Journal of Molecular Structure 1017 (2012) 32–37

Contents lists available at SciVerse ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

Synthesis and crystal structures of 7-bromo-5-(2′-chloro)phenyl-3-hydroxy-1-methyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one and 7-bromo-5-(2′-chloro)phenyl-1-hexyl-1,2,4,5-tetrahydro-3*H*-1,4-benzodiazepin-2,3-dione

Victor Ch. Kravtsov [a,*], Marina S. Fonari [a], Maria Gdaniec [b], Victor I. Pavlovsky [c], Sergei A. Andronati [c], Ekaterina A. Semenishyna [c]

[a] *Institute of Applied Physics, Academy of Sciences of Moldova, Chişinău, Republic of Moldova*
[b] *Faculty of Chemistry, Adam Mickiewicz University, 60-780 Poznań, Poland*
[c] *A.V. Bogatsky Physico-Chemical Institute of the National Academy of Sciences of Ukraine, Odessa, Ukraine*

ARTICLE INFO

Article history:
Received 30 December 2011
Received in revised form 29 February 2012
Accepted 29 February 2012
Available online 10 March 2012

Dedicated to the memory of Yurii Simonov

Keywords:
1,4-Benzodiazepine
Synthesis
Crystal structure
Conformation
Intermolecular interaction

ABSTRACT

Treatment of 7-bromo-5-(2′-chloro)phenyl-3-hydroxy-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one (**1**) with methyl or hexyl tosylate resulted in 7-bromo-5-(2′-chloro)phenyl-3-hydroxy-1-methyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one (**2**) and 7-bromo-5-(2′-chloro)phenyl-1-hexyl-1,2,4,5-tetrahydro-3*H*-1,4-benzodiazepin-2,3-dione (**3**). As confirmed by X-ray crystallography, the two products differ not only in the identity of the alkyl substituent in position 1 of the benzodiazepine fragment but also crystallize in different molecular forms resulting from proton migration. This alteration of the molecular structure leads to a significant change in the conformation of the central molecular fragment and influences the assembly mode in the crystal. In **3**, centrosymmetric dimers formed *via* a pair of N—H···O hydrogen bonds are further linked into chains *via* C—Br···O=C halogen bond interaction. In turn in **2** there are two symmetry independent molecules, each giving a different set of intermolecular interactions. One of the molecules forms a dimer *via* O—H···O interactions whereas the second one generates chain *via* C—Br···O=C halogen bond that is also assisted by a weak O—H···Br hydrogen bond.

1. Introduction

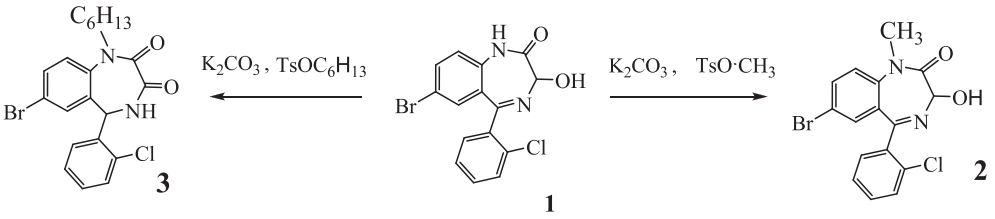
3-Hydroxy-1,2-dihydro-3*H*-1,4-benzodiazepine and its derivatives have attracted much attention as they exhibit pronounced anxiolytic, sedative, hypnotic, anticonvulsant activity and low toxicity [1–4]. Moreover, 3-hydroxy-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one is an active metabolite of the most drugs of the benzodiazepine group [5,6] and therefore 3-hydroxy-1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones are of particular interest as they may act as active pharmaceutical ingredients (APIs).

The effect of substituents in position 1 of the benzodiazepine fragment on the molecular geometry and anticonvulsant properties of 1,2-dihydro-3H-1,4-benzodiazepin-2-ones was shown by us previously [7]. Recently, a series of alkyl derivatives was synthesized using different alkylating agents [8]. As reported earlier, 3-hydroxy derivatives of 1,4-benzodiazepin-2-one undergo a pH-dependent prototropic migration with conversion into the corresponding 1,2,4,5-tetrahydro-1,4-benzodiazepin-2,3-diones [9–11] as it was well illustrated by the synthesis of two structural isomers, 7-bromo-5-(2′-chloro)phenyl-1-dodecyl-3-hydroxy-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one (**2c**) and 7-bromo-5-(2′-chloro)phenyl-1-dodecyl-1,2,4,5-tetrahydro-3*H*-1,4-benzodiazepin-2,3-dione (**3c**), whose crystal structures were confirmed by X-ray crystallography [8].

Herein we report synthesis, spectroscopic and crystallographic studies of two new alkyl derivatives, pure phases of 7-bromo-5-(2′-chloro)phenyl-3-hydroxy-1-methyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one (**2**) and 7-bromo-5-(2′-chloro)phenyl-1-hexyl-1,2,4,5-tetrahydro-3*H*-1,4-benzodiazepin-2,3-dione (**3**) obtained by alkylation of 7-bromo-5-(2′-chloro)phenyl-3-hydroxy-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one (**1**) with methyl or hexyl tosylate, respectively (Scheme 1). It should be emphasized that in the same reaction conditions different compounds, 3-hydroxy derivative (**2**) or 2,3-dione (**3**) were obtained subject to the size of alkyl residue of alkylation agent (methyl or hexyl). By the *in vitro* radioligand method, it has been determined that compound **2** possesses affinity for central benzodiazepine receptors (K_i 7.4 ± 0.6 nM) and neurotropic activity.

