SYNTHESIS AND STUDY OF THE HYPOTENSIVE AND ANTIARRHYTHMIC ACTIVITY OF 2,9-DISUBSTITUTED 3-ALKOXYCARBONYLIMIDAZO[1,2-a]BENZIMIDAZOLES

V. A. Anisimova,[1] T. A. Kuz'menko,[1] A. A. Spasov,[2] I. A. Bocharova,[2] and T. A. Orobinskaya[2]

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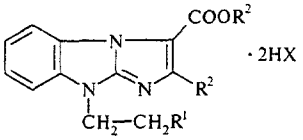
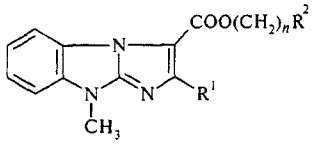
Investigations of the relationship between chemical structure and hypotensive activity in a series of imidazo[1,2-a]benzimidazole derivatives showed that introduction of the diethylaminoethyl group instead of an alkyl radical in position 9 of 2-methyl-3-methoxycarbonylimidazo[1,2-a]benzimidazole enhances the ability of this compound to reduce arterial pressure and increases duration of the hypotensive action [1].

In order to search for new, more active, and less toxic compounds among the esters of some imidazo[1,2-a]benzimidazoles, we have synthesized a series of 3-alkoxycarbonyl derivatives of these heterocycles so as to introduce dialkylaminoalkyl groups either into position 9 of the tricyclic nucleus (compounds I, II) or into the alkoxycarbonyl group (compounds III, IV).



Ia - Ig, IIa - IIe



IIIa - IIIe, IVa - IVc

Ia, g: R^2 = Me; a, b: R^1 = NEt_2; c, d: R^1 = N⬡; e, g: R^1 = N⬡O;

a, e, f: R^3 = Me; b - c, g: R^3 = Et; a, c, e, g: X = Cl; b, d, f: X = Br.

IIa - d: R^2 = Ph; e: R^2 = α-$C_{10}H_7$; a, b: R^1 = NEt_2; c, e: R^1 = N⬡;

d: R^1 = N⬡O; a, c - e: R^3 = Me; b: R^3 = Et; a, c, e: X = Br; b, d: X = Cl.

IIIa - e: R^1 = Me; a, b: n = 2, R^2 = NEt_2; c, d: n = 2, R^2 = N⬡O;

e: n = 3, R^2 = NMe_2; a, c, e: X = Cl; b, d: X = Br.

IVa - c: R^1 = Ph; a, b: n = 2, R^2 = NEt_2; c: n = 3, R^2 = NMe^2;

a, c: X = Cl; b: X = Br.

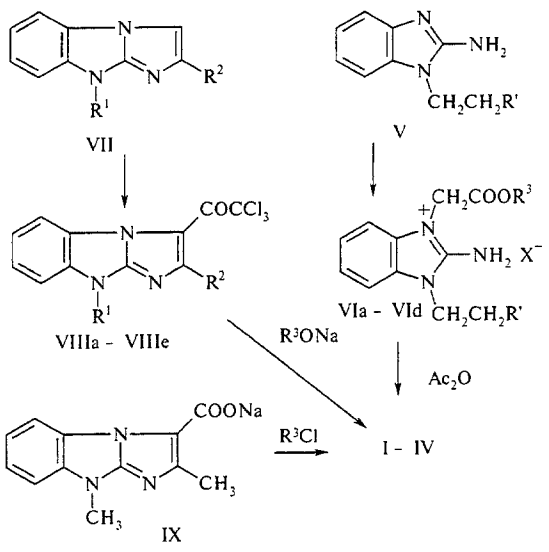
[1] Research Institute of Physical and Organic Chemistry, Rostov State University, Rostov-on-Don, Russia;.

[2] Volgograd State Medical Academy, Volgograd, Russia.

