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SYNTHESIS AND CRYSTALLINE AND MOLECULAR STRUCTURE OF HYDROCHLORIDE OF 1-[2(2,3-DIHYDRO-1,3,4-OXADIAZOLYL-5-ONE)]METHYL-7-BROMO-5-PHENYL-1,2-DIHYDRO-3H-1,4-BENZODIAZEPIN-2-ONE

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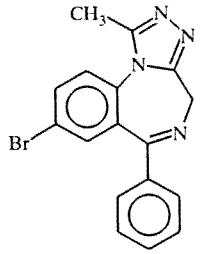
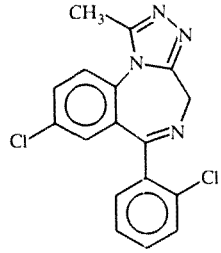
By the interaction of 1-hydrazinocarbonylmethyl-7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one with phosgene, the compound 1-[2(2,3-dihydro-1,3,4-oxadiazolyl-5-one)]methyl-7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one has been synthesized. Spectroscopic methods and x-ray structure analysis have been used to establish the crystalline and molecular structure of this new derivative of 1,4-benzodiazepine.

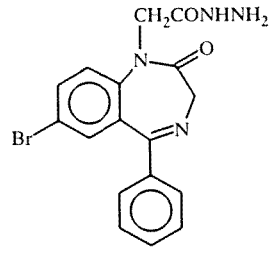
Among the derivatives of 1,4-benzodiazepine containing hydrazide or hydrazone fragments, certain valuable psychopharmaceutical preparations have been found, with an original spectrum of action on the central nervous system. Examples of this class are preparations widely used in medical practice, such as alprazalam (I) and ketazolam (II) [1], and also a selective antianxiety drug recently developed in our country, gidazepam (III) [2]:



I



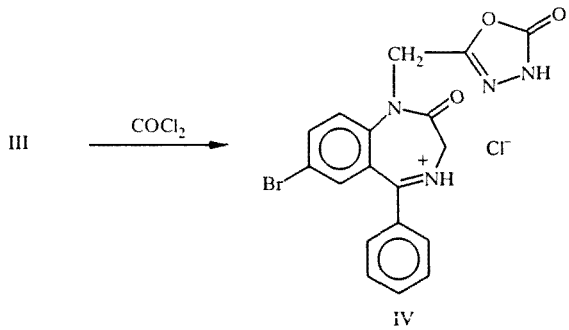
II



III

Here we are reporting on a study of the structure of the product obtained by the interaction of gidazepam with phosgene. The individuality of the synthesized compound was confirmed by TLC on Silufol UV-254 plates.

It was established that the interaction of gidazepam with phosgene forms the hydrochloride of 1-[2(2,3-dihydro-1,3,4-oxadiazolyl-5-one)]methyl-7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one (IV).



IV

*Deceased.

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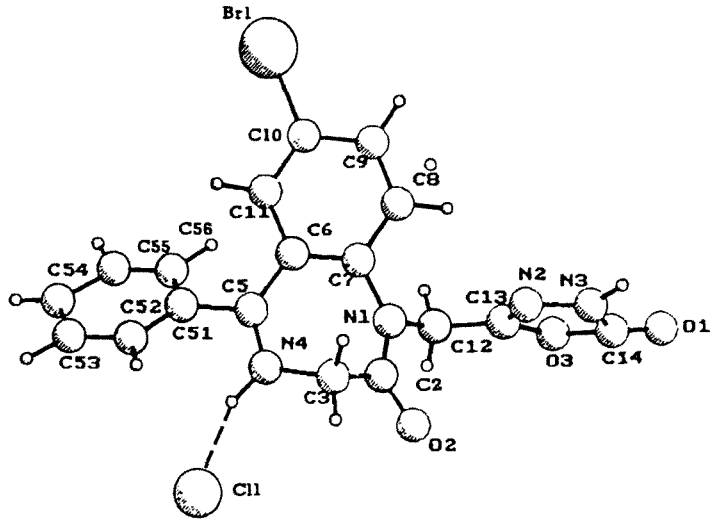

Fig. 1. Molecular structure of 1-[2(2,3-dihydro-1,3,4-oxadiazolyl-5-one)]-methyl-7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one.