* Corresponding author. Fax: +373 22 72 58 87.
E-mail addresses: kravtsov@phys.asm.md (V.Ch. Kravtsov), magdan@amu.edu.pl (M. Gdaniec), medchem_department@ukr.net (V.I. Pavlovsky).

0022-2860/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.molstruc.2012.02.071



Scheme 1.

2. Results and discussion

2.1. Spectroscopic analysis

The details of alkylation of 3-hydroxy-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one were described previously [8]. The resulting compounds were identified by IR, mass and ^{1}H NMR spectroscopic methods. The IR spectrum of compound **2** has a broadened band at 3280 cm^{-1} corresponding to the vibrations of OH bond, and a band at 1700 cm^{-1} corresponding to vibrations of C=O bond. The IR spectrum of compound **3** contains band at 3217 cm^{-1} corresponding to N—H vibrations of amino groups, and bands corresponding to C=O vibrations of amide and carbonyl groups at 1660 and 1687 cm^{-1}, respectively.

In the ^{1}H NMR spectrum of 3-hydroxy-1-methyl derivative **2,** measured in deuterated chloroform solution, the characteristic features are a doublet for C(3)H proton at 5.00–5.03 ppm, and a doublet for OH proton at 4.76–4.79 ppm. In the case of 1-hexyl-2, 3-dione derivative **3** the characteristic signals are a singlet C(5)H proton at 5.95 ppm and a singlet for N(4)H proton at 9.47 ppm.

Mass spectra for **2** and **3** obtained by the electron impact differ significantly (Fig. 1). A small number of peaks in the spectrum of **2**, which is not typical for this class of compounds, might be explained by insufficient energy of the resulting fragment with $m/z = 351$ that is not amenable to further fragmentation.

2.2. X-ray structural study

Single crystals of **2** and **3** suitable for single crystal X-ray structure determination were obtained by recrystallization from ethanol and acetonitrile, respectively. The crystal structures confirmed that the 1-methyl derivative **2** represents 3-hydroxy-substituted compound, *viz.* the form that has been earlier observed in its solvate (**2** · 0.5(benzene)) [12], while 1-hexyl derivative **3** represents the dione form. Both compounds crystallize in monoclinic centrosymmetric space groups $P2_1/n$ and $P2_1/c$ with two (hereinafter labeled as **a** and **b**) and one symmetry-independent molecules in the asymmetric unit (Fig. 2) in **2** and **3**, respectively. Conformations of the molecules **2a** and **2b** are similar as shown by the superposition diagram in Fig. 3. In turn, a nonplanar conformation adopted by the seven-membered heterocyclic ring fused with a bromophenyl group differs in the two compounds.

The seven-membered heterocyclic ring in **2a** and **2b** has a boat-like conformation (Fig. 4a). The deviation of atoms N(1), C(2), N(4) and C(5), which constitute bottom of the boat, from their mean plane is less than 0.0183(2) Å in both molecules, while atoms C(3), C(10) and C(11) are displaced from this plane in the same direction by 0.793(5), 0.745(6) and 0.689(6) Å in **2a** and 0.782(5), 0.771(5) and 0.678(6) Å in **2b**.

The skeleton of the molecule **2** is similar to that found in the solvated crystalline form of **2** · 0.5(benzene) [12] and 1-dodecyl (**2c**) [8] and 1-methoxycarbonylmethyl (**2d**) derivatives [13], as well as in α- and β-polymorphs of phenazepam [14,15]. Arrangement of the 5-phenyl substituent in the molecules and conformation of the seven-membered ring can be described by three dihedral angles: θ_1 – angle between the aromatic rings, θ_2 – angle between N(1)C(2)N(4)C(5) and N(1)C(10)C(11)C(5), θ_3 – angle between N(1)C(2)N(4)C(5) and C(2)C(3)N(4). Table 1 reveals a remarkable similarity of these conformational parameters in a series of relative compounds.

