(3*H*)-benzoxazolones was first reported by Close *et al*. [4]. Subsequently it was found, that the introduction of alkanoic acid residues at position 3 led to favorable antinociceptive compounds. Renard *et al.* [5] demonstrated that (6-acyl-2-oxo-3*H*-benzoxazol-3-yl) alkanoic acids and their esters exhibited a greater analgesic activity than aspirin. Önkol *et al*. [6, 7] indicated that [2(3*H*)-benzoxazolon-3-yl]propanamide and propanoic acid derivatives were more active than the corresponding acetic acid derivatives. In addition, Gülcan *et al.* [8] showed that 4-[5-chloro-2(3*H*)-benzoxazolon-3-yl]butanoic acid exhibits a greater analgesic potential than analogous amide derivatives. Therefore, in the course of our research we planned to synthesize the title compound (**I**) as potential anti-inflammatory and analgesic agent and clarify its structure.

EXPERIMENTAL

Melting point of compound **I** was determined on a Boetius hot-stage microscope. The IR spectrum was recorded on a Specord 71 spectrometer. The ^{1}H-NMR spectrum was obtained on a Tesla BS 487 C spectrometer operating at 80 MHz in DMSO-d$_6$. Chemical shifts were reported in δ units (ppm) relative to tetramethylsilane as internal standard. Single crystal data was collected on a CAD-4 diffractometer.

Synthesis of 2-[(2,3-Dihydro-2-oxo-3-benzoxazolyl)methyl]benzoic acid (I)

To a stirred solution of 2(3*H*)-benzoxazolone (6.76 g, 0.05 mol) in dry N,N-dimethylformamide (DMF, 20 mL), 2 g of sodium hydride (80% suspension in oil) were added slowly. After addition was completed, the mixture was stirred for further 10 minutes. Then, phthalide (6.71 g, 0.05 mol) was added and the reaction mixture was refluxed for 6 hours, cooled, poured into 200 mL ice-water and acidified with 10% hydrochloric acid. The product

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was precipitated, filtered and washed with water. Yield 7.72 g (57%). M.p. 214–216 °C (ethanol). IR (nujol, cm^{-1}): 1680, 1780 (v_{CO}); 2400–2750 (v_{CO}). ^{1}H-NMR (DMSO-d$_6$): 5.60 (s, 2H, C**H$_2$**), 7.0–8.1 (m, 8H, Ar**H**). Anal. Calcd. for C$_{15}$H$_{11}$NO$_4$: C 66.91; H 4.12; N 5.20. Found C 66.68; H 4.47; N 5.29.

X-ray analysis

A crystal of the title compound having approximate dimension 0.31×0.28×0.24 mm was placed on a glass fiber and mounted on an Enraf-Nonius CAD-4 diffractometer. X-ray data collection was carried out at 290 K with graphite monochromatized Mo-Kα radiation (λ = 0.71073 Å). The unit cell parameters were determined from 15 reflections and refined employing 22 higher-angle reflections, $18 < \theta < 20°$. The *ω/2θ* technique was used for data collection using Nonius Diffractometer Control Software [9]. Lorentz and polarization corrections were applied to intensity data using the WinGX [10]. The structure was solved by direct methods using SHELXS-97 [11] and refined by full-matrix least-squares procedure on F^2 with SHELXL-97 [11]. The hydrogen atom of the OH group (O4) has been located from difference Fourier map. All remaining hydrogen atoms were placed in idealized positions (C–H$_{aromatic}$ = 0.93 Å and C–H$_{methylen}$ = 0.97 Å) and were constrained to ride on their parent atoms, with $U_{iso}(H) = 1.2U_{eq}(C \text{ or } O)$.

Table 1. Crystal data and structure solution methods and refinement results for **I**