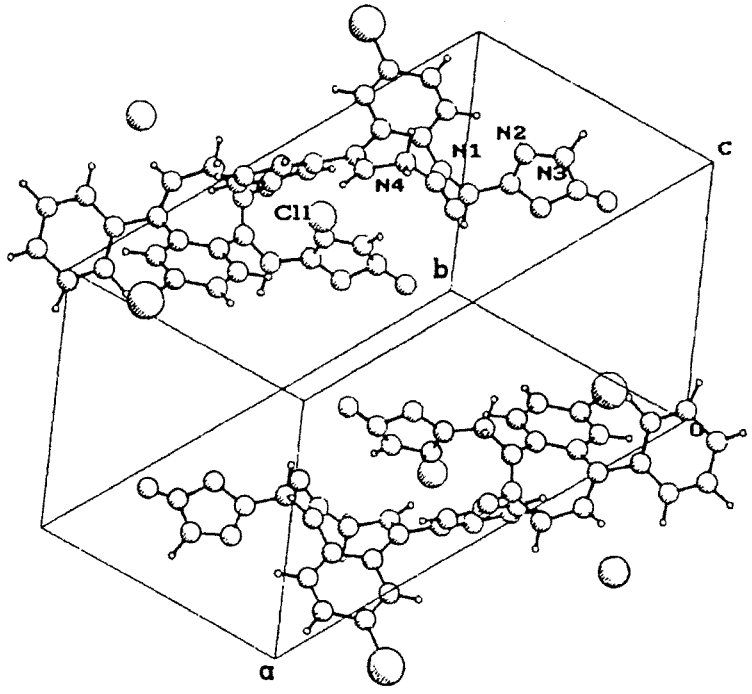

Fig. 2. Molecular cell packing of dimeric structures for 1-[2(2,3-dihydro-1,3,4-oxadiazolyl-5-one)]methyl-7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one.

The IR spectrum of compound IV contains absorption bands at 3440 (NH), 1683, 1783, 1826 (C=O), 1604, and 1640 (C=N) cm^{-1}. In the UV spectrum of IV in methanol or in an alkaline medium (NaOH, pH 11.5), there is a single maximum at 223 nm and a shoulder at 300 nm; in an acidic medium, the spectrum is much different, exhibiting four maxima at 204, 234, 279, and 349 nm, evidently because of protonation at the azomethine bonds.

In the PMR spectra of compound IV we observe an AB-quadruplet of methylene protons of the heterorings with the center at 4.385 ppm (2H, q, J_{AB} = 10.75 Hz) and an AB-quadruplet of exocyclic methylene protons with the center at 4.987 ppm (2H, q, J_{AB} = 16.75 Hz). In the mass spectrum of IV we find an intense peak of the molecular ion $[M]^+$ (100%) and

TABLE 1. Coordinates of Atoms and Structure of Hydrochloride of 1-[2(2,3-Dihydro-1,3,4-oxadiazolyl-5-one)]methyl-7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one (IV) ($\times 10^4$)

Atom	x/a	y/b	z/c
Br	1500(2)	2225(5)	544(3)
Cl	1908(5)	2585(12)	-6746(7)
$O_{(1)}$	239(19)	-6270(40)	-3220(29)
$O_{(2)}$	1024(14)	-1401(28)	-5257(19)
$O_{(3)}$	1039(15)	-4867(30)	-3422(21)
$N_{(1)}$	1368(14)	-1212(27)	-3565(18)
$N_{(2)}$	222(18)	-2705(36)	-3191(24)
$N_{(3)}$	-137(17)	-3767(36)	-3102(24)
$N_{(4)}$	1665(15)	1453(29)	4540(22)
$C_{(2)}$	1120(21)	-649(45)	-4513(32)
$C_{(3)}$	935(21)	933(43)	-4698(26)
$C_{(5)}$	2030(20)	1295(40)	-3608(25)
$C_{(6)}$	1726(10)	847(24)	-2662(12)
$C_{(7)}$	1402(10)	-332(24)	-2658(12)
$C_{(8)}$	1105(10)	-739(24)	-1710(12)
$C_{(9)}$	1133(10)	34(24)	-766(12)
$C_{(10)}$	1458(10)	1212(24)	-769(12)
$C_{(11)}$	1754(10)	1619(24)	-1718(12)
$C_{(12)}$	1572(21)	-2728(42)	-3499(25)
$C_{(13)}$	924(20)	-3358(41)	-3383(28)
$C_{(14)}$	262(30)	-5040(61)	-3378(45)
$C_{(51)}$	2728(11)	1905(27)	-3578(19)
$C_{(52)}$	2796(11)	3070(27)	-4219(19)
$C_{(53)}$	3473(11)	3509(27)	-4201(19)
$C_{(54)}$	4082(11)	2785(27)	-35843(19)
$C_{(55)}$	4013(11)	1620(27)	-2901(19)
$C_{(56)}$	3336(11)	1181(27)	-2919(19)