3-Alkoxycarbonyl-9-dialkylaminoalkyl-2-methylimidazo[1,2-a]benzimidazoles (Ia – Ig) were synthesized by a method developed previously [2], based on cyclization of 3-alkoxycarbonylmethyl-1-dialkylaminoalkyl-2-aminobenzimidazolium halides (VIa – VId) in acetic anhydride in the presence of anhydrous sodium acetate. The initial halides were obtained by the condensation of 1-dialkylaminoalkyl-2-aminobenzimidazoles (V) with alkyl esters of the corresponding haloacetic acids. 2-Aryl-substituted esters (IIa – IIe) are readily obtained by saponification of 3-chloroketones VIII (R^1 = dialkylaminoalkyl, R^2 = aryl) by sodium alcoholates. Compounds VIII were synthesized by interaction of 2,9-disubstituted imidazo[1,2-a]benzimidazoles (VII) with trichloroacetic acid anhydride in boiling xylene. Previously [3], a similar reaction was performed in benzene and the target trichloroketones were obtained at a yield not exceeding 40 – 45 %, because the initial imidazo[1,2-a]benzimidazoles served as acceptors of the liberated HCl. The resulting salts did not enter into the acylation reaction. The use of xylene, the solvent boiling at a higher temperature, allowed the yield of compounds VIII to be increased up to 79 – 92 % (Table 1).

TABLE 1. Physicochemical Characteristics of Intermediate Reaction Products VI and VIII

Compound	Yield, %	M.p. (decomp.), °C (solvent for crystallization)	IR spectrum, $\nu_{C=O}$, cm^{-1}	Empirical formula
VIa	92.5	205 (EtOH – Et_2O)	1750	$C_{17}H_{26}N_4O_2 \cdot HBr$
VIb	95.1	214 – 215 (EtOH)	1755	$C_{18}H_{26}N_4O_2 \cdot HBr$
VIc	91.0	199 (EtOH)	1750	$C_{16}H_{22}N_4O_3 \cdot HBr$
VId	93.7	210 (EtOH)	1755	$C_{17}H_{24}N_4O_3 \cdot HBr$
VIIIa	78.9	187 – 188 (EtOAc)	1635	$C_{13}H_{10}C_{13}N_3O$
VIIIb	91.8	230 (EtOH)	1640	$C_{18}H_{12}Cl_3N_3O$
VIIIc	92.0	228 (EtOH)	1640	$C_{23}H_{23}Cl_3N_4O$
VIIId	85.0	246 (MeCN)	1630	$C_{24}H_{23}Cl_3N_4O$



VIa, b, d: R^3 = Et, c: R^3 = Me; a: $R^1 = NEt_2$,

b: R^1 = N⟨⟩ ; c, d: R^1 = N⟨⟩O

VIII и VIa, b: R^1 = Me; c: $R^1 = CH_2CH_2NEt_2$;

d: $R^1 = CH_2CH_2N$⟨⟩ ; e: $R^1 = CH_2CH_2N$⟨⟩O ;

R^2 = Me; b - e: R_2 = Ph.

Dialkylaminoalkyl esters III and IV were synthesized by interaction of the corresponding ketones VIII (R^1 = alkyl, R^2 = alkyl, aryl) with sodium alcoholates. The latter were prepared by reactions of dialkylaminoalkyl alcohols with sodium in anhydrous benzene. Esters III containing a methyl group in position 2 are more conveniently obtained by interaction of 2,9-dimethylimidazo[1,2-a]benzimidazolyl-3-carboxylic acid sodium salt (IX) with dialkylaminoalkyl chlorides in the presence of a catalyst (triethylbenzylammonium chloride).

The proposed structures of target esters and intermediate compounds involved in the synthesis were confirmed by IR and ^{1}H NMR spectroscopic data. The IR spectra of salts VIa – VId exhibit the following characteristic absorption bands (cm^{-1}): 1675 – 1685 (immonium ion, $> N^+=C$), 1750 – 1755 (C=O), 1100 – 1150, 1210 – 1240 (C – O), and 3150 – 3350 (two bands due to NH_2 groups). The absorption of carbonyl groups in trichloroketones VIII is manifested as a band in the region of 1630 – 1640 cm^{-1}. In the spectra of esters I – IV, the bands due to the stretching vibrations of carbonyl groups are observed at 1680 – 1700 cm^{-1} (Table 2), and the stretching vibrations of C – O groups are manifested by the band at 1110 – 1135 cm^{-1}. The bands due to vibrations of the C=C and C=N groups in the tricyclic nuclei of these compounds are observed at 1490 – 1505, 1585 – 1600, and 1600 – 1610 cm^{-1}.

