while in "mechanical pressing of the tail" test only compounds IIe and IIf are active, having a higher analgetic activity than other compounds in the series (Table 3).

Derivatives of 6-hydroxytetrahydrobenzofuran Ia-d can, in particular, according to the "mechanical pressing of the tail" test, lower the analgesic action of morphine by 2-40%.

Compound IIg, which by itself has no analgetic properties and compound III cause a weakening of the morphine action by 15-40%.

It should be noted that the analgetic action of tetrahydrodibenzofuranols III-IV and compounds I-II is completely eliminated by the opiate antagonist naloxone (1 mg/kg).

Thus, the study of the pharmacological activity of the aminomethyl derivatives of tetrahydrodibenzofurans showed that most of them have analgetic activity, which is probably mediated by opiodergic mechanisms, since, this activity is eliminated by naloxone. This investigation also enabled the detection of compounds possibly exhibiting weak naloxone-like properties.

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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF N-SUBSTITUTED DERIVATIVES OF 1-AMINOETHYL-2,3-DIHYDROIMIDAZO[1,2-A]BENZOIMIDAZOLE

V. A. Anisimova, M. V. Levchenko,
G. V. Kovalev, A. A. Spasov,
G. P. Dudchenko, A. V. Tsibanev,
and E. A. Aleksandrova

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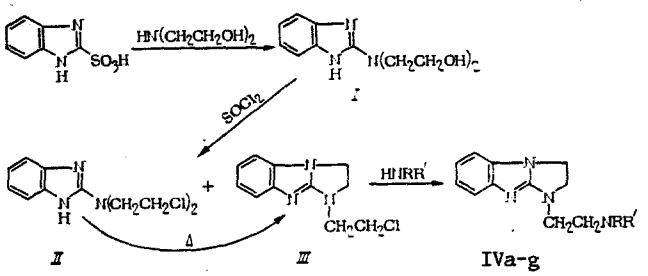
As a continuation of our efforts [2, 5] to identify compounds with a high degree of pharmacological activity among derivatives of 2,3-dihydroimidazo[1,2-a]benzoimidazole, we synthesized 1-alkyl(aryl, dialkyl) aminoethyl substituted derivatives of this heterocyclic compound (IVa-g). We felt that 2-bis(2-hydroxyethyl)aminobenzoimidazole (I) would be a convenient starting point for their synthesis since it enabled us to annelate the imidazoline ring and simultaneously introduce a substituent into position 1 of the tricyclic compound that is easily converted into an aminoethyl group.

The amino alcohol I was obtained by reacting benzoimidazole-2-sulfonic acid and diethanolamine. The best results were obtained when the reaction proceeded at 155-160°C and the ratio of the aforementioned reagents was 1:3.



IVa: R = R′ = Et, IVb: R + R′ = $(CH_2)_4$, IVc: R + R′ = $(CH_2)_5$, IVd: R + R′ = $(C_2H_4)_2O$, IVe-g: R = H, IVe: R′ = Bu-*t*, IVf: R′ = C_6H_{11}, IVg: R′ = Ph.

The amino alcohol I was successfully chlorinated by boiling it for 1.5-3 h with $SOCl_2$ or $POCl_3$ both in an excess of these reagents as well as in a medium of dry organic solvents

Scientific-Research Institute of Physical and Organic Chemistry, Rostov University. Volgograd Medical Institute.

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(benzene, toluene, chloroform, octane). The reaction with $SOCl_2$ in DMFA proceeded at room temperature, probably due to the good solubility of the starting compound I in this solvent and the heightened chlorinating ability of the DMFA–$SOCl_2$ complex [6]. However, because of that reaction a mixture of the two substances was obtained in all cases. On the basis of element analysis, IR- and PMR-spectroscopic data the structure 1-(2-chloroethyl)-2,3-dihydroimidazo[1,2-a]benzoimidazole (III) was ascribed to one of those compounds which had a higher degree of chromatographic mobility. The absorption bands of the NH and OH groups which were present in the starting compound I disappeared in the IR-spectrum of compound III in the 2800-3200 cm^{-1} region. The stretching vibrations of the intracyclic bonds C=C and C=N of the heterocyclic compound were manifested at 1500, 1580, 1600, and 1630 cm^{-1}. The PMR spectrum exhibited two four-proton singlets at 3.67 and 3.95 ppm which might be ascribed to the proton signals of the intracyclic and extracyclic ethylene cross links. The four aromatic protons yield a multiplet signal in the 6.86-7.25 ppm region.

