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MOLECULAR AND CRYSTAL STRUCTURE OF 1,2-DIHYDRO-3H-1,3,4-BENZOTRIAZEPINES

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Three novel 1,2-dihydro-3H-1,3,4-benzotriazepines have been synthesized: 7-bromo-5-phenyl-3-phenylcarbamoyl-1,2-dihydro-3H-1,3,4-benzotriazepin-2-one, 7-bromo-5-phenyl-1,2-dihydro-3H-1,3,4-benzotriazepin-2-thione, and 7-methyl-5-phenyl-1,2-dihydro-3H-1,3,4-benzotriazepin-2-one. Their crystal structures have been determined using X-ray analysis.

Keywords: benzotriazepine, hydrogen bonds, crystal structure, X-ray analysis.

A current route to searching for biologically active compounds is based on their geometric and conformational parameters in the crystal state. The latter are used in calculations and in structure–biological activity studies.

1,4-Benzodiazepines [1] are a class of materials giving medical practitioners such known neurotropic compounds as diazepam, nitrazepam, oxazepam, lorazepam, phenazepam etc. Their hetero analogs are 1,3,4-benzotriazepines which also have valuable pharmacological properties according to [2, 3]. The limited literature data regarding the structure of 1,3,4-benzotriazepines as a crystal hampers a study of a structure–activity relationship for this class of heterocyclic compound.

In [4, 5] we noted that 1,2-dihydro-3H-1,3,4-benzotriazepines occur in a *pseudo boat* conformation in the solid state. 7,9-Dimethyl-5-dimethylamino-2-phenyl-3H-1,3,4-benzotriazepine [6] has a similar conformation.

Data concerning the crystal structure is also interesting and important since, in their turn, systems of H bonds and weak intermolecular interactions (halogen–halogen, C–H···X, π–π and C–H···π) determine their solubility and hence the bioavailability of these compounds.

The features of the interaction of 1,4-benzodiazepines in the crystal state has been analyzed in [7] and it was shown that dimerization *via* the amide group of the molecule predominates. In the molecules of 1,2-dihydro-3H-1,4-benzodiazepin-2-ones which are unsubstituted in position one, there is one donor (in position 1) or two acceptor groups (the oxygen atom at position 2 and the nitrogen atom at position 4). The 1,2-dihydro-3H-1,3,4-benzotriazepin-2-ones molecules which are unsubstituted in positions 1 and 3 generally have two donor (positions 1 and 3) and two acceptor groups. The latter significantly broadens the combinatorial analysis of organized systems of crystalline hydrogen bonded structures.

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This study concerns the molecular and crystalline structure of 1,2-dihydro-3H-1,3,4-benzotriazepines **1-3** using X-ray analysis.

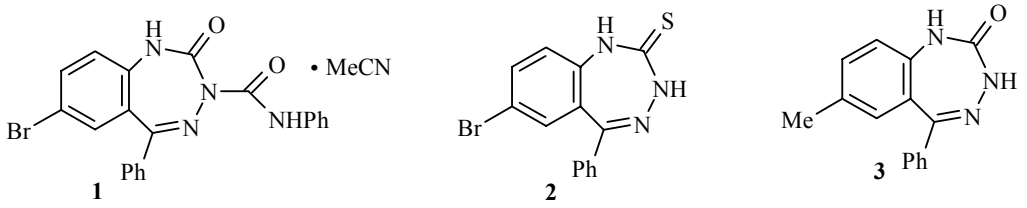

Fig. 1 shows the molecular structure of compounds **1-3** and their atomic numbering. As general for this class of compound the structure has a nonplanar seven-membered ring conjugated to a substituted benzene fragment and has a phenyl substituent in position 5 of the heterocycle. As in other 1,3,4-benzotriazepines the