Parameters of the ^{1}H NMR spectra of esters I – IV are listed in Table 3.

EXPERIMENTAL CHEMICAL PART

The course of the reactions was monitored and the purity of target compounds was checked by TLC on Al_2O_3 plates (eluted with $CHCl_3$ and developed by exposure to iodine vapors in a wet chamber). The IR spectra were measured on a Specord IR-75 spectrophotometer (Germany) using samples prepared as Nujol mulls. The ^{1}H NMR spectra were recorded on a Varian Unity-300 spectrometer operating at a working frequency of 300 MHz. The results of elemental analyses agree with the values calculated using the empirical formulas.

3-Alkoxycarbonylmethyl-1-dialkylaminoethyl-2-aminobenzimidazolium bromides (VIa – VId). Method A. To a solution of 10 mmole of 1-dialkylaminoalkyl-2-aminobenzimidazole V prepared on heating in 80 – 120 ml acetone was added 10 – 11 mmole of a bromoacetic acid methyl

TABLE 2. Physicochemical Characteristics of 3-Alkoxycarbonylimidazo[1,2-a]benzimidazoles (I – IV)

Compound	Yield, %	M.p., °C (solvent for crystallization)	IR spectrum, $\nu_{C=O}$, cm^{-1}	Empirical formula
Ia	96.5	186 (EtOH)	1690	$C_{18}H_{24}N_4O_2 \cdot 2HCl$
Ib	91.3	214 – 215** (EtOH – Et_2O)	1695	$C_{19}H_{26}N_4O_2 \cdot 2HBr$
Ic	90.8	248 – 250 (*i*-PrOH)	1700	$C_{20}H_{26}N_4O_2 \cdot 2HCl \cdot H_2O$
Id	92.2	203 – 204** (EtOH)	1695	$C_{20}H_{26}N_4O_2 \cdot 2HBr$
Ie*	95.1	230** (90 % EtOH)	1690	$C_{18}H_{22}N_4O_3 \cdot 2HCl$
If	96.4	235 – 236** (90 % EtOH)	1695	$C_{18}H_{22}N_4O_3 \cdot 2HBr$
Ig*	89.8	239** (80 % EtOH)	1685	$C_{19}H_{24}N_4O_3 \cdot 2HCl \cdot H_2O$
IIa*	85.0	165 (EtOH)	1680	$C_{23}H_{26}N_4O_2 \cdot 2HBr \cdot H_2O$
IIb*	87.3	145 – 146** (*i*-PrOH)	1695	$C_{24}H_{28}N_4O_2 \cdot 2HCl$
IIc*	87.0	254 (EtOH)	1685	$C_{24}H_{26}N_4O_2 \cdot 2HBr$
IId*	85.2	255** (EtOH)	1690	$C_{23}H_{25}N_4O_3 \cdot 2HCl$
IIe	80.7	183 (PrOH)	1680	$C_{28}H_{28}N_4O_2 \cdot 2HBr$
IIIa*	83.4	250 (EtOH – Et_2O)	1700	$C_{18}H_{24}N_4O_2 \cdot 2HCl$
IIIb	85.5	215** (EtOH)	1700	$C_{18}H_{24}N_4O_2 \cdot 2HBr$
IIIc*	93.2	216** (EtOH)	1700	$C_{19}H_{24}N_4O_2 \cdot 2HCl$
IIId	95.2	204 – 205 (EtOH)	1700	$C_{19}H_{24}N_4O_2 \cdot 2HBr$
IIIe	91.5	184** (*i*-PrOH)	1700	$C_{17}H_{22}N_4O_2 \cdot 2HCl$
IVa	71.8	223** (EtOH)	1685	$C_{23}H_{26}N_4O_2 \cdot 2HCl$
IVb	74.3	232 (MeCN)	1685	$C_{23}H_{26}N_4O_2 \cdot 2HBr$
IVc	67.9	210 – 211** (EtOH – Et_2O)	1680	$C_{22}H_{24}N_4O_2 \cdot 2HCl$

* Data for bases: Ia, yield, 82%; m.p., 57°C (EtOAc); Ie, yield, 87.4%; m.p., 135°C (MeCN); Ig, yield, 85.8%; m.p., 109 – 110°C (MeCN); IIa, yield, 84.0%; m.p., 74°C (aqueous EtOH); IIb, yield, 82.0%; m.p., 85°C (isooctanol); IIc, yield, 87.0%; m.p., 128 – 129°C (aqueous EtOH); IId, yield, 85.0%; m.p., 153°C (EtOAc); IIIa, yield, 71.0%; m.p., 68°C (hexane); IIIc, yield, 74%; m.p., 78°C (hexane).

