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SYNTHESIS AND CRYSTAL STRUCTURE OF TWO DERIVATIVES OF BENZODIAZEPINES

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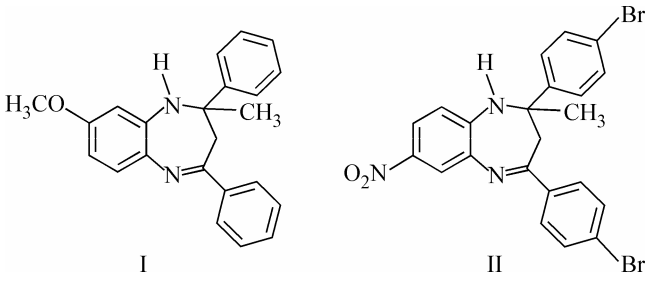
Two benzodiazepine derivatives, $C_{23}H_{22}N_2O$ (I), 2-methyl-8-methoxy-2,4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepine, and $C_{22}H_{17}N_3O_2Br_2$ (II), 2-methyl-7-nitro-2,4-bis(4′-bromophenyl)-2,3-dihydro-1H-1,5-benzodiazepine, were studied by single crystal X-ray diffraction method. Compound (I) crystallizes in the monoclinic system, space group $P2_1/c$, $a = 13.1703(17)$, $b = 11.1990(14)$, $c = 12.9093(16)$ Å, $\beta = 107.831(2)°$, $V = 1812.6(3)$ Å^3, $Z = 4$. Compound (II) crystallizes in the monoclinic system, space group $P2_1/n$, $a = 11.7345(12)$, $b = 12.7477(13)$, $c = 13.5965(14)$ Å, $\beta = 95.221(2)°$, $V = 2025.4(4)$ Å^3, $Z = 4$. The molecules of (I) and (II) have T-shape form with the diazepine ring at the junction point. The seven membered central benzodiazepine ring in both structures adopt a twist-boat conformation. The crystal packing is stabilized by C—H…π (in I) and C—H…O (in II) interactions.

K e y w o r d s: Crystal structure, X-ray diffraction, benzodiazepines, hydrogen bonding.

Introduction. Benzodiazepines are well studied due to their pharmacological properties, such as antibacterial, antifungal, analgesic and anti-convulsant [1, 2]. Benzodiazepine derivatives containing additional rings are potential pharmacological agents [3] because of their efficacy in the treatment of central nervous system [4]. We have synthesized the title molecules (I) and (II) (Scheme 1) in our laboratory [5] and describe here their crystal structures.



Experimental. For the compound (I), a mixture containing methoxy-o-phenylenediamine (5 mmol), acetophenone (10 mmol) and $ZrCl_4$ (10 mol %) in 1,2-dichloroethane (15 ml) was refluxed for 150 min. After completion of the reaction, as indicated by TLC, the reaction mixture was cooled to room temperature, washed with water (3×10 ml) and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography on silica gel (100—200 mesh) using hexane and ethylacetate (98:2) as an eluent to afford pure product (yield 85 %).

For the compound (II), the above procedure was repeated with nitro-o-phenylenediamine (5 mmol) and bromoacetophenone (10 mmol) with reflux time of 180 min (yield 80 %).

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Table 1

Crystal data and experimental details

Parameter	Compound (I)	Compound (II)
Chemical formula	$C_{23}H_{22}N_2O$	$C_{22}H_{17}N_3O_2Br_2$
M	342.4	515.2
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/n$
Uni cell dimensions		
a, *b*, *c*, Å	13.1703(17), 11.1990(14), 12.9093(16)	11.7345(12), 12.7477(13), 13.5965(14)
β, град.	107.831(2)	95.221(2)
V, Å^3	1812.6(3)	2025.4(4)
Z	4	4
Calculated density(g/cm^3)	1.255	1.690
Crystal dimensions (mm)	0.22×0.17×0.15	0.20×0.15×0.14
Crystal shapeandcolor	needle, yellow	prism, yellow
μ (mm^{-1})	0.077	4.026
Measured data	19800	22215
Unique data	4228	4758
Observed data ($I > 2\sigma(I)$)	3476	3061
Refined parameters	241	267
R	0.0485	0.0478
wR (F^2)	0.1493	0.1121
GOOF	1.119	1.013
CCDC deposition number	658683	658684

Diffraction data were measured at room temperature with a Bruker SMART CCD area detector [6]. Preliminary unit cell parameters and orientation matrix were obtained from three sets of frames. Intensity data were collected using graphite-monochromated MoK_α radiation (λ = 0.71073 Å) .