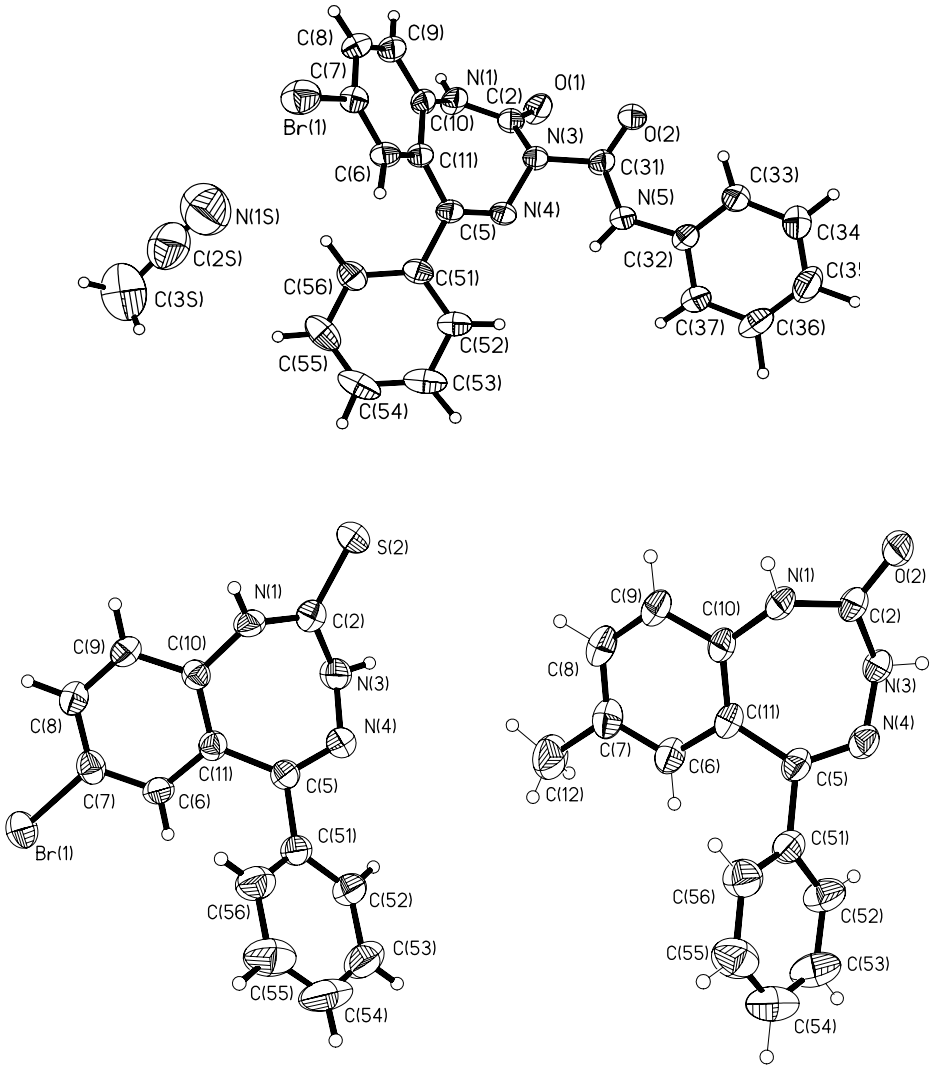

Fig. 1. Structure of compounds **1-3**.

TABLE 1. Crystallographic Data, Experimental Parameters, and Refinement Parameters for Structures **1-3**