Crystal data	
C$_{15}$H$_{11}$N$_1$O$_4$	$F_{000} = 280$
$M_r = 269.25$	$D_x = 1.44$ Mg m^{-3}
Triclinic, *P–1*	Melting point: 487–489 K
Hall symbol: –P 1	Mo *K*α radiation λ = 0.71073 Å
$a = 6.716$ (3) Å	Cell parameters from 22 reflections
$b = 7.828$ (4) Å	θ = 18.0–19.9°
$c = 13.283$ (5) Å	μ = 0.11 mm^{-1}
α = 78.029 (12)°	$T = 290$ (2) K
β = 81.360 (17)°	Prism, yellow
γ = 65.7100 (10)°	Crystal size:
$V = 621.0$ (4) Å^3	0.31 × 0.28 × 0.24 mm
$Z = 2$	
Data collection	
Enraf Nonius CAD4 diffractometer	$R_{int} = 0.028$
Radiation source: sealed tube	$θ_{max} = 26.0°$
Monochromator: graphite	$θ_{min} = 1.6°$
$T = 290(2)$ K	$h = -8 \rightarrow 8$
non–profiled ω/2θ scans	$k = -9 \rightarrow 9$
Absorption correction: none	$l = -16 \rightarrow 16$
4782 measured reflections	3 standard reflections
2436 independent reflections	every 120 min
1801 reflections with $I > 2σ(I)$	intensity decay: –1%
Refinement	
Refinement on F^2	Secondary atom site location: difference Fourier map
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2σ(F^2)] = 0.039$	H-atom parameters constrained
$wR(F^2) = 0.106$	$w = 1/[σ^2(F_o^2) + (0.0507P)^2 + 0.0515P]$ where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.04$	$(Δ/σ)_{max} < 0.001$
2436 reflections	$Δρ_{max} = 0.14$ e Å^{-3}
181 parameters	$Δρ_{min} = -0.20$ e Å^{-3}
0 constraints	Extinction correction: none
Primary atom site location: structure-invariant direct methods	
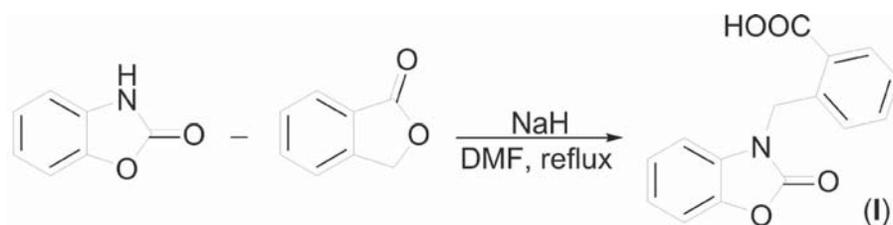
Scheme 1. Synthesis of the compound (I)

RESULTS AND DISCUSSION

As illustrated in Scheme 1, the preparation of 2-[(2,3-dihydro-2-oxo-3-benzoxazolyl)methyl] benzoic acid (**I**) was carried out by the reaction of 2(3*H*)-benzoxazolone with phthalide, which were refluxed in DMF in the presence of sodium hydride as base. The product **I** was isolated in good yield and purified by recrystallization from ethanol. The chemical structure of the title compound **I** was elucidated by IR, ^{1}H-NMR spectral data and X-ray analysis.

Crystal structure of 2-[(2,3-dihydro-2-oxo-3-benzoxazolyl)methyl]benzoic acid

Experimental conditions are summarized in Table 1. Selected bond distances and bond angles
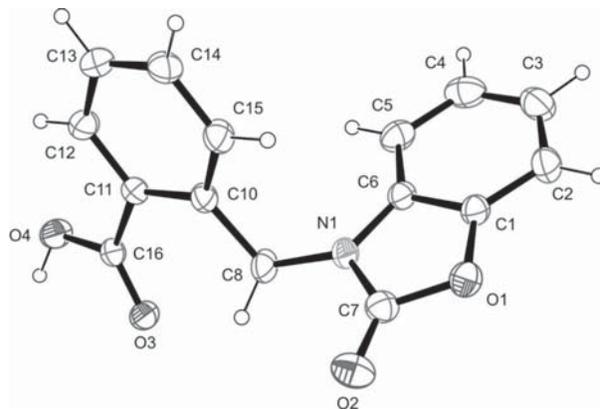
Fig. 1. A view of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level for all non-H atoms. All H atoms are rendered as spheres with arbitrary radii.

