1,4-BENZODIAZEPINES, THEIR CYCLIC HOMOLOGS AND ANALOGS. STRUCTURE AND PHARMACOLOGICAL PROPERTIES OF 7-HALO-5-(SUBSTITUTED PHENYL)-1,2-DIHYDRO-3H-1,4-BENZODIAZEPIN-2-ONES

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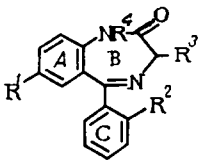
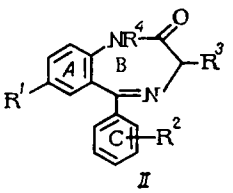
Among the 1,4-benzodiazepines, 1,2-dihydro-3H-1,4-benzodiazepin-2-ones (I) containing an electronegative substituent in the o position of the benzene nucleus have been shown to be extremely effective tranquilizing agents. Some preparations with the indicated structure (Klonazepam, Lorazepam, Fluorazepam, Fluornitrazepam) are presently finding ever-widening application in medical practice [1].



I

R^1=NO_2, R^2=Cl, R^3=R^4=H Klonazepam
R^1=R^2=Cl, R^3=OH, R^4=H Lorazepam
R^1=Cl, R^2=F, R^3=H, R^4=$(CH_2)_2NEt_2$ Fluorazepam
R^1=NO_2, R^2=F, R^3=H, R^4=CH_3 Fluornitrazepam

In the present work, in order to search for new effective tranquilizers based on a study of the effect of the character and position of substituents in the phenyl nucleus of 1,2-dihydro-3H-1,4-benzodiazepin-2-one on its properties, we synthesized 7-halo-5-(substituted phenyl)-1,2-dihydro-3H-1,4-benzodiazepin-2-ones (II), and studied some aspects of their pharmacological activity.



II

a: R^1 = Cl, R^2 = o-Cl, R^3 = R^4 = H;
b: R^1 = Cl, R^2 = o-Br, R^3 = R^4 = H;
c: R^1 = Br, R^2 = o-Cl, R^3 = R^4 = H;
d: R^1 = Br, R^2 = m-Cl, R^3 = R^4 = H;
e: R^1 = Br, R^2 = p-Cl, R^3 = R^4 = H;
f: R^1 = Br, R^2 = o-Cl, R^3 = H, R^4 = CH_3;
g: R^1 = Br, R^2 = o-Br, R^3 = R^4 = H;
h: R^1 = Br, R^2 = m-Br, R^3 = R^4 = H;
i: R^1 = Br, R^2 = p-Br, R^3 = R^4 = H;
j: R^1 = Br, R^2 = m-NO_2, R^3 = R^4 = H;
k: R^1 = Br, R^2 = p-NO_2, R^3 = R^4 = H;
l: R^1 = Br, R^2 = m-NO_2, R^3 = H, R^4 = p-CH_3;
m: R^1 = Br, R^2 = o-Cl, R^3 = CH_3, R^4-H.

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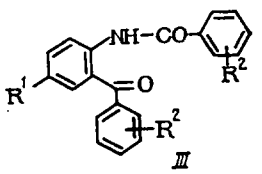
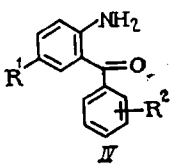
TABLE 1. 7-Halo-5-(substituted phenyl)-1,2-dihydro-3H-1,4-benzodiazepin-2-ones (II)

Compound	Yield, %	Melting point, °C	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
IIa	76	200—1	59,3	3,4	9,2	$C_{15}H_{10}Cl_2N_2O$	59,0	3,3	9,2
IIb	87	210—1	51,4	2,9	8,1	$C_{15}H_{10}BrClN_2O$	51,5	2,9	8,0
IIc	95	228—30	51,6	2,6	8,2	$C_{15}H_{10}BrClN_2O$	51,5	2,9	8,0
IId	92	237—8	51,8	2,8	8,3	$C_{15}H_{10}BrClN_2O$	51,5	2,9	8,0
IIe	94	251—2	51,7	2,6	8,4	$C_{15}H_{10}BrClN_2O$	51,5	2,9	8,0
IIf	32	134—5	52,9	3,7	7,9	$C_{16}H_{12}BrClN_2O$	52,8	3,3	7,7
IIg	88	231—2	45,6	2,2	7,3	$C_{15}H_{10}Br_2N_2O$	45,7	2,5	7,1
IIh	81	244—6	45,7	2,1	7,2	$C_{15}H_{10}Br_2N_2O$	45,7	2,5	7,1
IIi	87	249—50	45,6	2,2	7,1	$C_{15}H_{10}Br_2N_2O$	45,7	2,5	7,1
IIj	89	232—4	50,2	3,1	11,8	$C_{15}H_{10}BrN_3O_3$	50,0	2,8	11,7
IIk	60	240—2	49,8	3,0	11,9	$C_{15}H_{10}BrN_3O_3$	50,0	2,8	11,7
IIl	34	179—80	51,1	3,5	11,3	$C_{15}H_{10}BrN_3O_3$	51,3	3,2	11,2
IIm	62	230—2	53,0	3,6	7,9	$C_{16}H_{12}BrClN_2O$	52,8	3,3	7,7