	1	**2**	**3**
Empirical formula	$C_{23}H_{18}BrN_5O_2$	$C_{14}H_{10}BrN_3S$	$C_{15}H_{13}N_3O$
Molecular weight	476.33	332.22	251.28
Temperature, K	293(2)	293(2)	293(2)
Wavelength, Å	0.71073	0.71073	0.71073
Symmetry	Monoclinic	Rhombic	Rhombic
Space group	$P2_1/c$	$P2_12_12_1$	$Pca2_1$
Unit cell parameters			
a, Å	6.8540(14)	4.7390(9)	16.392(2)
b, Å	25.404(5)	16.525(3)	11.896(1)
c, Å	12.398(3)	16.982(3)	6.918(1)
β, deg	90.33(3)		
V, Å^3	2158.7(8)	1329.9(5)	1349.1(2)
Z	4	4	4
Density (calc.), g/cm^3	1.466	1.659	1.237
Absorption coefficient, mm^{-1}	1.934	3.236	0.081
F(000)	968	664	528
Crystal size, mm	0.2 × 0.3 × 0.4	0.25 × 0.35 × 0.4	0.25 × 0.35 × 0.3
Range of collected data (θ°)	1.60-30.72	1.72-30.48	3.43-25.03
Range of collected data indices	-9 <= h <= 9, -36 <= k <= 35, -17 <= l <= 17	-6 <= h <= 6, -23 <= k <= 22, -14 <= l <= 23	-15 <= h <= 19, -13 <= k <= 14, -7 <= l <= 8
Number of measured reflections	30891	10764	6728
Number of independent reflections	6176 [R(int) = 0.043]	10341 / 3670 [R(int) = 0.046]	2082 [R(int)=0.066]
Ratio of number of reflections to number of parameters	6176/341	3670/2	2082 / 181
Refinement Q factor for F^2	1.037	0.899	0.997
Final R- factor [$I > 2\sigma(I)$]	$R1$ = 0.0476, $wR2$ = 0.1175	$R1$ = 0.0397, $wR2$ = 0.0847	$R1$ = 0.0570, $wR2$ = 0.1385
R-factor (all weights)	$R1$ = 0.086, $wR2$ = 0.126	$R1$ = 0.0823, $wR2$ = 0.0938	$R1$ = 0.0825, $wR2$ = 0.1567
Residual peaks in difference synthesis e·Å^{-3}	0.408 and -0.500	0.332 and -0.241	0.141 and -0.168

seven-membered ring shows a *boat* conformation with deviation of the planes $N_{(1)}C_{(10)}C_{(11)}C_{(5)}$ (A) and $C_{(2)}N_{(3)}N_{(4)}$ (B) from the "bottom" plane $C_{(2)}N_{(1)}C_{(5)}N_{(4)}$ (C). The degree of twist of the latter fragment for compound **1** is 0.034-0.041, for compound **2** 0.071-0.077, and for compound **3** 0.052-0.054 Å.

The dihedral angles between the AB and AC fragments are 36.0(3) and 60.4(3)° for compound **1**, 33.7(3) and 44.9(3)° for compound **2**, and 31.7 and 45.4° for compound **3**. The angles between the aromatic fragments in compounds **1-3** are 58.4, 59.6, and 72.9° respectively. They are close to those found in [4] for 7-bromo-5-phenyl-1,2-dihydro-3H-1,3,4-benzotriazepin-2-one (**4**) where the angles AB and BC are 35.6 and 42.8° and the angle between the aromatic rings 63.5°.

The deviation from an ideal symmetry for a seven-membered ring is described by the ΔC_s parameter [7] which is 20.7 for compound **4**. For compound **1** ΔC_s is 11.41, for compound **2** 15.29, and for compound **3** 15.07. We have previously reported [2] that the change from 1,2-benzodiazepines to 1,3,4-benzotriazepines is accompanied by a large distortion from C_s symmetry in the seven-membered ring. Exchanging the oxygen atom at position two for sulphur has virtually no effect on the degree of deviation of the seven-membered ring from C_s-symmetry.

TABLE 2. Interatomic Distances (*d*) in Structures **1-3**

Bond	*d*, Å		
	1	**2**	**3**
$N_{(1)}$–$C_{(2)}$	1.355(4)	1.348(5)	1.335(5)
$N_{(1)}$–$C_{(10)}$	1.407(4)	1.415(5)	1.407(5)
$N_{(3)}$–$C_{(2)}$	1.423(3)	1.357(5)	1.378(5)
$N_{(3)}$–$N_{(4)}$	1.440(3)	1.416(5)	1.417(4)
$N_{(4)}$–$C_{(5)}$	1.292(3)	1.271(5)	1.282(4)
$C_{(5)}$–$C_{(11)}$	1.472(4)	1.479(5)	1.476(5)
$C_{(5)}$–$C_{(51)}$	1.496(4)	1.494(5)	1.485(5)
$C_{(6)}$–$C_{(7)}$	1.383(4)	1.375(5)	1.388(6)
$C_{(6)}$–$C_{(11)}$	1.403(4)	1.401(5)	1.413(5)
$C_{(7)}$–$C_{(8)}$	1.390(4)	1.376(6)	1.379(6)
$C_{(8)}$–$C_{(9)}$	1.372(5)	1.374(6)	1.368(5)
$C_{(9)}$–$C_{(10)}$	1.394(4)	1.395(6)	1.394(5)
$C_{(10)}$–$C_{(11)}$	1.404(3)	1.394(5)	1.392(5)
$C_{(51)}$–$C_{(52)}$	1.392(4)	1.400(6)	1.394(6)
$C_{(51)}$–$C_{(56)}$	1.393(4)	1.376(6)	1.378(6)
$C_{(52)}$–$C_{(53)}$	1.401(4)	1.382(7)	1.364(6)
$C_{(53)}$–$C_{(54)}$	1.379(6)	1.371(9)	1.376(8)
$C_{(54)}$–$C_{(55)}$	1.368(6)	1.369(9)	1.376(8)
$C_{(55)}$–$C_{(56)}$	1.397(4)	1.380(7)	1.376(6)