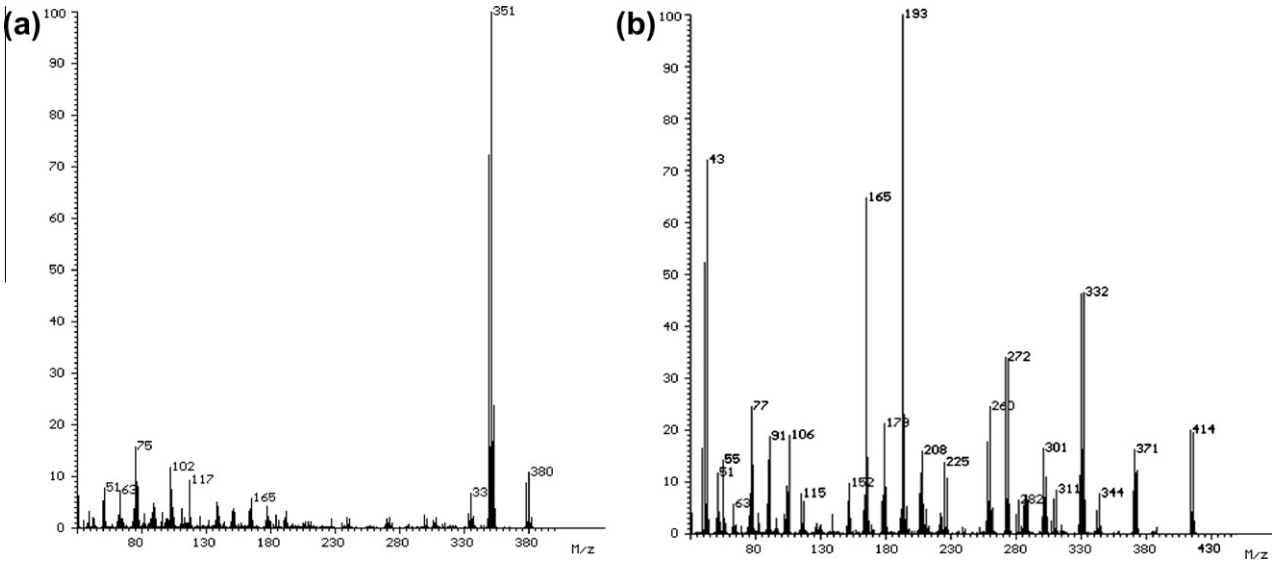


Fig. 1. Mass-spectra for **2** (a) and **3** (b).

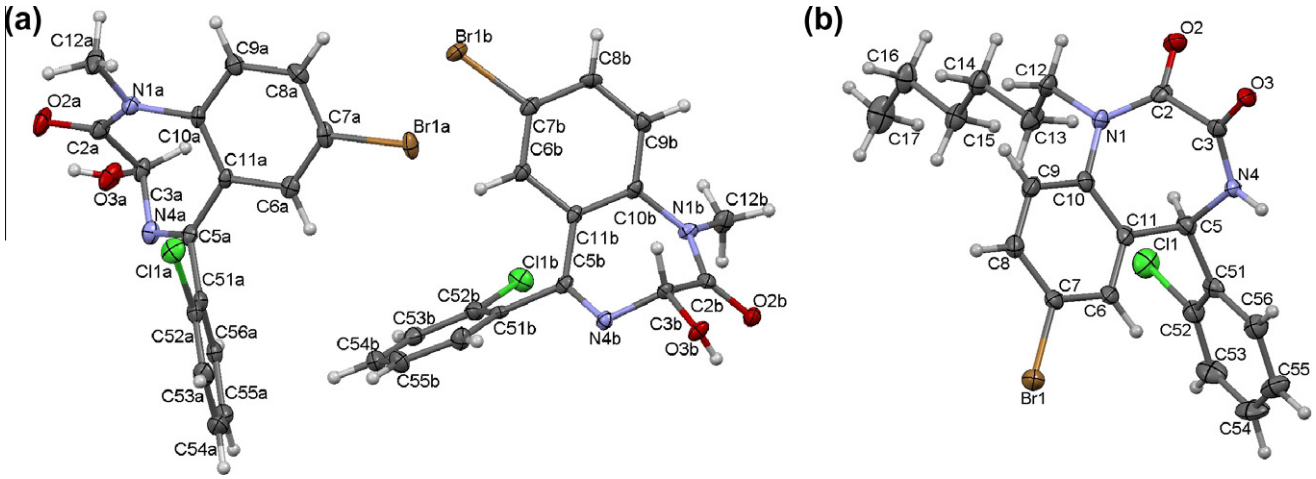


Fig. 2. Molecular structure of **2** (a) and **3** (b) with atom labeling scheme. Displacement ellipsoids are drawn at the 50% probability level.

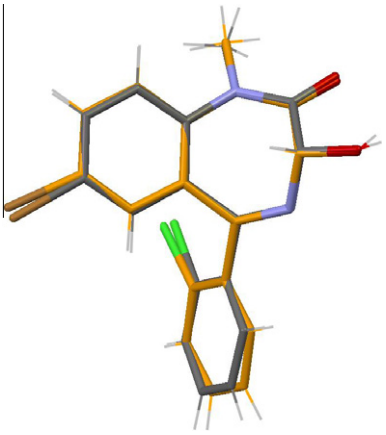


Fig. 3. Superposition of the molecules **2a** and **2b**, carbon atoms are shown by yellow color for **2a** and gray for **2b**. All non-hydrogen atoms were included in fitting (RMSD = 0.1395 Å). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Selected geometric characteristics of **2** and **3** and relative compounds.