Integration and scaling of intensity data were accomplished using SAINT [6]. The structure was solved by direct methods and refined by a full matrix least-squares procedure based on F^2 [7]. Non-hydrogen atoms were refined with anisotropic displacement parameters and hydrogen atoms were included in calculated positions in the riding model approximation and refined isotropically. The details of the data collection and refinement are summarized in Table 1. The geometry and molecular graphics were computed using programs PARST [8], ORTEP-3 [9] and PLATON [10].

Results and Discussion. The molecules of the title compounds (I) and (II) (Figs. 1 and 2) are built around a central benzodiazepine C_5N_2 seven-membered ring, which is fused with a benzene ring at atoms C4 and C9. The compounds (I) and (II) possess a stereogenic centre C3 (S). The molecule has a near T-shaped form in both compounds with the diazepine ring as the junction point. The diazepine ring adopts a twist-boat conformation in both structures (the asymmetry parameters [8] are

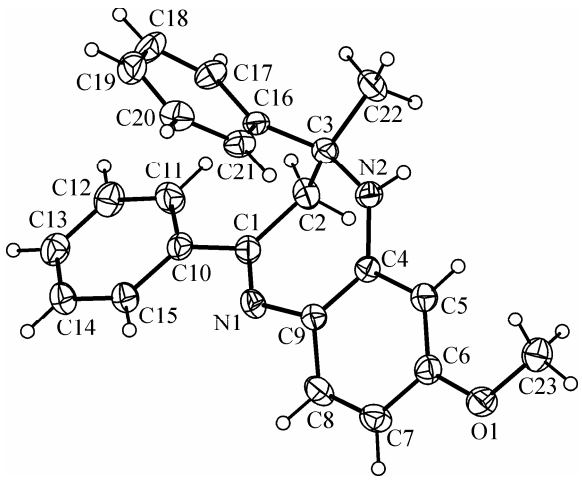
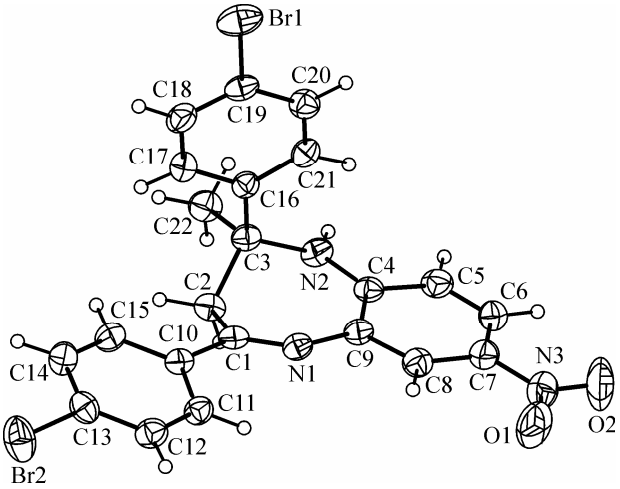


Fig. 1. Asymmetric unit of (I) with atomic numbering scheme. Displacement ellipsoids are drawn at the 30 % probability level



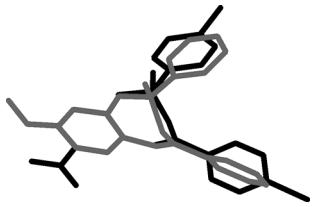


Fig. 2 (*left*). Asymmetric unit of (II) with atomic numbering scheme. Displacement ellipsoids are drawn at the 30 % probability level