The interatomic distances presented in Table 2 are typical of other compounds of this type. At the same time, the nature of the intermolecular interactions in compounds **1-3** are markedly different. In the formation of the crystal structure of all three compounds hydrogen bonds and van der Waal forces play an important role. Blocking of the 3-NH group in compound **1** affords it donor-acceptor properties like 1,4-benzodiazepines.

In the crystal, the molecules of **1** are combined as dimers by two $N_{(10)}$–H···$O_{(1)}$ intermolecular bonds (Fig. 2). The position of the substituent at atom $N_{(3)}$ is stabilized by hydrogen bonds $N_{(5)}$–H···$N_{(4)}$ = 2.574(3) and $C_{(8)}$–H···$O_{(2)}$ = 3.174(4) Å. The hydrogen bond parameters are given in Table 4. Solvated acetonitrile molecules are found in packing cavities of the basic molecules and are bound by van der Waal interactions.

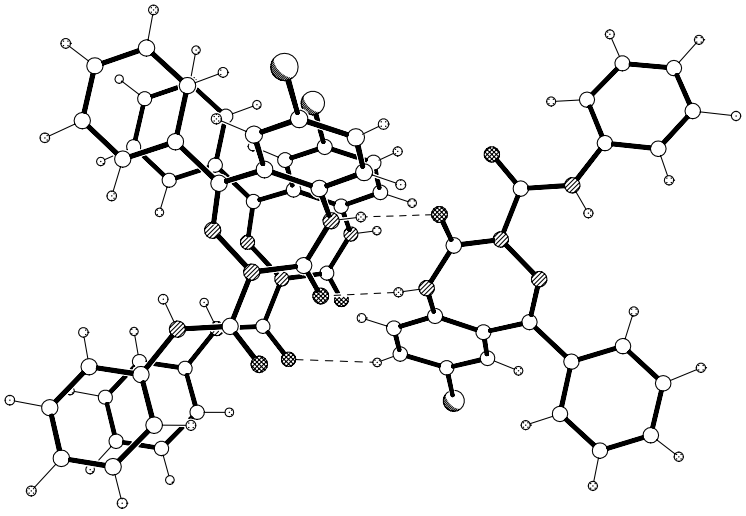

Fig. 2. Packing fragment for compound **1**.