Compound	θ (°)			Reference/ref. code
	θ_1	θ_2	θ_3	
2a	76.4(1)	35.6(2)	62.7(3)	Present study
2b	80.9(1)	36.0(2)	61.3(2)	Present study
2 · 0.5(benzene)	77.9	39.4	59.8	[12], QEMGIY01
2c[a]	85.3	36.6	61.6	[8], CCDC 630347
2d[a]	84.3	33.8	61.7	[13], JIPHAR
Phenazepam,	75.4	33.8	59.8	[14], BCHBZP
α-Polymorph				
Phenazepam	86.2	31.1	53.1	[15], BCHBZP01
β-Polymorph				
3	80.0(1)	47.0(1)	54.6(3)	Present study
3c[a]	86.1	45.5	55.7	[8], CCDC 630346

[a] The geometrical parameters were calculated using CSD data or deposited in CCDC CIFs.

Redistribution of hydrogen atoms in the core of molecule **3**, when compared with that in **2**, results in significant conformational changes (Fig. 4b). Although, like in **2**, the seven membered heterocycle in **3** has a boat-like conformation, here the other set of atoms constitutes the bottom of the boat. The atoms C(3), N(4), C(10) and (C11) are coplanar within 0.045(2) Å and the atoms N(1), C(20) and C(5) deviate from their plane by 0.893(5), 0.957(5) and 0.728(5) Å, respectively. The dihedral angles θ_2 (angle between C(3)N(4)C(11)C(10) and C(3)C(2)N(1)C(10)), θ_3 (angle between C(3)N(4)C(11)C(10) and N(4)C(5)C(11)) indicate some difference of boat conformation in **2** and **3**, while θ_1 angles are rather similar. Very similar conformation of the seven-membered ring was observed in the structure of **3c** [8] (Tables 1 and 2).

A quantitative measure of distortion of seven-membered heterocyclic ring from an ideal cycloheptatriene "boat" with mirror symmetry C_s may be evaluated by Duax asymmetry parameter [2,3] given by $\Delta C_s = \{1/5[T1^2 + T4^2 + T6^2 + (T2 + T3)^2 + (T5 + T7)^2]\}^{1/2}$, where T1–T7 denote torsion angles along seven-membered heterocyclic ring starting from torsion angle about N(1)—C(2) bond (Table 3). The values ΔC_s 4.3° and 6.9° for **2a** and **2b,** respectively are well within the range found in 1,4-benzodiazepin-2-ones [3]. The corresponding formal calculation of ΔC_s for compound **3** reveals a huge magnitude 35.9°, which does not describe the "boat" conformation. However, the ΔC_s asymmetry parameter equals 12.8° and corresponds to "boat", if T1–T7 sequence starts from torsion angle about C(3)—N(4) bond (Fig. 4(b)). Table 3 demonstrates that **3** possesses more distorted seven-membered ring than **2a** and **2b** as well as relative **3c** (ΔC_s = 10.9°).

Bond lengths and angles in **2a** and **2b** are in a good agreement (Table 3), and a small difference in C(2)═O(2) bond length is most probably due to the involvement of the atoms O(2a) and O(2b) in intermolecular interactions of different strength. The N(1) atom is sp^2 hybridized in both compounds and deviation from 360° of the total angle at N(1) is not exceeding 0.2°. The bond angles at atoms C(3) and C(5) correspond to their sp^3- and sp^2-hybridization in **2** and vice versa in **3** (Table 2). In compound **2** the torsion angles at the C—C bonds in the aliphatic chain are close to 180° (*trans* conformation) similar to 7-bromo-5-(2′-chloro)phenyl-1-dodecyl-1,2,4,5-tetrahydro-3*H*-1,4-benzodiazepin-2,3-dione [8].

Crystal packing in **2** and **3** is illustrated in Fig. 5. In general, lack of a substituent at position 1 (for example both polymorphs of phenazepam [14,15] and nitrazepam [16]) leads to the formation of dimers *via* amide···amide interactions that generate $R_2^2(8)$ hydrogen-bond pattern [17]. In turn, the presence of a substituent at position 1 as well as redistribution of hydrogen atoms like in **2** and **3** give rise to different hydrogen-bonding patterns including dimers *via* $R_2^2(10)$ synthon, $R_4^4(8)$ tetramers, homomeric $R_2^2(8)$ synthons either *via* a pair of C(3)—OH···N(4) hydrogen bonds or involving another amide group [8,12]. In the crystal structure of **2** each of the symmetry independent molecules forms a different

Table 2
Selected torsion angles (°) in **2** and **3** and relative compounds **2** · 0.5(benzene), **2c** and **3c**.

	2a	**2b**	**2** · 0.5(benzene)	**2c**	**3**	**3c**
T1=C(10)—N(1)—C(2)—C(3)	−0.3(5)	1.7(5)	11.9(5)	0.9(4)	−6.1(5)	−8.1(3)
T2=N(1)—C(2)—C(3)—N(4)	76.3(4)	74.7(4)	67.5(4)	75.5(3)	63.5(4)	61.1(3)
T3=C(2)—C(3)—N(4)—C(5)	−73.7(4)	−72.2(4)	−75.5(4)	−72.5(3)	−19.3(4)	−14.4(3)
T4=C(3)—N(4)—C(5)—C(11)	−0.5(5)	−0.9(5)	1.2(6)	−1.7(5)	−61.7(4)	−65.3(3)
T5=N(4)—C(5)—C(11)—C(10)	40.3(5)	38.5(5)	44.7(6)	41.2(5)	70.8(4)	70.4(3)
T6=C(5)—C(11)—C(10)—N(1)	6.9(5)	10.2(5)	1.5(6)	7.4(5)	3.7(4)	4.5(3)
T7=C(11)—C(10)—N(1)—C(2)	−46.3(5)	−49.5(5)	−51.7(6)	−47.5(4)	−45.7(4)	−44.4(3)
ΔC_s(T1)	4.3	6.9	7.2	4.6	35.9	38.0
ΔC_s(T3)					12.8	10.9

Table 3
Selected bond distances (Å) and angles (°) in **2** and **3**.