** Melting with decomposition.

TABLE 3. Parameters of the ^1H NMR Spectra of Esters I – IV

Compound	Solvent	Proton chemical shifts, ppm
Ia	DMSO-d_6 – CCl_4	1.15 (t, 6H, $N(CH_2\underline{CH_3})_2$), 2.58 (s, 3H, C – CH_3), 3.25 (q, 4H, $N(\underline{CH_2}CH_3)_2$), 3.6 (t, 2H, CH_2N), 3.9 (s, 3H, OCH_3), 4.8 (q, 2H, NCH_2), 7.2 – 7.48 (2m, 2H, H_{arom}), 7.9 (m, 2H, N+H, H_{arom}), 8.4 (d, 1H, H_{arom}), 11.5 (bs, 1H, N^+H)
Ib	DMSO-d_6 – CCl_4	1.3 (t, 6H, $N(CH_2\underline{CH_3})_2$), 1.4 (t, 3H, $OCH_2\underline{CH_3}$), 2.6 (s, 3H, C – CH_3), 3.3 (q, 4H, $N(\underline{CH_2}CH_3)_2$), 3.64 (t, 2H, CH_2N), 4.4 (q, 2H, $\underline{OCH_2}CH_3$), 4.6 (q, 2H, NCH_2), 7.25 – 7.42 (dt, 2H, H_{arom}), 7.82 (d, 1H, N^+H, H_{arom}), 8.4 (d, 1H, H_{arom})
Ic	DMSO-d_6 – CCl_4	1.42 (t, 3H, $OCH_2\underline{CH_3}$), 1.82 (m, 6H, $(CH_2)_3$-piperidine), 2.6 (s, 3H, C–CH_3), 3.1 (t, 2H, CH_2N), 3.58 (m, 4H, $N(CH_2)_2$-piperidine), 4.42 (q, 2H, $\underline{OCH_2}CH_3$), 4.9 (t, 2H, NCH_2), 7.3 – 7.45 (dt, 2H, H_{arom}), 8.0 (d, 2H, N^+H, H_{arom}), 8.4 (d, 1H, H_{arom}), 11.6 (bs, 1H, N^+H)
Ie	DMSO-d_6 – CCl_4	2.4 (s, 3H, C – CH_3), 3.05 – 3.7 (mod. m, 4H, $N(CH_2)_2$), 3.6 (t, 2H, CH_2N), 3.85 – 4.0 (m, 7H, OCH_3 + $O(CH_2)_2$), 4.84 (t, 2H, NCH_2), 7.22 – 7.42 (dt, 2H, H_{arom}), 7.86 (d, 1H, H_{arom}), 8.4 (d, 1H, H_{arom})
IIa	DMSO-d_6 – CCl_4	1.25 (t, 6H, $N(CH_2\underline{CH_3})_2$), 3.3 (q, 4H, $N(\underline{CH_2}CH_3)_2$), 3.95 (s, 3H, OCH_3), 3.62 (t, 2H, CH_2N), 4.7 (t, 2H, NCH_2), 7.25 – 7.7 (m, 8H, H_{arom}), 8.45 (d, 1H, H_{arom})
IIb	DMSO-d_6 – CCl_4	1.15 (t, 6H, $N(CH_2\underline{CH_3})_2$), 1.4 (t, 3H, OCH_2CH_3), 3.25 (q, 4H, $N(\underline{CH_2}CH_3)_2$), 3.65 (t, 2H, CH_2N), 4.45 (q, 2H, $O\underline{CH_2}CH_3$), 4.75 (2, 2H, NCH_2), 7.2 – 7.7 (m, 8H, H_{arom}), 8.45 (d, 1H, H_{arom})
IIc	DMSO-d_6 – CCl_4	2.85 (t, 4H, $N(CH_2)_2$), 2.35 (t, 2H, CH_2N), 3.62 (t, 4H, $(CH_2)_2O$), 3.98 (s, 3H, OCH_3), 4.65 (t, 2H, NCH_2), 7.2 – 7.8 (m, 8H, H_{arom}), 8.52 (d, 1H, H_{arom})
IIIa*	$CDCl_3$	1.08 (t, 6H, $N(CH_2\underline{CH_3})_2$), 2.62 (q + s, 7H, $N(\underline{CH_2}CH_3)_2$ + C – CH_3), 2.82 (t, 2H, CH_2N), 3.79 (s, 3H, NCH_{23}), 4.42 (ts, 2H, NCH_2), 7.18 – 7.36 (m, 3H, H_{arom}), 8.55 (d, 1H, H_{arom})
IIIc*	$CDCl_3$	1.42 (m, 2H, CH_2-piperidine), 1.6 (m, 4H, $2CH_2$-piperidine), 2.5 (m, 4H, $N(CH_2)_2$-piperidine), 2.76 (t, 2H, CH_2N), 3.8 (s, 3H, NCH_3), 4.48 (t, 2H, NCH_2), 7.2 – 7.38 (m, 2H, H_{arom}), 8.55 (d, 1H, H_{arom})
IVa	DMSO-d_6 – CCl_4	1.05 (t, 6H, $N(CH_2\underline{CH_3})_2$), 2.82 (q, 4H, $N(\underline{CH_2}CH_3)_2$), 3.28 (t, 2H, CH_2N), 3.88 (s, 3H, NCH_3), 4.65 (t, 2H, OCH_2), 7.2 – 7.8 (m, 8H, H_{arom}), 8.5 (d, 1H, H_{arom})