TABLE 3. Valence Angles (ω) in Structures **1-3**

Angle	ω, deg		
	1	**2**	**3**
$C_{(2)}$–$N_{(1)}$–$C_{(10)}$	125.7(2)	126.1(4)	127.0(3)
$C_{(2)}$–$N_{(3)}$–$N_{(4)}$	115.2(2)	125.7(3)	123.2(3)
$C_{(5)}$–$N_{(4)}$–$N_{(3)}$	115.6(2)	118.7(3)	119.3(3)
$N_{(1)}$–$C_{(2)}$–$N_{(3)}$	113.2(2)	117.1(4)	118.5(3)
$N_{(4)}$–$C_{(5)}$–$C_{(11)}$	124.8(2)	120.7(3)	127.6(3)
$N_{(4)}$–$C_{(5)}$–$C_{(51)}$	115.0(2)	126.5(3)	114.3(3)
$C_{(11)}$–$C_{(5)}$–$C_{(51)}$	120.2(2)	119.2(3)	118.1(3)
$C_{(7)}$–$C_{(6)}$–$C_{(11)}$	120.6(2)	121.0(4)	121.4(4)
$C_{(6)}$–$C_{(7)}$–$C_{(8)}$	120.7(3)	120.8(4)	118.3(4)
$C_{(9)}$–$C_{(8)}$–$C_{(7)}$	119.2(3)	119.4(4)	121.9(4)
$C_{(8)}$–$C_{(9)}$–$C_{(10)}$	121.2(3)	120.6(4)	120.0(4)
$C_{(9)}$–$C_{(10)}$–$C_{(11)}$	120.0(3)	120.4(4)	120.2(3)
$C_{(9)}$–$C_{(10)}$–$N_{(1)}$	118.6(2)	121.3(4)	121.4(3)
$C_{(11)}$–$C_{(10)}$–$N_{(1)}$	121.4(2)	118.3(4)	118.3(3)
$C_{(10)}$–$C_{(11)}$–$C_{(6)}$	123.2(3)	122.2(3)	118.2(3)
$C_{(10)}$–$C_{(11)}$–$C_{(5)}$	121.7(2)	117.8(3)	123.2(3)
$C_{(6)}$–$C_{(11)}$–$C_{(10)}$	118.3(2)	123.0(4)	118.7(3)
$C_{(52)}$–$C_{(51)}$–$C_{(56)}$	119.4(3)	119.1(4)	117.8(4)
$C_{(52)}$–$C_{(51)}$–$C_{(5)}$	119.7(3)	119.1(4)	121.7(4)
$C_{(56)}$–$C_{(51)}$–$C_{(5)}$	120.9(3)	121.9(4)	120.5(4)
$C_{(51)}$–$C_{(52)}$–$C_{(53)}$	120.1(3)	119.0(4)	120.8(5)
$C_{(54)}$–$C_{(53)}$–$C_{(52)}$	119.5(3)	119.5(6)	120.8(5)
$C_{(55)}$–$C_{(54)}$–$C_{(53)}$	121.0(3)	120.5(6)	119.3(5)
$C_{(54)}$–$C_{(55)}$–$C_{(56)}$	120.1(3)	120.1(6)	119.9(5)
$C_{(51)}$–$C_{(56)}$–$C_{(55)}$	119.9(3)	120.1(6)	121.4(5)

The molecules of compound **2** are bond in spiral symmetry 2_1 by the $N_{(1)}$–H hydrogen bond but the $N_{(3)}$–H group does not take part in the formation of the hydrogen bond. Hence the sulphur atom in the **2** molecule takes part in the formation of a single hydrogen bond (Fig. 3). Overall, in compound **2**, the molecules form a chain along the double helical axis.

Compound **3** forms a band due to the N–H···O hydrogen bonds (Fig. 4). Both N–H groups take part in its formation. The oxygen atom behaves as acceptor. The hydrogen bond parameters are given in Table 4. The remaining contacts have van der Waal character.

Summarizing data about intermolecular interactions in the compounds **1-3** we can affirm that small changes in the molecular structure bring to significant changes in the crystalline structure. This can notify the bioavailability of the compound.

TABLE 4. Hydrogen Bonds for Structures **1-3**

Com-pound	D	*d*(H···A)	∠ DHA	*d*(D···A)	A	Symmetry element for A
1	$N_{(5)}$	2.12(3)	112(3)	2.574(3)	$N_{(4)}$	*x, y, z*
	$N_{(1)}$	2.13(4)	175(3)	2.918(3)	$O_{(1)}$	*-x* + 1, *-y* + 1, *-z* + 1
	$C_{(8)}$	2.46(4)	135(3)	3.174(4)	$O_{(2)}$	*-x* + 2, *-y* + 1, *-z* + 1
2	$N_{(1)}$	2.89(3)	171(3)	3.618(4)	$S_{(2)}$	*x*-1/2, *-y* + 3/2, *-z*
3	$N_{(3)}$	2.113	175.32	2.933	$O_{(2)}$	*-x* + 1/2, *y*, *z* - 1/2
	$N_{(1)}$	2.088	176.08	2.853	$O_{(2)}$	*-x* + 1/2, *y*, *z* + 1/2