	2		**3**		**2**		**3**
	a	**b**			**a**	**b**	
Br(1)—C(7)	1.890(4)	1.894(3)	1.896(3)	C(3)—O(3)	1.399(4)	1.397(4)	1.229(4)
Cl(1)—C(52)	1.743(4)	1.741(4)	1.751(4)	C(3)—N(4)	1.462(5)	1.462(4)	1.337(4)
N(1)—C(2)	1.358(5)	1.355(5)	1.363(4)	N(4)—C(5)	1.284(5)	1.280(4)	1.478(4)
N(1)—C(10)	1.425(4)	1.429(4)	1.435(4)	C(5)—C(11)	1.490(5)	1.485(5)	1.525(4)
N(1)—C(12)	1.474(4)	1.472(5)	1.487(4)	C(5)—C(51)	1.504(5)	1.497(5)	1.492(4)
C(2)—O(2)	1.221(4)	1.230(4)	1.221(4)	C(6)—C(11)	1.405(5)	1.402(5)	1.390(4)
C(2)—C(3)	1.521(5)	1.528(5)	1.540(4)	C(10)—C(11)	1.397(5)	1.396(5)	1.402(4)
C(2)—N(1)—C(10)	122.9(3)	122.8(3)	124.0(3)	N(4)—C(5)—C(11)	124.6(3)	124.9(3)	107.1(3)
O(2)—C(2)—N(1)	123.6(3)	122.1(3)	124.0(3)				
N(1)—C(2)—C(3)	115.4(3)	115.6(3)	118.8(3)	C(11)—C(10)—N(1)	122.2(3)	121.0(3)	119.7(3)
C(2)—C(3)—N(4)	106.5(3)	106.9(3)	116.9(3)	C(10)—C(11)—C(5)	122.3(3)	123.0(3)	118.3(3)
C(5)—N(4)—C(3)	116.9(3)	117.4(3)	119.5(3)				

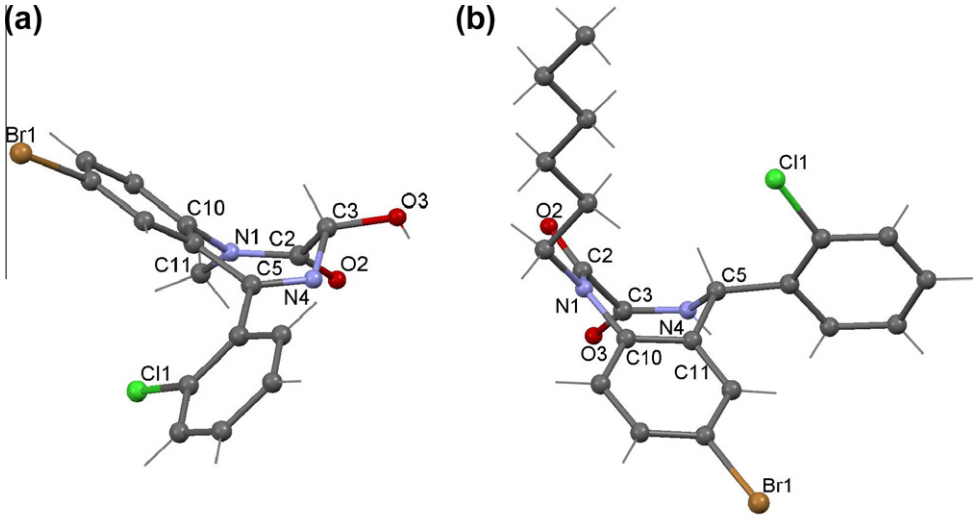


Fig. 4. Boat-like conformations of the heterocyclic ring in **2a** (a) and **3** (b).

set of intermolecular interactions. The centrosymmetric H-bonded dimers *via* $R_2^2(10)$ synthon are generated by the molecule **2b** [O(3b)—H···O(2b) $(2-x,\ 1-y,\ 2-z)$ = 2.832(3), O(3b)—H = 0.76(5), H···O(2b) = 2.12(5) Å, angle O(3b)—H···O(2b) = 157(5)°], while molecules **2a** form short C—Br···O=C halogen bond assembling them into chains parallel to the *a* axis [Br(1a)···O(2a) = 2.885(3) Å; angle C(7a)—Br(1a)···O(2a) = 157.0(1)°] [18]. The hydroxy group of **2a** is involved in a multicenter hydrogen bond acting as H-donor in intramolecular hydrogen bond to the carbonyl oxygen atom and as a donor in a weak hydrogen bond to the bromine atom, assisting thus the halogen bond interaction. The dimeric associates of molecules **2b** are stacked along the *a* axis *via* anti-parallel 2-chlorophenyl groups with interplanar spacing of 3.489 Å. The centroid···centroid distance between the phenyl rings of 4.583 Å and Cl(1b)···centroid separation of 3.537 Å indicate halogen···π rather than π···π interactions [19,20]. These interactions organize the dimeric associates of molecules **2b** into chains which alternate in the structure of **2** with the chains of molecules **2a**. It should be mentioned the absence of Br···O short contacts and another way of H-bond interactions in the inclusion complex of **2** · 0.5(benzene) [12]. The intermolecular interactions differ in **2a**, **2b** and in inclusion complex **2** · 0.5(benzene) and influence on the conformation of seven-membered ring and asymmetry parameter ΔC_s° which varies from 4.3° to 7.2° (Tables 1 and 2). A

