controls. The chemotherapeutic index was calculated as the ratio between the maximum concentration tolerated by the cell culture, and the minimum concentration causing a reduction in the viral titer by an amount equal to 1.25 log PFU/ml.

Details of the methods used and evaluation of the results have been reported previously [11].

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SYNTHESIS AND LOCAL-ANESTHETIZING ACTIVITY OF SUBSTITUTED 6-(α-AMINO-ω-PHENYLALKYL)-1,4-BENZODIOXANES

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6-(ω-Amino-ω-phenylalkyl)-1,4-benzodioxanes and their N,N-dimethyl derivatives display local-anesthetizing activity [4]. To search for new medicinals we therefore synthesized and studied the similarly constructed N-methyl- and N,N-dimethyl-substituted 6-(α-amino-ω-phenylalkyl)-1,4-benzodioxanes IIIa,b and IVa, b.

Methylamino derivatives IIIa,b were obtained by reduction with lithium aluminum hydride of 6-(α-formylamino-ω-phenyl-alkyl)-1,4-benzodioxanes IIa,b, which were synthesized via the Leuckart reaction by heating 6-(ω-phenacyl)-1,4-benzodioxanes Ia,b with ammonium formate, while dimethylamino derivatives IVa,b were obtained by N-methylation of methylamino derivatives IIIa,b with formaldehyde and formic acid. Ketone Ia was previously described in [2], while ketone Ib was synthesized via the Friedel–Crafts reaction by acylation of 1,4-benzodioxane [3] with 3-phenylpropionyl chloride in the presence of anhydrous aluminum chloride.

The structures of the synthesized new compounds were confirmed by IR and PMR spectral data (Tables 1 and 2). The UV spectra of IIa,b-IVa,b do not differ substantially (see Table 1).

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TABLE 1. Characteristics of the Synthesized Ib, IIa,b, IIIa,b, and IVa,b

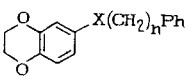
Compound	Yield, %	mp, °C (solvent)	UV spectrum		IR spectrum, $\nu_{C=O}$, cm^{-1}	Empirical formula
			λ_{max}, nm	lg ε		
Ib	84	48—9 ethanol	232 276 310	4,25 4,05 3,81	1660	$C_{17}H_{16}O_3$
IIa	38	101—2 cyclohexane	230 284	3,95 3,57	1660	$C_{17}H_{17}NO_3$
IIb	45	forms a glass	229 284	3,73 3,57	1665	$C_{18}H_{19}NO_3$
IIIa	82	245—246 ethanol	235 285	Shoulder 3,57	—	$C_{17}H_{19}NO_2 \cdot HCl$
IIIb	75	222—224 acetone	232 285	Shoulder 3,58	—	$C_{18}H_{21}NO_2 \cdot HCl$
IVa	70	234—235* acetone	234 285	3,79 3,54	—	$C_{18}H_{21}NO_2 \cdot HCl$
IVb	85	201—202** ethanol–ether	235 286	Shoulder 3,53	—	$C_{19}H_{23}NO_2 \cdot HCl$

*This compound had bp 177-179°C (1 mm).
**This compound had bp 187-189°C (1 mm).

TABLE 2. Data from the PMR Spectra (δ, ppm) of Ib, IIa,b, IIIa,b, and IVb

Compound	NH	CH_2	NCH_3	$ArCH_2$	OCH_2CH_2O	ArCHN	ArH	C_6H_5	NCHO
Ib	—	3,01 t[a]	—	2,88 t[a]	4,01 s	—	6,68 d[b] (8—H), 7,30 m (5—H, 7—H)	7,00 m	—
IIa	—	—	—	2,95 d[a]	4,10 s	5,00 t[a]	6,68 m	7,08 m	78,5 s
IIb	—	1,95 m	—	2,47 t[a]	4,00 s	4,69 t[a]	6,61 m	7,17 m	7,80 s
IIIa[c]	1,12 m	—	2,11 s	2,71 m	4,07 s	3,40 m	6,65 m	7,05 m	—
IIIb[c]	1,15 m	1,85 m	2,12 s	2,46 t[a]	4,05 s	3,09 t[a]	6,60 m	6,97 m	—
IVb[c]	—	2,00 q[a]	2,05 s	2,43 t[a]	4,08 s	3,03 t[a]	6,65 m	7,05 m	—

[a]J = 6-7 Hz.
[b]J = 9 Hz.
[c]The free base.