Condensation of p-chloro- and p-bromoaniline with substituted benzoyl chlorides in the presence of anhydrous zinc chloride with subsequent acid hydrolysis of the intermediate o-acylanilines (III) gave the 2-aminobenzophenones (IV) (cf. Experimental),



III



IV

R^1 = Br, Cl; R^2 = o-Cl, m-Cl, p-Cl, o-Br, m-Br, p-Br, m-NO_2, p-NO_2, CH_3.

Compounds IIa-e,g-k were prepared by condensation of the corresponding 2-aminobenzophenone IV with the acyl chloride of glycine hydrochloride, compound IIm by condensation of 2-amino-5-bromo-2'-chlorobenzophenone with the acyl chloride of α-alanine hydrochloride, and 1-methyl-substituted IIf,l by methylation of IIc,j with dimethyl sulfate in the presence of sodium methylate (Table 1).

The structure of compounds II was established by spectroscopy (IR, UV, and PMR), mass spectrometry, and polarography.

In the IR spectra of these compounds (dissolved in carbon tetrachloride), the most intense absorption band corresponded to the valence vibrations of the C=O bond (1700-1680 cm^{-1}); intense bands corresponding to the azomethine band were observed in the 1605-1595 cm^{-1} region. In the 3390-3180 cm^{-1} region of the spectrum of compound IIc, there are bands resulting from vibrations of free and associated N–H groups. These bands are absent in the spectra of compounds IIf,l. Various positions (o, m, or p) of the halogen atom in the phenyl nucleus and of substituents R^2 do not significantly influence the wave number of the fundamental absorption band of the structural fragment of the compounds in question. At the same time, the absorption of the planar deformation vibrations of the C–H bond of the aromatic group is involved with the location of the halogen atom in substituent R^2, as expected [2]: for the o- or p-halophenyl derivatives (compounds IIc,e) these bands occurred at 1123 and 1126 cm^{-1}, respectively, and at 1161 cm^{-1} for the m isomer (compound IId).

The UV spectra of compounds II, as for the earlier-described 5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-ones [3, 4], show the presence of characteristic double bands with maximum absorption in the 225-240 nm (log ε 4.61-4.52) and 325-333 nm (log ε 3.47-3.39) range.

In agreement with the structure of compounds II, their PMR spectra (dissolved in a mixture of pyridine-D_5 and acetone-D_6, 9:1) showed resonance signals for the amide protons at 10.80-11.50 ppm, a singlet peak for the methylene protons at 4.35-4.50 ppm, and a multiplet for the aromatic protons in the 7.26-8.05 ppm range.

In contrast to compounds IIa-e,g-k,n,o, compounds IIf,l, as well as the other 1-substituted-1,2-dihydro-3H-1,4-benzodiazepin-2-ones [5], showed a quadruplet for the methylene protons, centered at 4.29-4.40 ppm, with a spin–spin coupling constant equal to 8.5-11.0 Hz. A singlet peak for the methyl protons in the spectra of these substances was located at 3.50-3.60 ppm.

Under electron impact, the compounds II disintegrated similarly to the related 1,2-dihydro-3H-1,4-benzodiazepin-2-ones [6]. Characteristic mass-spectral features of the halophenyl substituents included peaks at $(M-\text{halogen})^+$. This peak has maximum intensity in the spectrum of compound IIc.

The azomethine bond in the 7-halo-5-(halophenyl)-1,2-dihydro-3H-1,4-benzodiazepin-2-one molecule is reduced polarographically at the mercury electrode (reference electrode = saturated calomel) with a half-wave potential of 0.98-1.05 V.

The influence of compounds II on the central nervous system of experimental animals (white mice) was studied by testing the antagonism to Pentylenetetrazole-induced convulsions, maximal electroshock, potentiation of Hexobarbital Soluble, depression of the orientation reflex, and disturbance of coordination, according to methods described earlier [7].

The experimental data presented in Table 2 indicate the considerable influence of the nature and position of substitution in the phenyl nucleus of compounds II on their pharmacological activity spectra.