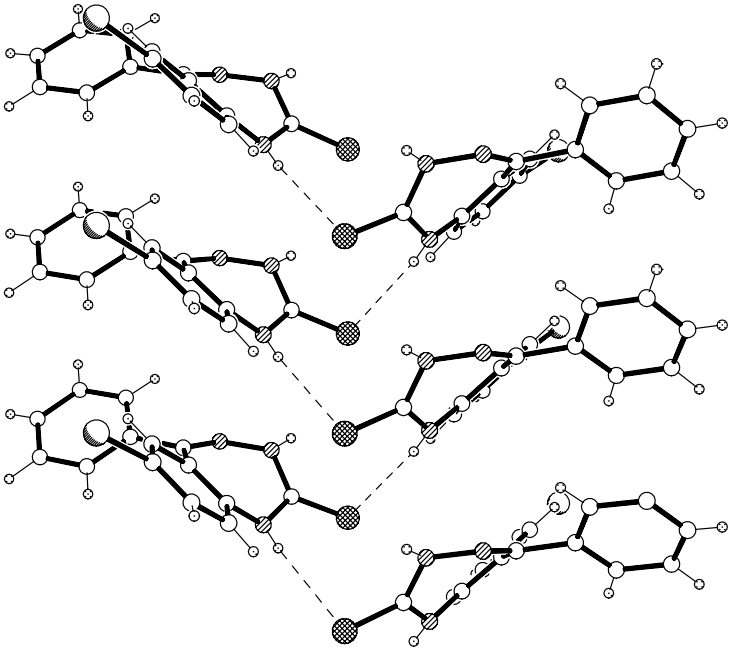

Fig. 3. Packing fragment for compound **2**.

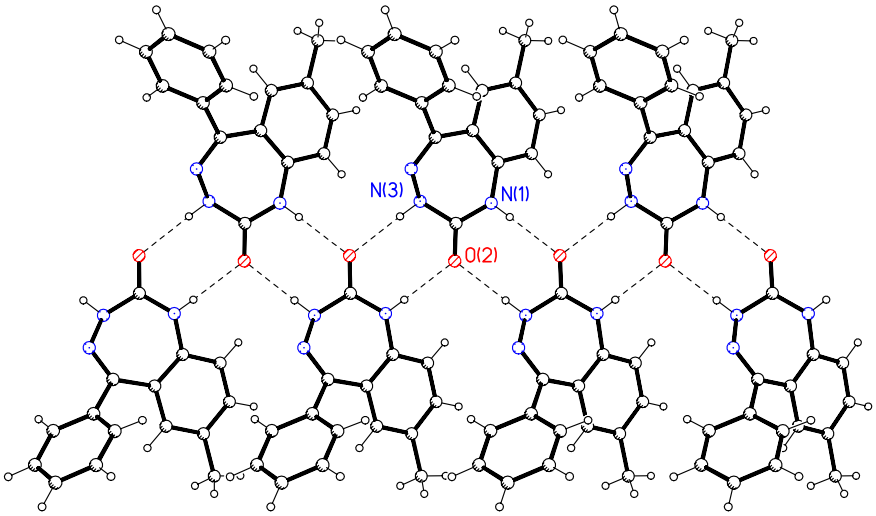

Fig. 4. Packing fragment for compound **3**.

EXPERIMENTAL

Compounds **1-3** were synthesized by previously reported methods [8-10]. The recrystallization and crystal growth were carried out from acetonitrile solution for compound **1** or chloroform for compounds **2** and **3**. This explains the cocrystallization of compound **1** with a solvent molecule.

X-ray diffraction experiments for compounds **1** and **2** were performed using a Bruker AXS Smart diffractometer with CCD detector (MoKα irradiation, room temperature). A correction for absorption in the intensity was introduced using the SHELXTL-NT V5 programs [11]. The compounds structures were solved by direct methods with least squares refinement using the SHELX-97 programs [12] in the anisotropic approximation for non-hydrogen atoms and isotropic for hydrogens. The positions of the latter were localized from difference Fourier synthesis.

Experimental data for compound **3** was obtained on a KUMA CCD diffractometer with an amorphous fragment of crystal of size 0.25 × 0.35 × 0.3 mm. On conversion from intensity to F^2, absorption was not included.

The basic experimental parameters are given in Table 1, the interatomic distances and valence angles in Tables 2 and 3, and the fixed atom coordinates have been deposited in the CCDC bank (No. 255324-255326)

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