* Spectra of bases.

or ethyl ester and the mixture was vigorously stirred until the onset of precipitation and then allowed to stand for 4 – 6 h at room temperature. The precipitate was separated by filtration and thoroughly washed with acetone and ether.

Method B. A mixture of 10 mmole of the corresponding 2-aminobenzimidazole V with 15 – 20 mmole of bromoacetic acid ester was heated at 65 – 70°C for 10 min. Then the melt was cooled and treated with 20 – 25 ml acetone. The precipitate was separated by filtration and thoroughly washed with acetone. If necessary, the resulting salts were purified by recrystallization from ethyl alcohol.

3-Alkoxycarbonyl-9-dialkylaminoalkyl-2-methylimidazo[1,2-a]benzimidazole dihydrohalides (Ia – Ig). A mixture of 10 mmole of the corresponding bromide VIa – VId, 2 g of anhydrous AcONa, and 30 ml of Ac_2O was boiled until completion of the cyclization process (3 – 5 h) and cooled. The excess acetic anhydride was decomposed by adding ice-cold water, after which the mixture was neutralized with $NaHCO_3$ or Na_2CO_3 to pH 7 – 8. The target product was extracted with $CHCl_3$ (3 × 15 ml). The extracts were combined, evaporated to a sufficiently small volume, and purified by chromatography on a column (diameter, 4 cm; height, 10 cm) filled with Al_2O_3 and eluted with $CHCl_3$. The eluate was evaporated and the residue was either crystallized from an appropriate solvent or immediately converted into salt by dissolving in acetone and acidifying the acetone solution with a selected acid (Table 2).

TABLE 4. Hypotensive and Antiarrhythmic Activity of 3-Alkoxycarbonylimidazo[1,2-a]benzimidazoles (I – IV)