The introduction of a halogen atom or a nitro group into the p position of the phenyl nucleus (compounds IIe,i,k) results in a reduction of activity in all tests in comparison with IIo, which is unsubstituted in the p position.

(5-m-Halophenyl)- and (5-m-nitrophenyl)-1,2-dihydro-3H-1,4-benzodiazepin-2-ones IId,h,j also are less active than compound IIo. However, the transition from p isomers IIe,o,k to the corresponding m isomers IId,h is not accompanied by a discernible trend in activity in the various tests (cf. Table 2).

Introduction of a halogen atom (chlorine or bromine) into the o position of the phenyl nucleus gives a two- to fivefold increase in activity in one of the characteristic effects of the benzodiazepine tranquilizers, as evaluated by the Pentylenetetrazole antagonism test, in comparison with the corresponding substances with an unsubstituted phenyl radical in the 5 position (IIn,o). The influence of halogen atoms in the o position of the phenyl nucleus on the activity of compounds II in the remaining tests is of a lower degree.

A comparison of the m and p isomers of 5-(o-halophenyl)-1,2-dihydro-3H-1,4-benzodiazepin-2-ones shows significantly higher activity on all of the above treatments. Thus, in Pentylenetetrazole antagonism and in potentiation of Hexobarbital Soluble, compound IIc is more than 2 times more active than its m isomer; in capability for the prevention of convulsions by maximal electroshock, 6 times; in disturbance of coordination, 10 times; in depression of the orientation reflex, 2.7 times.

Methylation of compound IIc in position 1 (compound IIf) gives an increase of antispasmodic activity in the Pentylenetetrazole antagonism and maximal electroshock tests, and a decrease in the disturbance of coordination and depression of orientation reflex tests. In contrast to this, methylation in position 1 of compound IIj gives a weakening of antispasmodic activity and an increase in the depression of orientation reflex test.

Introduction of a methyl group into position 3 of compound IIc (compound IIm) leads to diminished activity in all tests. An analogous reduction of activity with the introduction of an alkyl radical in position 3 was observed for 1,2-dihydro-3H-1,4-benzodiazepin-2-one, as well as for the rest of the compounds of this class [8].

Thus, the highest tranquilizer activity in the compounds studied is seen in compounds II. The activity of these substances in the Pentylenetetrazole antagonism test is practically independent of the nature of the halogen (chlorine, bromine, fluorine) in the o position: thus ED_{50} in the Pentylenetetrazole test for compounds IIc,g is 0.037 and 0.050 mg/kg, and

TABLE 2. Pharmacological Activity, ED_{50}, of Compounds II

Compound	T_{in}				
	Pentylenetetrazole antagonism	potentiation of Hexobarbital Soluble	maximal electroshock	depression of orientation reflex	disturbance of coordination
	ED_{50}, mg/kg				
IIa	0,074 (0,056–0,091)	0,05 (0,04–0,06)	12,0 (7,03–20,4)	4,7 (3,2–6,8)	8,6 (5,0–13,8)
IIb	0,075 (0,068–0,079)	0,025 (0,012–0,031)	8,1 (5,41–12,0)	4,0 (3,07–5,2)	8,5 (5,7–12,9)
IIc	0,037 (0,026–0,052)	0,09 (0,03–0,31)	10,2 (2,4–18,5)	1,05 (0,4–3,7)	2,1 (1,5±2,9)
IId	7,5 (4,8–12,2)	4,5 (3,2–6,3)	60,0 (42,8–84,0)	2,7 (1,08–6,8)	23,0 (17,7–29,9)
IIe	12,8 (7,5–19,2)	4,7 (3,3–6,5)	10,5 (7,0–15,8)	3,8 (2,7–5,3)	6,8 (2,7–17,0)
IIf	0,025 (0,008–0,055)	0,13 (0,068–0,24)	4,8 (2,4–6,3)	2,4 (0,72–6,4)	2,3 (1,82–6,4)
IIg	0,05 (0,032–0,077)	0,2 (0,1–0,4)	6,0 (3,6–9,9)	5,4 (3,8–7,9)	7,5 (5,2–9,4)
IIh	46,0 (20,0–105,8)	2,0 (1,4–2,72)	300,0 (193,0–465,0)	45,0 (30,0–60,0)	54,0 (39,1–74,3)
IIi	1,15 (0,8–1,43)	3,2 (2,5–4,3)	22,0 (15,7–30,8)	—	—
IIj	7,2 (6,06–11,1)	10,0 (6,06–16,5)	150,0 (101,1–225,3)	33,0 (11,1–99,3)	~200
IIk	>80,0	20,0 (13,3–30,0)	≈100	50,0 (38,2–65,0)	77,0 (63,8–93,1)
III	60,0 (31,6–114,0)	18,5 (10,9–31,4)	>100	6,4 (4,3–8,0)	9,0–20%
IIm	0,14 (0,11–0,18)	0,4 (0,25–0,64)	4,5 (2,4–8,6)	—	5,6 (4,3–7,2)
IIn*	0,35 (0,23–0,53)	0,9 (0,57–1,41)	18,0 (16,9–19,1)	3,7 (2,4–6,5)	14,0 (9,6–20,3)
IIo*	0,11 (0,05–0,24)	0,1 (0,06–0,15)	17,0 (11,7–24,6)	4,5 (3,9–5,0)	4,6 (3,2–6,7)