Table 2. Selected geometrical parameters for **I** (Å, °)

C1—C2	1.366 (2)	C10—C15	1.385 (2)
C1—C6	1.377 (2)	C10—C11	1.403 (2)
C1—O1	1.3797 (19)	C11—C12	1.393 (2)
C2—C3	1.381 (3)	C11—C16	1.485 (2)
C3—C4	1.378 (3)	C12—C13	1.377 (2)
C4—C5	1.386 (3)	C13—C14	1.372 (3)
C5—C6	1.373 (2)	C14—C15	1.382 (2)
C6—N1	1.391 (2)	C16—O3	1.2225 (18)
C7—O2	1.197 (2)	C16—O4	1.3092 (19)
C7—N1	1.364 (2)	O4—H4O	0.9426
C7—O1	1.377 (2)	C8—C10	1.514 (2)
C8—N1	1.4557 (19)		
C2—C1—C6	123.39 (16)	C15—C10—C11	117.77 (14)
C2—C1—O1	127.39 (15)	C15—C10—C8	120.46 (14)
C6—C1—O1	109.22 (13)	C11—C10—C8	121.75 (13)
C1—C2—C3	116.07 (18)	C12—C11—C10	119.65 (14)
C4—C3—C2	121.19 (18)	C12—C11—C16	118.29 (14)
C3—C4—C5	122.11 (18)	C10—C11—C16	121.93 (14)
C5—C6—C1	120.74 (15)	C13—C12—C11	121.07 (16)
C5—C6—N1	133.32 (15)	C14—C13—C12	119.66 (16)
C1—C6—N1	105.93 (13)	C14—C15—C10	122.14 (16)
O2—C7—N1	129.73 (17)	O3—C16—O4	122.13 (14)
O2—C7—O1	122.56 (16)	O3—C16—C11	123.27 (14)
N1—C7—O1	107.70 (14)	O4—C16—C11	114.55 (14)
N1—C8—C10	113.40 (12)	C6—N1—C8	126.57 (14)
C7—N1—C6	109.49 (13)	C7—O1—C1	107.62 (12)
C7—N1—C8	123.47 (14)		

Table 3. Hydrogen bonds and weak interactions for **I** (Å, °)

D–H···A	D(D–H)	d(H···A)	d(D···A)	<(DHA)
O(4)–H(4)···O(3)[i]	0.943	1.702	2.644(4)	177.4
C(12)–H(12)···O(4)[ii]	0.93	2.619	3.346(5)	135.5
C(5)–H(5)···O(1)[iii]	0.93	2.578	3.352(6)	141.0
Cg1···Cg1[iv]	–	–	3.529(8)	–

Symmetry codes: (i) *1-x, 1-y, -z* ; (ii) *1-x, 2-y, -z*; (iii) *-x+1, y, z* ; (iv) *-x, 1-y, -z*
*Cg*1 includes atoms C1, N1, C3, C4, C5, C6, C7, N1, O1

Fig. 2. A representation of the unit-cell contents of (I). Atoms involved in hydrogen bonding interactions are shown. Hydrogen bonds are rendered as dashed lines.
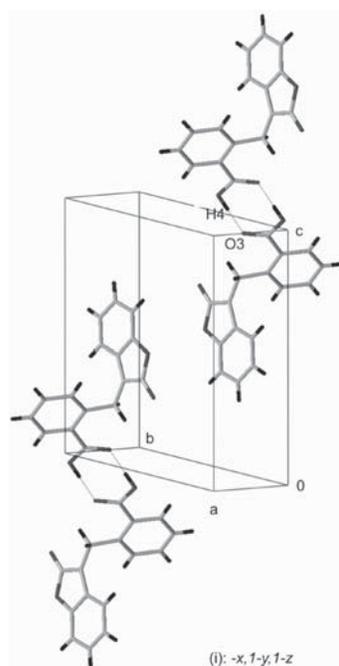
are listed in Table 2. Hydrogen bonds and weak interactions geometry are presented in Table 3. *ORTEP* [12] drawing diagram of the molecular structure with 50% probability and the atom numbering scheme is shown in Fig. 1. The data for publication were prepared with WinGX [10], *ORTEP* [12], and Mercury [13] program packages.