Fig. 3 (*right*). A least-squares fit of the (I) and (II), (r.m.s. deviation = 0.021 Å) based on the atoms C4—C9

Δ_s(C9) = 0.155(1), Δ_2(N1) = 0.074(1) and Δ_s(C1) = 0.123(2), Δ_2(N1) = 0.097(2) for compounds (I) and (II), respectively), which means that a local pseudo two fold axis runs along N1 and the mid-point of the C3—N2 bond. In (I) and (II), the C4—N2 bond (Table 2) of the benzodiazepine ring has a length about half-way between the C—N pure single and double bond distances [11]. The valency angles at the N atom are near 120° (Table 2), and the overall geometry of the C—N bond resembles that of a regular double bond. This is further illustrated by the planar connectivity around C—N bond as the torsion angle C3—N2—C4—C9 equals –10.8(2) and 11.6(6)° for (I) and (II), respectively.

The phenyl ring in (I) (C16—C21 ring in (II)) protrudes axially from the tricyclic core of the molecule due to the sp^3 character and tetrahedral angle configuration of the C3 atom (Table 2). Again, the phenyl ring (C16—C21 in (II)) is oriented almost perpendicular (dihedral angle is 82.4(1)° (84.0(1)° in II)) to the plane of the diazepine ring. The other six-membered rings are almost coplanar with the diazepine ring in both compounds.

A geometrical feature commonly used to describe benzodiazepines is the dihedral angle between the phenyl and the benzo rings ranging from 54 to 75° for the unsubstituted phenyl rings [12, 13]. In the present work, in (I), the 2- and 4-phenyl rings sustain dihedral angles of 30.9(1) and 82.8(1)°, respectively, well outside the range cited in the literature. With respect to the core ring, the equatorial orientation of the methyl group substituted at the atom C3 in the compounds (I) and (II) is evident from the corresponding torsion angles C1—C2—C3—C22 of –167.9(1) and –168.7(3)°. Substitution of bromine (in (II)) at atoms C13 and C19 does not affect the overall molecular geometry. An overlay fitting of the fused benzene ring of the compounds (I) and (II) is shown in Fig. 3.

T a b l e 2

Selected bond distances d, Å *and angles* φ, deg.

Bond	*d*	Angle	φ	Bond	*d*	Angle	φ
Compound (I)				Compound (II)			
C(1)—N(1)	1.285(2)	N(3)—C(3)—C(16)	111.9(3)	C(1)—N(1)	1.271(4)	N(3)—C(3)—C(16)	111.5(3)
C(4)—N(2)	1.373(2)	N(3)—C(3)—C(22)	106.6(1)	C(4)—N(2)	1.361(5)	N(3)—C(3)—C(22)	106.8(3)
		C(16)—C(3)—C(22)	109.6(1)			C(16)—C(3)—C(22)	109.8(3)
		N(2)—C(3)—C(2)	109.1(1)			N(2)—C(3)—C(2)	109.7(7)
		C(16)—C(3)—C(2)	110.9(9)			C(16)—C(3)—C(2)	111.0(3)
		C(22)—C(3)—C(2)	108.6(1)			C(22)—C(3)—C(2)	107.9(3)
		C(4)—N(2)—C(3)	129.2(1)			C(4)—N(2)—C(3)	128.4(3)
		C(4)—N(2)—H2N(3)	115.3(1)			C(4)—N(2)—H2N(3)	116.0(3)
		C(3)—N(2)—H2N(3)	115.3(1)			C(3)—N(2)—H2N(3)	114.0(3)