The second substance obtained by chlorination could not be separated in an individual form since it completely converted to the hydrochloride of III either during chromatographic separation or when we tried to decrystallize the mixture. This led us to assume that 2-bis(2-chloroethyl)aminobenzoimidazole (II) was formed in the reaction mixture and that it was readily susceptible to intramolecular cyclization (see [1]).

Compound II or III could not be obtained as the primary products through a more rigid chlorination procedure (higher temperature and longer reaction time) or under relatively moderate conditions (DMFA, 20°C). One might conclude in that connection that $SOCl_2$ in this reaction acts both as a chlorinating and dehydrating agent.

When compound III is heated in an excess of a secondary or primary amine the chlorine atom is easily substituted by an amino group with the resultant formation of 1-aminoethyl-2,3-dihydroimidazo[1,2-a]benzoimidazoles (IV). The substitution proceeds much more slowly in organic solvents in which case the reaction time is reduced and the boiling point of the solvent is increased. For example, the reaction with piperidine in benzene or toluene takes 11-13 h to complete, while the reaction is completed in 4 h in xylene, and in 2.5-3 h in DMFA. In view of the considerable ease with which the dichloride of II undergoes intramolecular cyclization when it is heated in inert solvents in comparison to the replacement of a chlorine atom by an amino group in compound III, under these conditions a mixture of compounds II and III can be introduced into the reaction in order to obtain the amines of IV.

EXPERIMENTAL (CHEMISTRY)

The IR-spectra were recorded on a Specord-75 IR (GDR) instrument in petroleum jelly. The PMR-spectra were recorded on a Tesla BS-467 spectrometer (80 MHz; Czechoslovakia) in $CDCl_3$ internal standard was HMDS. Al_2O_3 TLC ($CHCl_3$ eluent, development by iodine vapor in a humidity chamber) was employed to control the reaction and substance identity. Data on the synthesized compounds IVa-g and their hydrochlorides are given in Table 1.

2-Bis(2-hydroxyethyl)aminobenzoimidazole (I). A mixture of 4 g (0.02 mole) of benzoimidazole-2-sulfonic acid [8] and 12.6 g (0.06 mole) of freshly distilled diethanolamine was heated at 155-160°C (bath temperature) for 3 h. The melt was cooled to 80-90°C. A 30 ml portion of ice water was added to the melt upon vigorous agitation and the mixture was stirred until it was completely crystallized. The mass was kept on an ice bath for 30 min and the precipitate was filtered off and thoroughly washed with water until they yielded a neutral reaction. Yield of I was 3.4 g (70%). Snow white crystals with a mp of 196°C (from water). Found, %: C 60.0; H 6.8; N 19.2. $C_{11}H_{15}N_3O_2$. Calculated %: C 59.8; H 6.8; N 19.0. IR-spectrum, ν_{max}, cm^{-1}: 1630 (C=N), 2800-3200 (NH, OH).

1-(2-Chloroethyl)-2,3-dihydroimidazo[1,2-a]benzoimidazole (III). A. A 1.3 ml portion of $SOCl_2$ was carefully added while stirring to a solution of 1.16 g (15 mmole) of compound I in 5 ml of DMFA. The mixture was kept at room temperature until the reaction was completed (4-5 h). It was then decanted into 10 ml of water and made alkaline with 22% NaOH up to pH 8.0-9.0 and extracted with $CHCl_3$ (3 × 10 ml). The extract was washed twice with water, dried with anhydrous Na_2SO_4, and evaporated. The residue (1.15 g) which consisted of a mixture of the chloride of III and 2-bis(2-chloroethyl)aminobenzoimidazole (II), was boiled in 15 ml of octane for 2-3 h. The reaction mixture was then cooled, the precipitate was filtered off and treated with 10 ml of 10% NH_4OH and extracted with $CHCl_3$ (3 × 5 ml). The mother liquor and the extract were combined, evaporated to dryness, and the residue was crystallized from octane, yielding 0.93 g (80%) of the 1-chloroethyl substituted derivative of III. Snow-

TABLE 1. N-Substituted 1-Aminoethyl-2,3-dihydroimidazo[1,2-a]benzoimidazole Derivatives and Their Dihydrochlorides (D)