peaks of fragment ions $[M - CO]^{+\cdot}$ (84-94%), $[M -$ substituent at $N_{(1)}]^{+\cdot}$ (27.72%), and $[M -$ CO-substituent at $N_{(1)}]^{+\cdot}$ (44.65%). The crystalline and molecular structures of the hydrochloride of IV were established by x-ray structure analysis: Crystals of compound IV, prismatic habit of monoclinic system, space group of symmetry $P2_{1/a}$, a = 18.064(12), b = 9.474(6), c = 12.472(12) Å, γ = 74.30(2)°, Z = 4, composition $C_{17}H_{14}N_4O_3BrCl$. The final R-factor was 0.089 (ω = 1). The coordinates of the basis atoms are listed in Table 1. In the crystal, the organic cations and chlorine anions are connected by hydrogen bonds to form dimers. The proton donors for these bonds are $N_{(3)}$ and $N_{(4)}$ (Fig. 1). The hydrogen bonds are characterized by the following parameters: $N_{(3)}$—H...Cl (−x, −y, −1 − z) = 3.096 Å, angle at H = 143°; $N_{(4)}$—H...Cl = 3.028 Å, H...Cl = 2.08 Å; angle 155°. There are no significant intermolecular interactions between dimers in the crystal (Fig. 2). The seven-membered ring is characterized by a set of torsion angles (beginning with the $N_{(1)}$—$C_{(2)}$ bond) −6.1°, 62.0°, −60.8°, −9.4°, 46.0°, 2.3°, −48.7°, which are characteristic for 1,4-benzodiazepines [3] having the boat conformation. The $C_{(12)}$ and $O_{(2)}$ atoms are in the cis configuration, making a dihedral angle of 5.1° with the $C_{(12)}$—$N_{(1)}$—$C_{(2)}$—$O_{(2)}$ fragment. The five-membered oxadiazole heteroring is practically planar, with the maximum deviation from the mean square plane of its atoms having values from −0.067 to −0.077 Å for the $N_{(3)}$ and $C_{(14)}$, respectively. The distances (Table 2) indicate a high degree of delocalization of electron density in this ring. Thus, the lengths of the formally double bond $N_{(2)}$—$C_{(13)}$ and the $N_{(3)}$—$C_{(14)}$ bond are 1.28 and 1.27 Å, respectively. The C—O distances are 1.39 and 1.46 Å for the $C_{(13)}$—O and $C_{(14)}$—$O_{(3)}$ bonds, respectively. The two aromatic rings form a dihedral angle of 113.4°. The oxadiazole substituent at $N_{(1)}$ makes a dihedral angle of 67.1° with the bromophenyl ring, and an angle of −51.4° with the phenyl ring. We consider that the values of the these angles are determined mainly by the packing conditions.

The entire molecule acts as a cation with localization of a proton at $N_{(4)}$ (Fig. 1). Its localization has practically no effect on the $N_{(4)}$—$C_{(5)}$ and $N_{(4)}$—$C_{(3)}$ distances (Table 2) in comparison with other 1,4-benzodiazepin-2-ones [1, 3].

TABLE 2. Bond Lengths (Å) and Bond Angles (deg) in Structure of 1-[2(2,3-Dihydro-1,3,4-oxadiazolyl-5-one)]methyl-7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one (IV)