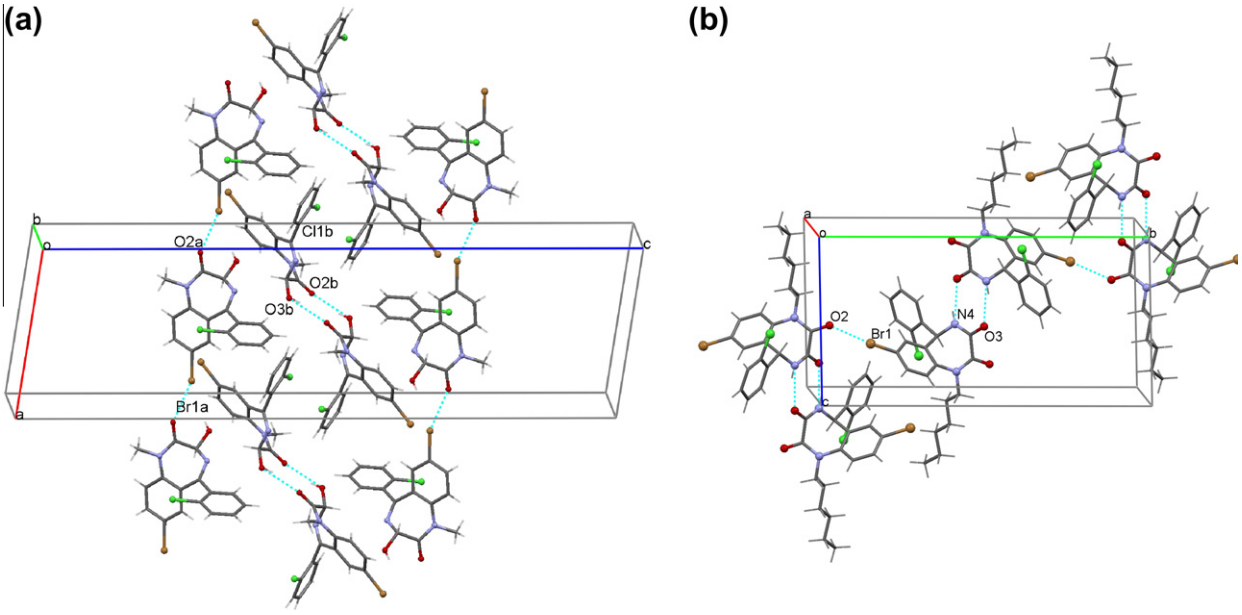


Fig. 5. Fragments of crystal packing in **2** (a) and **3** (b).

weaker C—Br···O=C interaction [Br(1)···O(2) = 3.030(2) Å; angle C(7)—Br(1)···O(2) = 174.9(1)°] in **3** connects the hydrogen-bonded centrosymmetric dimers [$R_2^2(8)$ synthon, N(4)—H···O(3)(2 − *x*, 1 − *y*, 1 − *z*) = 2.923(4), N(4)—H = 0.86(3), H···O(3) = 2.09(3) Å, angle N(4)—H···O(3) = 163(3)°] into the layers parallel to the (*bc*) crystallographic plane.

3. Experimental

3.1. Synthesis

The IR spectra were recorded on a Specord IR-75 in chloroform solution, and the ^{1}H NMR spectra on a Varian WXP 300 instrument (300 MHz) in $CDCl_3$, at 25 °C, internal standard was TMS. Mass spectra were recorded by electron impact on a MX 1321 mass spectrometer (ionizing voltage 70 eV, temperature of ionization chamber 200 °C). The purity of compounds was checked by HPLC, Shimadzu chromatograph LC 8A, analytical column Zorbax C 18, mobile phase, methanol + 2% TFA: water + 2% TFA, 9:1. TLC checked the progress of reactions. Thin layer chromatography was carried out on Silufol UV 254 plates in acetonitrile:chloroform:hexane, 1:1:3, visualization was with UV light at λ 254 nm.

3.1.1. 7-Bromo-5-(2′-chloro)phenyl-3-hydroxy-1-methyl-1,2-dihydro-3H-1,4-benzodiaze-pin-2-one (**2**)

Potassium carbonate (1.00 g, 7.2 mmol) was added to a suspension of compound **1** (1.00 g, 2.7 mmol) and methyl tosylate (0.66 g, 4.0 mmol) in anhydrous dioxane (20 mL), and the mixture was stirred at 40–50 °C for 10 h. Chloroform (40 mL) was added to the reaction mixture, which was washed with water (4 × 20 mL). The solvent was evaporated on a rotary evaporator at reduced pressure. The residue obtained in amount of 0.53 g was recrystallized from benzene as colorless crystals of compound **2**. Yield: 51%, m.p. = 120–127 °C, R_f = 0.4.