Compound	mp, °C*	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	Cl	N		C	H	Cl	N	
IVa	Oil	69,5	8,8	—	21,5	$C_{15}H_{22}N_4$	69,7	8,6	—	21,7	78,5
IVaD	248—9	54,2	7,5	21,0	16,0	$C_{15}H_{22}N_4 \cdot 2HCl$	54,4	7,3	21,4	16,9	85,1
IVb	99—100	70,1	8,0	—	21,6	$C_{15}H_{20}N_4$	70,3	7,9	—	21,9	78,2
IVbD	252—3	54,5	7,0	21,1	16,5	$C_{15}H_{20}N_4 \cdot 2HCl$	54,7	6,7	21,5	17,0	87,0
IVc	114	70,8	8,0	—	19,7	$C_{16}H_{22}N_4$	71,0	8,2	—	20,0	86,3
IVcD	272—3	55,8	7,3	20,3	16,1	$C_{16}H_{22}N_4 \cdot 2HCl$	56,0	7,0	20,7	16,3	95,2
IVd	122	65,9	7,5	—	20,4	$C_{15}H_{20}N_4O$	66,1	7,4	—	20,6	74,0
IVdD	254—5	51,9	6,6	20,2	15,9	$C_{15}H_{20}N_4O \cdot 2HCl$	52,2	6,4	20,5	16,2	78,7
IVe	114—5	69,4	8,7	—	21,5	$C_{15}H_{22}N_4$	69,7	8,6	—	21,7	77,5
IVeD	278—9	54,1	7,6	21,0	16,6	$C_{15}H_{22}N_4 \cdot 2HCl$	54,4	7,3	21,4	16,9	76,9
IVf	57—8	72,0	8,6	—	19,5	$C_{17}H_{24}N_4$	71,8	8,5	—	19,7	84,5
IVfD	269—70	56,9	7,2	19,5	15,9	$C_{17}H_{24}N_4 \cdot 2HCl$	57,1	7,3	19,8	15,7	80,0
IVg	132—3	73,6	6,5	—	20,1	$C_{17}H_{18}N_4$	73,4	6,5	—	20,1	63,9
IVgD	180—1	57,8	5,9	19,9	15,7	$C_{17}H_{18}N_4 \cdot 2HCl$	58,1	5,7	20,2	16,0	83,3

*Dihydrochlorides of amines IVa-g melt with decomposition.

TABLE 2. Effect of Dihydrochlorides (D) of IV on Blood Sugar in Rats

Compound	Blood sugar content				
	prior to admin. of compound, mmole/liter	2 h after administration of compound		4 h after administration of compound	
		mmole/liter	Δ, %	mmole/liter	Δ, %
Control	5,60±0,10	5,54±0,14	—1,3	5,40±0,14	—3,8
IVaD	5,61±0,11	5,55±0,14	—1,9	5,38±0,13	—4,8
IVbD	4,55±0,29	2,44±0,26*	—46,8	4,16±0,21	—8,6
IVcD	5,05±0,17	3,44±0,23*	—33,3	3,55±0,19*	—29,8
IVdD	5,50±0,13	4,46±0,20*	—15,7	5,27±0,10	—4,1
IVeD	5,50±0,25	5,27±0,22	—3,8	5,11±0,17	—6,5
IVfD	5,27±0,16	4,50±0,12*	—14,8	5,22±0,16	—0,6
IVgD	5,44±0,21	4,88±0,12	—9,8	4,77±0,14	—12,5
Chloropropamide	6,93±0,15	6,21±0,14	—11,0	6,10±0,21	—12,0
Adebit	6,11±0,13	4,66±0,25	—24,0	4,72±3,41	—23,0

*Statistically reliable results ($p < 0.05$).

white fibrous crystals with a mp of 105-106°C. Found %: C 59.8; H 5.3; Cl 15.8; N 19.2. $C_{11}H_{12}ClN_3$. Calculated %: C 59.6; H 5.5; Cl 16.0; N 19.0.

B. A mixture of 1.16 g (5 mmole) of the amino alcohol I, 5 ml of DMFA, and 1.3 ml of $SOCl_2$ was boiled for 1 h. The solution was cooled and decanted into 10 g of finely crushed ice, made alkaline with an ammonia solution to pH 8.0-9.0, and extracted with $CHCl_3$ (3 × 5 ml). The extract was evaporated, and the remaining crystals were purified, first chromatographically on an Al_2O_3 column (C_6H_6 eluent), and then by recrystallization from octane. The yield of compound III obtained by the same method in A was 0.85 g (63%).