Ia-c, IIa-b, IIIa-b, IVa-b

X=CO(Ia, b), CHNHCHO (IIa, b), $CHNHMe \cdot HCl$ (IIIa, b), $CHNMe_2 \cdot HCl$ (IVa, b); n=1 (Ia—IVa), 2 (Ib—IVb).

EXPERIMENTAL (CHEMICAL)

The UV spectra of solutions of the compounds in ethanol were recorded with a Specord UV-VIS spectrophotometer (East Germany). The IR spectra of suspensions in mineral oil were obtained with a UR-20 spectrometer (East Germany). The PMR spectra of solutions in CCl_4 were recorded with a Tesla BS 487C spectrometer (Czechoslovakian SSR) at an operating frequency of 80 MHz with tetramethylsilane (TMS) as the internal standard.

The results of elementary analysis of the new compounds were in agreement with the calculated values. The characteristics and yields of the new compounds are presented in Tables 1 and 2.

6-(3-Phenylpropionyl)-1,4-benzodioxane (Ib). A 10.7-g (80 mmole) sample of anhydrous $AlCl_3$ was added at 10°C in the course of 0.5 h to a mixture of 45 ml of anhydrous CH_2Cl_2, 9.5 g (70 mmole) of 1,4-benzodioxane, and 11.8 g (70 mmole) of 3-phenylpropionyl chloride, and the mixture was stirred for 1 h at 30°C. It was then poured over ice, and the aqueous mixture was acidified with HCl and extracted with CH_2Cl_2. The extract was washed with water, dried, and concentrated.

6-(α-Formylamino-ω-phenylalkyl)-1,4-benzodioxanes IIa,b. A mixture of 50 mmole of ketone Ia or Ib and 15.7 g (250 mmole) of ammonium formate was heated for 6 h at 200°C (bath temperature), after which it was cooled and washed with water. The product was purified by crys-

TABLE 3. Acute Toxicites, Local-Anesthetizing Activity, and Local-Irritant Activity of Amine Hydrochlorides IIIa,b and IVa,b

Compound	Acute toxicity (LD_{50}), mg/kg	Infiltration anesthesia (relative activity as compared with novocaine)	Conductor anesthesia			Local-irritant activity		
			minimal concn. that blocks nerve conductivity, mM	time needed to decrease the AP to 50%,* min	time required to restore the AP from 50% to 100%,* min	degree of irritation with a 1% solution, points	tissue-irritating conc., %	
							Av.	threshold
IIIa	178 (138—230)	2,0	0,10	8,5	20,8	1,4	2,0	0,2
IIIb	276 (211—362)	6,5	0,04	10,2	59,0	1,5	2,7	0,2
IVa	110 (85—143)	2,2	0,10	6,7	16,0	1,6	1,8	0,1
IVb	190 (144—251)	2,5	0,01	8,5	64,0	1,2	2,6	0,3
Novocaine	570 (539—602)	1,0	0,75	13,5	46,2	0,0	6,6	1,8
Trimecaine	391 (372—410)	1,7	0,75	6,5	23,0	1,2	3,6	0,1
Lidocaine	270 (204—356)	1,9	0,85	50,0	38,0	0,3	6,9	0,7
Pyromecaine	300 (287—313)	2,5	0,25	5,6	48,7	1,9	1,2	0,6
Dicaine	44 (35—55)	5,6	0,02	1,5	>10 h	2,6	0,6	0,1

*From a 10 mM solution.

Note: The fluctuation limits are indicated in parentheses; the data are statistically reliable ($p < 0.05$).

tallization (in the case of IIa) or by dissolving in benzene and by passing the solution through silica gel and concentrating it (in the case of IIb).

6-(α-Methylamino-ω-phenylalkyl)-1,4-benzodioxane Hydrochlorides IIIa,b. A mixture of 200 ml of anhydrous ether, 0.8 g (20 mmole) of lithium aluminum hydride, and 20 mmole of IIa or IIb was refluxed for 2 h, after which it was cooled and treated successively with water and 30 ml of concentrated aqueous KOH solution. The mixture was extracted with ether, and the extract was dried and saturated with gaseous anhydrous HCl, and the hydrochloride was removed by filtration.