Table 3

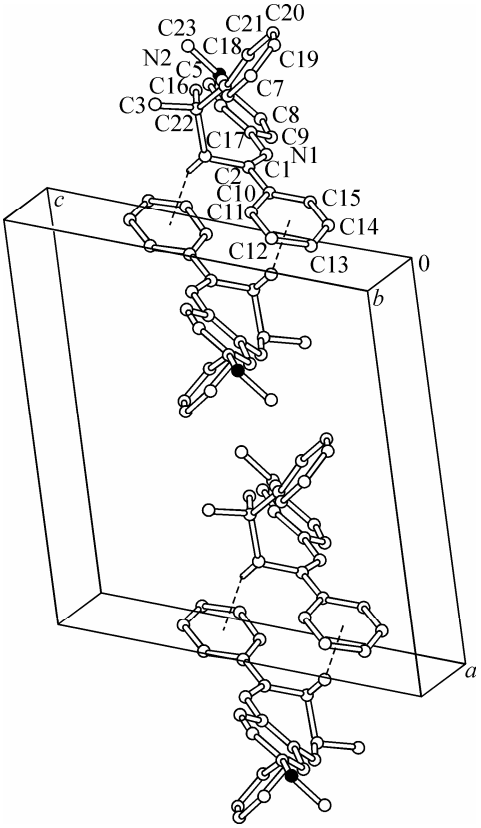
Hydrogen bonding geometry (Å, deg.)

D—H…A	(D—H)	(H…A)	(D…A)	(DHA)	D—H…A	(D—H)	(H…A)	(D…A)	(DHA)
Compound (I)					Compound (II)				
C21—H21…N2	0.930	2.45	2.812(2)	103	C17—H17…O2^{j}	0.930	2.38	3.221(5)	150
C2—H2B…Cg1^{i}	0.96	2.77	3.695	159	C21—H21…N2	0.930	2.45	2.816(5)	104

Symm. code: i) $-x, -y+1, -z$; Cg1 is the centroid of the C10—C15 ring.
Symm. code: j) $x+1, y, z$.

The important observation in the compounds (I) and (II) is that the amine hydrogen in the central diazepine ring does not participate in conventional hydrogen bonding, although the configuration of the atom N2 is planar (the sum of the angles at N being 359.9(2) and 359.0(3)° respectively in (I) and (II)). Literature survey reveals that this could be because of the irregular shape or conformation of the molecule [14].

Despite the close structural similarity, some differences in the packing mode were observed in the structures (I) and (II). An intramolecular C—H…N weak interaction between atoms C21 and N2 observed in both the structures closes the five-membered pseudo-ring N2—C3—C16—C21—H21 according to S(5) pattern [15] (Table 3). In (I), the packing is further stabilized by C—H…π (arene) (Fig. 4) interactions. Similar C—H…π (arene) interactions were observed previously in the crystal structure of an inclusion compound between a benzodiazepine compound and benzene [16]. In (II) (Fig. 5), supramolecular chains of C11 type are forming through C—H…O intermolecular hydrogen bonding along the *a*-axis.



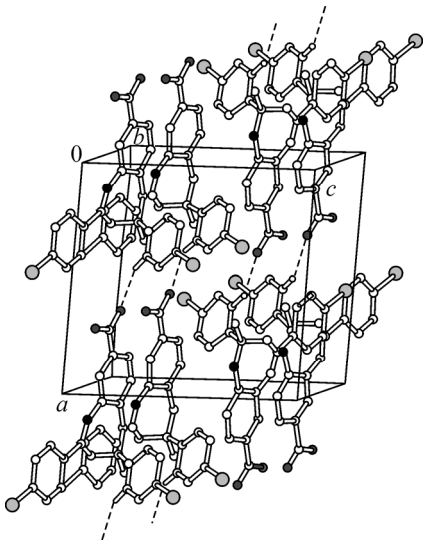


Fig. 4 (*left*). Part of the crystal structure of (I) highlighting the formation of centrosymmetric dimers along [100] generated by C—H…π (arene) hydrogen bond (dashed lines). For clarity H atoms not involved in the motif shown have been omitted

Fig. 5 (*right*). Part of the crystal structure of (II) showing the formation of C11 chains along [100]. For clarity H atoms not involved in the motif shown have been omitted

The intra- and intermolecular interactions seem to impact the physical properties of the compounds concerned. The compound (I) displays weak C—H…π interactions and has a relatively low melting point (120—121 °C). Whereas, the compound (II) displays somewhat stronger C—H…O interactions and has a higher melting point (160—162 °C).

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