*Described in [4].

Note. The confidence intervals for ED_{50} at P = 0.05 are indicated in brackets.

7-chloro-5-(o-fluorophenyl)-1,2-dihydro-3H-1,4-benzodiazepin-2-one gives 0.08 mg/kg [1]. At the same time, the degree of increase of activity in the Pentylenetetrazole antagonism test for II versus the p isomer apparently is very dependent on the electronegativity of the halogen atom on the phenyl nucleus: the more electronegative the halogen atom, the more active the o isomer in comparison with the p isomer. In these tests, compound IIg was more active than IIi by approximately 20 times; compound IIc was more active than IIe by 350 times, and 7-chloro-5-(o-fluorophenyl)-1,2-dihydro-3H-1,4-benzodiazepin-2-one [1] was more active than its p isomer by greater than a factor of 10^4.

EXPERIMENTAL

IR spectra were recorded on an IKS-14A instrument in carbon tetrachloride, UV spectra on a Specord UV-VIS instrument in ethanol, PMR spectra on a Tesla B-487-C instrument operated at 80 MHz, and mass spectra on a MX-1303 instrument with ionization potential of 50 V, emission current of 1.5 mA, and at a temperature of 30-50°C below the melting point of the compound under investigation. Polarograms were obtained in 50% dimethylformamide, with a base electrolyte of acetate buffer, using a PPT-1 polarograph.

2-Amino-5-bromo-2'-chlorobenzophenone. A mixture of 86 g (0.5 mole) of p-bromoaniline in 210 g (1.2 mole) of o-chlorobenzoyl chloride was heated at 110°C and maintained for 1 h. Then the reaction mass was heated at 160°C and 82 g (0.6 mole) of anhydrous zinc chloride was added at this temperature. The reaction mixture was then stirred for 2,5 h at 195-200°C. The reaction mixture was cooled to 120°C and 300 ml of 12% hydrochloric acid was added cautiously to it, after which the acid layer was separated. To the residue was added another portion of hydrochloric acid and the separation repeated. The mixture was twice treated with water (300 ml portions), heated to boiling, and the aqueous layer poured off. To the washed reaction mass was added 600 ml of 72% sulfuric acid, and the mixture obtained was stirred and heated to boiling. The resulting homogeneous dark-colored solution was boiled for 1.5 h, after which the still-hot acidic solution was poured into a mixture of ice and wa-

ter (1 kg ice and 500 ml of water). The resulting precipitate was filtered off and washed with water to neutrality. Then to the solid was added 500 ml of 20% sodium hydroxide, the mixture was stirred, filtered, and the solid was washed with water. The worked-up wet, basic precipitate was washed with 200 ml of 30% sulfuric acid and then with water to neutrality. The precipitate was dried in air and then in a drying cabinet at 60°C for 6 h. Yield 62 g (40%), mp 89-91°C. Found, %: C 50.3; H 2.7; N 4.7. $C_{13}H_9BrClNO$. Calculated, %: C 50.2; H 2.9; N 4.5.

Analogous preparations gave 2-Amino-5,2'-dichlorobenzophenone, yield 40 g (30%), mp 88-91°C. Found, %: C 58.9; H 3.8; N 5.1. $C_{13}H_9Cl_2NO$. Calculated, %: C 58.6; H 3.4; N 5.3. 2-Amino-2'-bromo-5-chlorobenzophenone, yield 54.3 g (35%), mp 94-96°C. Found, %: C 50.4; H 2.8; N 4.4. $C_{13}H_9BrClNO$. Calculated, %: C 50.2; H 2.9; N 4.5. 2-Amino-2', 5-dibromobenzophenone, yield 82 g (46%), oil. Found, %: C 44.0; H 2.6; N 3.7. $C_{13}H_9Br_2NO$. Calculated, %: C 43.9; H 2.5; N 3.9.