1-(2-Dimethylaminoethyl)-2,3-dihydroimidazo[1,2-a]benzoimidazole (IVa). A solution of 0.7 g (3.2 mmole) of compound III and 0.3 ml of diethylamine in 3 ml of DMFA was boiled for 3-4 h. The mixture was cooled and diluted with 10 ml of water, and extracted with $CHCl_3$ (3 × 5 ml). The extract was washed with water, dried with Na_2SO_4, and evaporated, yielding 0.62 g of compound IVa in the form of a yellowish oil which darkens when stored. IR-spectrum, ν_{max}, cm^{-1}: 1630 (C=N).

1-(2-Pyrrolidinoethyl)-2,3-dihydroimidazo[1,2-a]benzoimidazole (IVb). A solution of 1.1 g (5 mmole) of compound III in 3 ml of pyrrolidine was boiled for 30 min, cooled, and decanted into 15 ml of water. The resultant precipitate was filtered off and washed with water. The precipitate was first purified on an Al_2O_3 column ($CHCl_3$ eluent), and then crystallized from octane. Yield 1 g.

The amines IVc, d, f, and g were obtained in a similar manner. The boiling time of the reaction mixture was 1.5-2 h for compounds IVc, d, and 5 min for compound IVf. The IR spectra of amines IVb-d, and f exhibited stretching vibrations for the C=N bond in the 1640-1650 cm^{-1} region, and stretching vibration bands of the NH group in compound IVf were observed at 3285 cm^{-1}.

1-(2-tert-Butylaminoethyl)-2,3-dihydroimidazo[1,2-a]benzoimidazole (IVe). A mixture of 1.1 g (5 mmole) of the chloride of III and 4 ml of tert-butylamine was heated in a sealed ampule for 6 h at 140-145°C, cooled, and decanted into 15 ml of water. After 30 min the resultant precipitate was filtered off and crystallized from octane. Yield 1 g. IR-spectrum, ν_{max}, cm^{-1}: 1640 (C=N), 3265 (NH).

1-(2-Cyclohexylaminoethyl)-2,3-dihydroimidazo[1,2-a]benzoimidazole (IVf). A solution of 1.1 g (5 mmole) of chloride of III and 1 ml (10 mmole) of cyclohexylamine in 10 ml of dry xylene was boiled for 7 h. The solvent was distilled under reduced pressure and the residue was treated with 10 ml of water and extracted with $CHCl_3$ (3 × 5 ml). The extract was evaporated down to a small volume and passed through an Al_2O_3 layer (2.5 × 3 cm), eluting the amine of IVf with chloroform. Yield was 1.2 g. IR-spectrum, ν_{max}, cm^{-1}: 1640 (C=N), 3234 (NH).

Dihydrochlorides of Amines IVa-g. A solution of 1 g of the base of amine IV in 20 ml of acetone was acidified with an ether solution of HCl to pH 1.0-2.0. The resultant precipitate of the salt was filtered off and washed with acetone. The product was purified

TABLE 3. Antiarrhythmic and Antioxidant Activity of the Tested Compounds

Compound	Minimum effective concentration, mole/liter	Antioxidant activity	
		in scored points	EC_{50}, (mole/liter·10^6)
IVaD	$1{,}7 \cdot 10^{-4}$	4	—
IVbD	—	4	—
IVcD	$4{,}4 \cdot 10^{-4}$	4	—
IVdD	$8{,}7 \cdot 10^{-4}$	4	—
IVeD	$2{,}7 \cdot 10^{-4}$	4	—
IVfD	$1{,}9 \cdot 10^{-4}$	5	5
IVgD	$2{,}7 \cdot 10^{-4}$	4	—
Quinidine	$3{,}4 \cdot 10^{-4}$	—	—
Etmozin	$5{,}1 \cdot 10^{-5}$	—	—
Ionol	—	5	7,9
α-Tocopherol	—	6	3,3

by reprecipitation from an alcohol solution by ether and dried at 110-120°C until a constant mass was obtained.

EXPERIMENTAL (PHARMACOLOGY)

The water soluble dihydrochlorides of the synthesized amines IVa-g were tested for hypoglycemic, antiarrhythmic, and antioxidant activity.

Hypoglycemic action was tested by method [7] on white non-pedigree male rats weighing 180-220 g and which had been deprived of food for 18 h. The test substances as well as the comparison preparations, adebit and chloropropamide, were injected ip at a dose of 50 mg/kg. The control group of animals was given physiological solution. Glucose concentration in the blood samples taken from the caudal vein prior to injection of the compounds and 2 and 4 h after their injection was measured by the ortho-toluidine method which employed the Lya-Chema biochemical sets (Czechoslovakia). The blood sugar level was quantitatively expressed in millimoles per liter, and the change dynamics (Δ) was expressed as a percentage of the initial level. The test results were statistically processed on a microcomputer and are presented in Table 2.