Mass-spectrum: *m*/*z* ($I_{отн}$, %): 378 [M^+] (10), 349 [M—CHO]$^+$ (100), 334 [M—CO_2]$^+$(7).
IR: *ν*, cm^{-1}: 3280 (O—H_{asoc}), 1700 broaden band (C=O).

^{1}H NMR : *δ*, ppm ($CDCl_3$), (*J*, Hz): 7.21–7.45 (7H m, H-6, H-8, H-9, H-3′, H-4′, H-5′, H-6′); 5.02 (1H *d*, *J* = 9.34, H-3); 4.77 (1H *d*, *J* = 9.33, OH); 3.52 (3H s, —CH_3).

3.1.2. 7-Bromo-5-(2′-chloro)phenyl-1-hexyl-1,2,4,5-tetrahydro-3H-1,4-benzodiazepin-2,3-dione (**3**)

7-Bromo-5-(2′-chloro)phenyl-1-hexyl-1,2,4,5-tetrahydro-3H-1,4-benzodiazepin-2,3-dione (**3**) was obtained analogously to compound **2** from compound **1** (1.00 g, 2.7 mol) as colorless crystals. Yield: 38%, m.p. = 196–199 °C, R_f = 0.3.

Mass-spectrum: *m*/*z* (I,%): 448 [M^+] (34), 405 [M—NH—C=O]$^+$(28), 377 [M—C_5H_{11}]$^+$ (8), 364 [M—C_6H_{12}]$^+$ (52).
IR: *ν*, cm^{-1}: 3217 (N—H), 1660 (C=O amide), 1687 broaden band (C=O carbonyl).

Table 4
Crystal data and details on the structure refinement.

Compound	**2**	**3**
Empirical formula	$C_{16}H_{12}BrClN_2O_2$	$C_{21}H_{22}BrClN_2O_2$
Formula weight	379.64	449.77
Temperature (K)	100(2)	130(2)
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/c$
Unit cell dimensions		
a (Å)	10.9410(4)	9.3956(4)
b (Å)	7.4490(2)	20.8169(6)
c (Å)	37.518(1)	10.8163(4)
β°	98.021(1)	107.799(5)
V (Å^3)	3027.8(2)	2014.3(1)
Z	8	4
D (calc) (Mg/m^3)	1.666	1.483
μ (mm^{-1})	2.899	2.192
F(000)	1520	920
Reflections collected	13372	14,004
Independent reflections	5464 [*R*(int) = 0.0372]	3955 [*R*(int) = 0.0327]
Data/restraints/parameters	5464/0/405	3955/0/248
Goodness-of-fit on F^2	1.000	1.004
R indices [$I > 2\sigma(I)$] R_1, wR_2	0.0395, 0.1028	0.0391, 0.0979
R indices (all data) R_1, wR_2	0.0492, 0.1084	0.0617, 0.1080
Largest diff. peak and hole (e Å^{-3})	0.985 and −0.461	1.775 and −0.896

^{1}H NMR: δ, ppm, (DMSO-d6), (J, Hz): 7.32-7.68 (7H m, H-6, H-8, H-9, H-3′, H-4′, H-5′, H-6′); 5.95 (1H s, H-4); 6.45 (1H s, H-5); 4.37–4.47 (1H, m, —$\underline{CH_2}$—$(CH_2)_4$—CH_3); 4.69–4.75 (1H, m, —$\underline{CH_2}$—$(CH_2)_4$—CH_3); 1.23–1.50 (8H, m, —CH_2—$(\underline{CH_2})_4$—CH_3); 0.83 (3H t, J = 7.0, —CH_3).

3.2. X-ray crystallography

X-ray data for **2** and **3** were collected at 100 and 130 K with an Xcalibur Oxford Diffraction diffractometer, equipped with a CCD area detector and a graphite monochromator utilizing Mo Kα radiation. Final unit cell dimensions were obtained and refined on an entire data set. All calculations to solve the structures and to refine the model were carried out with the programs SHELXS97 and SHELXL97 [21]. The C–bound H atoms were placed in calculated positions and were treated in a riding model approximation with U_{iso}(H) = 1.2U_{eq}(C), while the O— and N-bound H–atoms of hydroxyl and amino groups were found from difference Fourier maps and were refined with isotropic displacement parameters U_{iso}(H) = 1.5U_{eq}(O), U_{iso}(H) = 1.2U_{eq}(N). The Figures were produced using Mercury [22]. Crystal data and details of the structure refinement are given in Table 4. Selected geometric parameters for **2** and **3** are given in Tables 2 and 3. CCDC 858024, 858025 contain the crystallographic data for **2–3**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk/data_request/cif.