Bond	Length	Angle	ω
Br—C(10)	1,91(2)	C(13)—O(3)—C(14)	104(3)
O(2)—C(2)	1,21(5)	C(2)—N(1)—C(12)	116(3)
O(3)—C(14)	1,46(6)	N(3)—N(2)—C(13)	106(3)
N(1)—C(7)	1,42(3)	C(3)—N(4)—C(5)	121(3)
N(2)—N(3)	1,34(5)	O(2)—C(2)—C(3)	117(4)
N(3)—C(14)	1,27(7)	N(4)—C(3)—C(2)	109(3)
N(4)—C(5)	1,32(4)	N(4)—C(5)—C(51)	115(3)
C(5)—C(6)	1,41(4)	C(5)—C(6)—C(7)	122(2)
C(12)—C(13)	1,46(5)	N(1)—C(7)—C(6)	124(2)
O(1)—C(14)	1,19(7)	Br—C(10)—C(9)	119(1)
O(3)—C(13)	1,39(5)	N(1)—C(12)—C(13)	114(3)
N(1)—C(2)	1,32(5)	O(3)—C(13)—C(12)	120(3)
N(1)—C(12)	1,39(5)	O(1)—C(14)—O(3)	114(5)
N(2)—C(13)	1,28(5)	O(3)—C(14)—N(3)	103(4)
N(4)—C(3)	1,54(5)	C(5)—C(51)—C(56)	117(2)
C(2)—C(3)	1,46(6)	C(2)—N(1)—C(7)	123(3)
C(5)—C(51)	1,52(4)	C(7)—N(1)—C(12)	121(2)
(C—C)Ph	1,395	N(2)—N(3)—C(14)	115(4)
		O(2)—C(2)—N(1)	122(4)
		N(1)—C(2)—C(3)	121(3)
		N(4)—C(5)—C(6)	123(3)
		C(6)—C(5)—C(51)	121(3)
		C(5)—C(6)—C(11)	118(2)
		N(1)—C(7)—C(8)	116(2)
		Br—C(10)—C(11)	121(1)
		O(3)—C(13)—N(2)	111(3)
		N(2)—C(13)—C(12)	129(2)
		O(1)—C(14)—N(3)	136(2)
		(C—C—C)Ph	128

It was established in animal experiments that compound IV has a distinct antispasmodic action in doses ED_{50} = 0.5 mg/kg according to the Korazole antagonism test; it does not have any depressant effect on the orientation—search behavior of animals in an open field; and in doses of 4-5 mg/kg it does not potentiate the sopoforic action of Nembutal; LD_{50} > 600 mg/kg.

EXPERIMENTAL

The PMR spectra were recorded in a Bruker AM-250 instrument (250 MHz), internal standard TMS, in $CDCl_3$. The IR spectra were recorded in KBr tablets on a Specord M-80 spectrometer. Mass spectra were registered in an MKh-1321 instrument with an ionizing electron energy of 70 eV. The UV spectra were recorded on a Specord M-40 spectrometer in methanol ($C = 1 \cdot 10^{-5}$ M). The individuality of the compounds was monitored in a thin layer on Silufol UV-254 plates, eluent chloroform—hexane—acetone, 2:2:1. The x-ray structure analysis was performed in an RÉD-4 diffractometer, MoKα radiation (μ = 22.72 cm^{-1}) from a crystal 0.4 × 0.4 × 0.7 mm. A total of 859 reflections were registered, of which those with $I \geq 3\delta$ (I) were used for the refinement and determination of structure of compound IV. The structure was resolved by the heavy-atom method from an analysis of the Patterson function. The refinement was performed in the anisotropic approximation for the nonhydrogen atoms. The hydrogen atoms were found objectively but were not refined. Because of the small volume of experimental material, the refinement of the aromatic rings was defined as rigid, with fixed distances.

Hydrochloride of 1-[2(2,3-Dihydro-1,3,4-oxadiazolyl-5-one)] methyl-7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one (IV, $C_{18}H_{14}BrClN_4O_3$). To a solution of 3.87 g (0.01 mole) of gidazepam (III) in 100 ml of dry chloroform, chilled to −5°C, 10 ml of a toluene solution of $COCl_2$ (0.01 mole) was added, and the reaction mixture was stirred for 1 h. At the conclusion of the reaction, the chloroform was removed under vacuum and the residue was crystallized

from ethanol, obtaining 2.1 g of the crude hydrochloride of IV, which was then dissolved in chloroform and washed with a 0.1 N sodium carbonate solution to pH 7, followed by washing with water. The chloroform was removed under vacuum and the residue was crystallized from ethyl alcohol, obtaining 1.45 g (yield 36.1%, mp 164-165°C) of 1-[2(2,3-dihydro-1,3,4-oxadiazolyl-5-one)]methyl-7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one (IV).

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