The effect of the substances on the excitability of isolated rat atrium by which their antiarrhythmic properties were judged, was tested by method [3]. The isolated rat atria were placed into a thermostabilized bath (25°C) with a Locke's solution for oxygen supply, and stimulated by a current at a frequency of 3 Hz and a voltage which was twice that of the threshold value. Contractions caused by the preparation were recorded under isometric conditions (at a diastolic load of 0.5 g) with the aid of tensiometric H 328-4 autorecorder. The minimum effective concentration (MEC) which blocked adaption to the affixed atrial rhythm within a 15-second period was taken as the active magnitude of the compounds. The test results as well as similar effects of such antiarrhythmic agents as quinidine and etmozin are presented in Table 3.

The antioxidant action of the salts of compound IV were measured by method [4]. The tests were made on an extract of rat liver homogenate (0.2 g in 15 ml of a Tris-HCl-buffer, pH 7.4) at 37°C. Peroxide oxidation of liver lipids was initiated by ascorbic acid. Peroxide oxidation of liver lipids kinetics was tracked by the accumulation of malonic dialdehyde which was measured with the aid of 2-thiobarbituric acid at 532 nm on a SF-26 spectrophotometer. Oxidation rate was described by the induction magnitude τ, the time in minutes required to increase the optical density of the incubation medium at 532 nm to 0.1. The activity of the test substances was rated in points (decimal logarithm of the substance's concentration at which complete inhibition of lipid peroxide oxidation takes place) or by the value of EC_{50} (effective concentration at which the substance suppresses one-half of the lipid peroxide oxidation). The EC_{50} was computed graphically as a concentration — effect. The food antioxidant ionol and α-tocopherol, used in medicine, were used as comparative substances (see Table 3).

Acute toxicity (LD_{50}) was determined for white non-pedigree mice weighing 18-24 g upon ip injection of the test substances. The LD_{50} was computed graphically by the Miller and Teitner method.

DISCUSSION AND RESULTS

Our experiments have demonstrated that the dihydrochlorides of IVa-g reduce blood sugar in rats to variable degrees (see Table 2). Thus, the salts IVg, IVf, and IVd equal the hypoglycemic activity of chloropropamide although the hypoglycemic effect of the latter two compounds is of short duration. Practically no hypoglycemic action is exhibited by compounds IVa,e which have ethyl and tert-butyl radicals in the amino group. The dihydrochlorides IVb and IVc reduce blood sugar at a statistically significant level and exceed chloropropamide and adebit activity by 2.5-4 times and 1.26-2 times respectively 2 h after administration. However, in spite of the pronounced hypoglycemic activity of compound IVb, its effect was of short duration, and 4 h after its administration its effect was below that of the reference preparations. In contrast, the hypoglycemic effect of the IVc salt was more pronounced than either chloropropamide or adebit even 4 h after its administration. The acute toxicity indices (LD_{50}) of the dihydrochlorides IVb, c were equal to 124.5 ± 16.5 and 175.0 ± 18.3 mg/kg respectively, i.e., these compounds were less toxic than the 1-substituted 2,3-dihydroimidazo[1,2-a]benzoimidazoles described in [2].

With the exception of the pyrrolidinoethyl substituted derivative of IVbD which did not exhibit any cardiotropic action, all of the tested compounds were less active than the antiarrhythmic agent etmozin with respect to stimulation of isolated rat atrium, although the action of most of the tested compounds was comparable to that of quinidine (see Table 3). Moreover, the salts IVa,e-g suppressed myocardial excitability at concentrations that were 1.25-2 times less than quinidine whereas the salts IVc,d were 1.29 and 2.5 less active respectively than quinidine.

One can see from our study of the antioxidant properties (see Table 3) that the tested salts generally exhibit slight activity. Only compound IVfD exceeded the antioxidant activity of ionol by 1.5 times, but was less active than the natural antioxidant α-tocopherol by the same factor. The acute toxicity of the compound was 113.0 ± 52.0 mg/kg.

Thus, our data indicate that the further search for biologically active substances, particularly for those that are hypoglycemic, among derivatives of 2,3-dihydroimidazo[1,2-a]-benzoimidazole, is warranted.

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