6-(α-Dimethylamino-ω-phenylalkyl)-1,4-benzodioxane Hydrochlorides IIIa,b. A mixture of 30 mmole of hydrochloride IIIa or IIIb, 3.2 g (40 mmole) of 38% formalin, and 4.4 g (80 mmole) of 85% HCOOH was refluxed for 7 h, after which it was cooled, made alkaline with aqueous KOH solution, and extracted with ether. The extract was dried and concentrated, and the residue was fractionated in vacuo; the hydrochlorides were obtained as in the case of amines IIIa,b.

EXPERIMENTAL (PHARMACOLOGICAL)

Noninbred white mice of both sexes with masses of 18-25 g and noninbred white rats of both sexes with masses of 150-230 g were used. Amine hydrochlorides IIIa,b and IVa,b were introduced subcutaneously in the form of 1% aqueous solutions.

The acute toxicities for mice were determined by the method of Litchfield and Wilcoxon in the Roth modification [1]. Infiltration anesthesia was studied in quinea pigs by the method in [6], surface anesthesia was studied in the cornea of rabbits by the method in [5], and conductor anesthesia was studied in isolated sciatic nerves of frogs by recording the action potential (AP) and establishing the minimal concentrations that block nerve conductivity [9]. The local-irritant properties were studied in rats by the method in [7] in the modification presented in [8].

It was found that N-methyl- and N,N-dimethylamino derivatives IIIa and IVa or IIIb and IVb differ with respect to their pharmacological indexes and have low activity under surface-anesthesia conditions. Their activity increases under infiltration- and conductor-anesthesia conditions, while the acute toxicities and local-irritant activity decrease with an increase in the number of methylene groups (n) in the side chain. Amine hydrochloride IVa considerably surpasses the hydrochloride of 6-(2-dimethylamino-2-phenylethyl)-1,4-benzodioxane with respect to local-anesthetizing activity [3]; however, it is more toxic and irritates tissue more strongly. With respect to their indexes amine hydrochlorides IIIb and IVb are similar to the local anesthetics that are used in medicine (Table 3).

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SYNTHESIS OF TWO PSYCHOTROPIC COMPOUNDS OF THE 1,4-BENZODIAZEPINE SERIES

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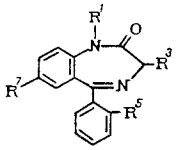
We have presented results of research on the establishment of a quantitative relationship between the structure and the activity in the 1,4-benzodiazepine series [3]. The Free–Wilson method was used to evaluate the contributions of the R^1, R^3, R^5, and R^7 substituents to the bioactivity (BA) with respect to



five psychotropic tests: antagonism with Corazole (AC), testing of the maximum electrical shock (MES), potentiation of hexenal-induced sleep (PS), disturbance of orientation (DO), and disturbance of motor coordination (DC). A comparison of the experimental and calculated data and the results of an examination showed that the values obtained for the contributions of the substituents a_{ij} make it possible to reliably evaluate the BA. It should be noted that in [3] Raevskii and coworkers deliberately did not indicate the a_i value for the methyl group in the R^1 position in connection with the fact that precisely this substituent could lead to obtaining new compounds with a useful set of properties. All of the calculations presented in [3] were performed with sampling that did not include compounds with $R^1 = CH_3$.

The next step in the research consisted in developing recommendations for the synthesis of compounds with high anti-convulsant and soporific effects vis-a-vis a decrease in side reactions involving disturbance of orientation and motor coordination. On the basis of the calculated contributions we predicted the activities of several compounds that were not found in the bibliographic data base of Chemical Abstracts from 1967 to the present.*

The results of research on the synthesis and biological testing of two new 1,4-benzodiazepine derivatives are the subject of the present communication.

EXPERIMENTAL (CHEMICAL)

7-Bromo-5-(o-chlorophenyl)-1-methyl-3-hydroxy-1,2-dihydro-3H-1,4-benzodiazepin-2-one (BD 1146). This compound was obtained from the corresponding 1,4-benzodiazepine N-oxide, which was subjected to the Polonovski rearrangement with subsequent deacylation [4-6].

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