4. Conclusion

7-Bromo-5-(2′-chloro)phenyl-3-hydroxy-1-methyl-1,2-dihydro -3*H*-1,4-benzodiazepin-2-one and 7-bromo-5-(2′-chloro)phenyl-1-hexyl-1,2,4,5-tetrahydro-3*H*-1,4-benzodiazepin-2,3-dione were obtained by alkylation of 7-bromo-5-(2′-chloro)phenyl-3-hydroxy -1,2-dihydro-3*H*-1,4-benzodiazepin-2-one, and their crystal structures were determined by single crystal X-ray diffraction. Redistribution of hydrogen atoms in the core of the molecules resulted in different self-association hydrogen-bonded patterns in two compounds. The availability of two crystallographically independent molecules and co-existence of two different associating chains either only *via* O···Br interactions or combination of H-bonds and halogen–π interactions in 7-bromo-5-(2′-chloro)phenyl-3-hydroxy-1-methyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one might be considered as a prerequisite for the possible polymorphism in this system as well as indicates the diverse modes of interaction of 1,4-benzodiazepines with various receptors. The selection of substitutient in position 1 of benzodiazepine fragment may allow the fine tuning of such interaction. Moreover, the intermolecular interaction may influence on conformation of seven-membered ring in 1,4-benzodiazepines and this variation of conformation parameters should be taken in account in attempts to establish correlation between geometrical parameters and biological activity.

Acknowledgements

This research was supported by joint award of State Agency on Science, Innovation and Informatization of Ukraine (No. M/268-2011) and Academy of Sciences of Moldova (10.820.09.13/UF).

References

[1] G. Bandoli, D.A. Clemente, J. Chem. Soc. Perkin II. (1976) 413.
[2] W.L. Duax, C.M. Weeks, D.C. Rohrer, Topics in Stereochemistry, in: E.L. Elial, N. Allinger (Eds.), vol. 9, 1976, p. 271.
[3] T.A. Hamor, I.L. Martin, Structure-activity relationships in a series of 5-phenyl-1,4-benzodiazepines,, in: A.S. Horn, C.J. Ranter (Eds.), X-ray Crystallography and Drug Action, Clarendon Press, Oxford, 1984, pp. 275–301.
[4] A.V. Bogatsky, S.A. Andronati, N. Ya Golovenko, Tranquillizers. 1.4-Benzodiazepines and Related Structures [in Russian], Science Council, Kiev, 1980.
[5] A. Mozayani, L.P. Raymon, Handbook of drug interactions. A clinical and forensic guide. New Jersey Humana Press Inc., Totowa NJ, 2004, 662 p.
[6] N.Ya. Golovenko, I.A. Kravchenko, Biokhimicheskaya farmakologiya prolekarstv (Biochemical pharmacology of prodrugs), Odessa, Ekologia, 2007, 360 p.
[7] S.A. Andronati, I.A. Prokopenko, A.S. Yavorsky, Yu.A. Simonov, A.A. Dvorkin, T.Sh. Gifeisman, V.M. Chepelev, Pharmazie 43 (1988) 730.
[8] V.I. Pavlovsky, E.A. Semenishina, S.A. Andronati, I.G. Filippova, Yu.A. Simonov, M. Gdaniec, J. Lipkowski, Chem. Heterocycl. Comp. 45 (2009) 1379.
[9] R. Ian Fryer, J. Heterocycl. Chem. 9 (1972) 744.
[10] S.C. Bell, S.J. Childress, J. Org. Chem. 27 (1962) 1691.
[11] A. Stempel, I. Douvan, E. Reeder, L.H. Sternbach, J. Org. Chem. 32 (1967) 2417.
[12] J. Lipkowski, K.S. Andronati, Yu.A. Simonov, V.Ch. Kravtsov, J. Struct. Chem. 46 (2005) 116.
[13] A.A. Mazurov, A.A. Dvorkin, Yu. A. Simonov, S.A. Andronati, Khim. Get. Soedin., SSSR (Russ.) Chem. Heterocycl. Compd., 1990, p. 685.
[14] A.A. Karapetyan, V.G. Andrianov, Yu.T. Struchkov, A.V. Bogatskii, S.A. Andronati, T.I. Korotenko, Bioorg. Khim. 5 (1979) 1684.
[15] G.B. Sergeev, B.M. Sergeev, Y.N. Morosov, V.V. Chernyshev, Acta Cryst. E66 (2010) o2623.
[16] G. Gilli, V. Bertolasi, M. Sacerdoti, P.A. Borea, Acta Crystallogr. B33 (1977) 2664.
[17] M.C. Etter, Israel J. Chem. 25 (1985) 312.
[18] Y. Lu, Y. Wang, W. Zhu, Phys. Chem. Chem. Phys. 12 (2010) 4543.
[19] M.D. Prasanna, T.N. Guru Row, Cryst. Eng. 3 (2000) 135.
[20] Ishu Saraogi, V.G. Vijay, Soma Das, K. Sekar, T.N. Guru Row, Cryst. Eng. 6 (2003) 69.
[21] G.M. Sheldrick, Acta Crystallogr. A64 (2008) 112.
[22] C.F. Macrae, P.R. Edgington, P. McCabe, E. Pidcock, G.P. Shields, R. Taylor, M. Towler, J. van de Streek, J. Appl. Crystallogr. 39 (2006) 453.