2-Amino-5-bromo-3'-nitrobenzophenone was prepared according to [9], yield 60 g (37%), mp 124-126°C. Found, %: C 48.5; H 3.0; N 8.9. $C_{13}H_9BrN_2O_3$. Calculated, %: C 48.6; H 2.8; N 8.7.

2-Amino-4',5-dibromobenzophenone. To 285 g (1.3 mole) of p-bromobenzoyl chloride, stirred and heated to 120°C, was added 86.0 g (0.5 mole) of p-bromoaniline. The mixture was heated to 180-200°C and 86.6 g (0.64 mole) of anhydrous zinc chloride were added. The temperature was gradually increased to 210°C and kept constant until the hydrogen chloride evolution ceased (~2 h). The reaction mixture was boiled with a mixture of 880 ml of glacial acetic acid and 190 ml of concentrated sulfuric acid for 19 h, then poured into ice (1.5 kg). The resulting precipitate was filtered off, washed with water, and then stirred with a 20% solution of sodium hydroxide for 2 h. The precipitate was washed with water to neutrality and crystallized from alcohol. Yield 73 g (41%), mp 134-135°C. Found, %: C 43.7; H 2.8; N 3.7. $C_{13}H_9Br_2NO$. Calculated, %: C 43.9; H 2.5; N 3.9.

Analogous preparations gave 2-amino-5-bromo-4'-chlorobenzophenone, yield 68 g (44%), mp 117-119°C. Found, %: C 50.0; H 2.9; N 4.5. $C_{13}H_9BrClNO$. Calculated, %: C 50.2; H 2.9; N 4.5. 2-Amino-5-bromo-4'-nitrobenzophenone, yield 45 g (28%), mp 212-214°C. Found, %: C 48.4; H 3.1; N 8.8. $C_{13}H_9BrN_2O_3$. Calculated, %: C 48.6; H 2.8; N 8.7. 2-Amino-5-bromo-3'-chlorobenzophenone, yield 64 g (41%), mp 118-120°C. Found, %: C 50.1; H 2.6; N 4.8. $C_{13}H_9BrClNO$. Calculated, %: C 50.2; H 2.9; N 4.5; 2-Amino-3'-5-dibromobenzophenone, yield 74.5 g (42%), mp 124-126°C. Found, %: C 44.1; H 2.5; N 4.1. $C_{13}H_9Br_2NO$. Calculated, %: C 43.9; H 2.5; N 3.9.

Acyl Chloride of Glycine Hydrochloride. A suspension of 45.8 g (0.61 mole) of glycine (preliminarily ground into powder and dried at 110°C for 2 h) in 600 ml of dry chloroform was saturated with dry hydrogen chloride at 20°C for 10-15 min (hydrogen chloride was dried by passage through a layer of concentrated sulfuric acid, followed by drying over calcium chloride). Saturation was indicated by the presence of hydrogen chloride in the reaction flask. To the suspension of glycine saturated with hydrogen chloride was then added 127 g (0.61 mole) of phosphorus pentachloride, and the reaction mixture was stirred at least 20 h at 20°C. After 20 h of stirring, the reaction mixture was quickly filtered, the solidified residue was washed with 200 ml of dry carbon tetrachloride, flooded with 200 ml of dry chloroform, and stored at less than 10°C until needed for further synthesis, mp 110°C.

7-Bromo-5-(o-chlorophenyl)-1,2-dihydro-3H-1,4-benzodiazepin-2-one (IIc). To a solution of 108 g (0.35 mole) of 2-amino-5-bromo-2'chlorobenzophenone in 600 ml of dry chloroform was added the acyl chloride of glycine hydrochloride, obtained as described above from 45.8 g (0.61 mole) of glycine (total volume of solution, 800 ml). The reaction mixture was stirred and boiled until the evolution of hydrogen chloride ceased (3.5 h). The reaction mixture was cooled to room temperature, and to it was added 500 ml of water, followed by the gradual addition with stirring of an aqueous solution of ammonia to the establishment of a stable, weakly alkaline reaction. After separation of the aqueous layer, the chloroform solution was washed once with 300 ml of water, and then evaporated in vacuum. To the residue was added 500 ml of toluene (preliminary drying of purchased toluene is not required), and the solution was concentrated to complete removal of solvent at atmospheric pressure. After cooling to room temperature, the residue was dissolved in hot toluene (700 ml) and the solution was quickly filtered. The desired product, 106 g (87%), was obtained from the cooled solution; mp 220-222°C.

Compounds IIa,b,d,e,g-k,m were obtained in an analogous manner.

Compound IIf,l were prepared according to [4].

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