In the asymmetric unit of **I**, only one independent molecule is present (Fig. 1). The structural parameters of the title compound are comparable with those reported earlier [14–16]. The phenyl and benzoxazol fused ring systems are essentially planar with r.m.s. deviations of 0.008(6) and 0.018(9) Å respectively. The angle between the mean planes of the two ring systems is 71.12(3)°. In the three-dimensional arrangement of the molecules of **I** only one classical hydrogen bond was found (Fig. 2). A head-to-head O-H…O[i] (2.644(4) Å) interaction produces bicyclical dimmers. A subsequent careful examination of the intermolecular contacts shows that weak C–H…O and π…π interactions are responsible for the packing of the molecules in the crystal structure of **I**. Adjacent pairs of dimmers are connected through π…π [Cg1…Cg1[i]] interactions with shortest centroid-to-centroid distance of 3.529(8) Å (Fig. 3) [symmetry codes: (i) − *x*, 1 − *y*, 1 − *z*]. Two alternating C-H…O interactions of 3.346(5) Å and 3.352 (6) Å produce pseudo layers along *ac* (Fig. 4).
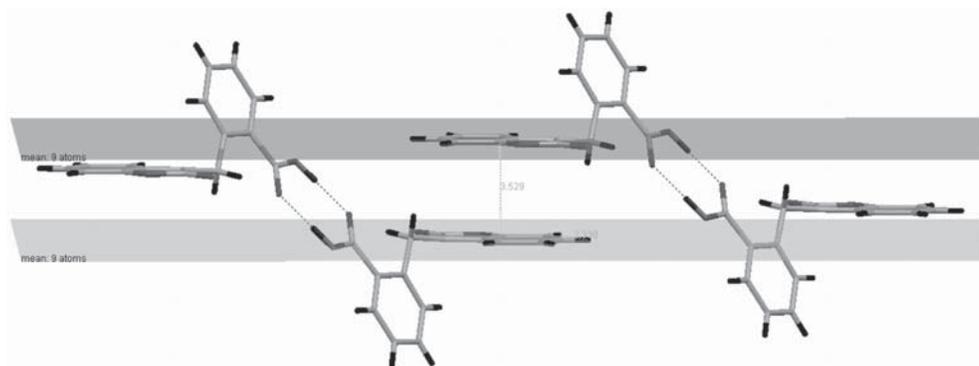
Fig. 3. A representation of the π…π interactions between the fused ring(represented by the mean planes) system in I.
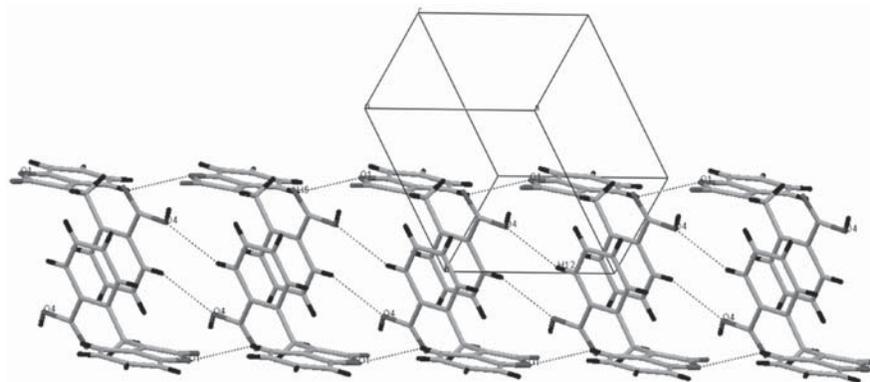
Fig. 4. A representation of C-H…O interactions interaction in I producing pseudo-layers along *ac*.

CONCLUSION

The crystallographic and spectroscopic data are in good agreement. There are no obvious discrepancies between solid-state and solution data.

SUPPLEMENTARY MATERIALS

CCDC 805276 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, 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.

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СИНТЕЗ И КРИСТАЛНА СТРУКТУРА НА 2-[(2,3-DIHYDRO-2-OXO-3-BENZOXAZOLYL)METHYL] БЕНЗОЕНА КИСЕЛИНА

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(Резюме)

Отразени са синтезът, монокристален рентгеноструктурен, ИЧ и ЯМР спектроскопски изследвания на 2-[(2,3-dihydro-2-oxo-3-benzoxazolyl)methyl]benzoic acid. Веществото кристализира в *P*-1 пространствена група и параметри на елементарна клетка: a = 6.716(3), b = 7.828(4), c = 13.283(5) Å, α = 78.029(12), β = 81.360(17), γ = 65.7100(10) °, V = 621.0 (4) Å^3, M_w = 269.25 и Z = 2. Тримерната подредба на молекулите се стабилизира от една (O-H…O) водородна връзка. Слаби C–H…O и π…π взаимодействия допринасят за допълнителна стабилност на кристалната структура.