Compound	Hypotensive effect (ED_{20}), mg/kg (i.v.)	Antiarrhythmic effect (MEC), M	Acute toxicity (LD_{50}), mg/kg (i.p.)	Therapeutic breadth (LD_{50}/MEC)
Ia	5.0	–	85.0	–
Ib	6.3	8.9×10^{-5}	263.0	21.35
Ic	38.0	6.5×10^{-5}	301	10.76
Id	20.0	1.2×10^{-4}	–	–
Ie	1.8	–	230.0	–
If	20.0	$>1 \times 10^{-3}$	–	–
Ig	23.9	6.7×10^{-4}	–	–
IIa	–	1.9×10^{-4}	135.0	1.2
IIb	5.6	1.0×10^{-4}	309.0	6.4
IIc	–	2.2×10^{-4}	–	–
IId	13.5	–	–	–
IIe	–	2.8×10^{-4}	–	–
IIIa	3.3	–	250.0	–
IIIb	6.5	1.2×10^{-4}	302.0	5.3
IIIc	24.4	2.9×10^{-4}	–	–
IIId	2.2	–	383.0	–
IIIe	20.4	6.6×10^{-4}	–	–
IVa	8.0	1.3×10^{-4}	234	3.8
IVb	–	1.7×10^{-4}	–	–
IVc	–	2.4×10^{-4}	–	–
Dibazole	22.1		310.0	–
Quinidine		3.1×10^{-4}	210.0	2.09
Ethmozine		3.9×10^{-5}	131.0	7.24

2,9-Disubstituted 3-trichloroacetylimidazo[1,2-a]benzimidazoles (VIIIa – VIIIe). To a boiling solution of 20 mmole of the corresponding 2,9-disubstituted imidazo[1,2-a]benzimidazole VII in 50 ml of anhydrous xylene was gradually added dropwise (over 20 – 30 min) with intensive stirring 3.75 ml (30 mmole) of fleshly distilled trichloroacetic acid chloroanhydride. The mixture was boiled until completion of the reaction (2 – 4 h) and cooled. The yellow precipitate was separated by filtration, washed with petroleum ether, dried in air, treated with dilute $NaHCO_3$ solution, filtered once again, and washed with water. For compounds VIc and VId, upon separation of the target ketone the mother liquor was evaporated to 1/3 of the initial volume and diluted with two volumes of petroleum ether. The additional ketone precipitated was separated by filtration and combined with the first portion (Table 1).

3-Alkoxycarbonyl-9-dialkylaminoalkyl-2-phenylimidazo[1,2-a]benzimidazole dihydrohalides (IIa – IIe). To a solution of sodium alcoholate, prepared by dissolving 0.3 – 0.4 g sodium in 15 ml of absolute methanol or ethanol, was added with stirring 3 mmole of the corresponding trichloroketone VIIIc – VIIIe. The mixture was carefully heated to boiling and boiled for 5 – 10 min. Then the alcohol was evaporated to dryness and the residue was treated with 10 ml of water, filtered, thoroughly washed with water, and dried in air. The resulting esters were purified by chromatography of chloroform or benzene solutions on Al_2O_3 columns, followed by crystallization from an appropriate solvent. The target dihydrohalides were obtained by adding concentrated HCl or HBr to acetone solutions of the esters (Table 2).

2,9-Dimethylimidazo[1,2-a]benzimidazolyl-3-carboxylic acid sodium salt (IX). A mixture of 2.58 g (10 mmole) of 2,9-dimethylimidazo[1,2-a]benzimidazolyl-3-carboxylic acid ethyl ester [2] and 0.45 g (10 mmole) NaOH in 10 ml of 50% aqueous ethyl alcohol was boiled until completion of the reaction (2 – 3 h). Then the solution was evaporated to dryness and the residue recrystallized from aqueous acetone (1 : 5). The target salt is well soluble in water and insoluble in organic solvents; yield, 87 – 91%; m.p., 315°C; $C_{12}H_{10}N_3NaO_2 \cdot 2H_2O$.

3-Dialkylaminoalkoxycarbonylimidazo[1,2-a]benzimidazole dihydrohalides (IIIa – IIIe, IVa – IVc). Method A. To a suspension of 4 mmole of Na-salt IX in a mixture of 10 ml benzene and 10 ml $CHCl_3$ was added a solution of 5.0 – 5.5 mmole of the corresponding dialkylaminoalkyl chloride in 10 ml of benzene (dialkylaminoalkyl chlorides were isolated by treating hydrochloride suspensions in benzene with excess 50% KOH solution) and 0.1 g of triethylbenzylammonium bromide. The mixture was boiled for 5 h and cooled. The precipitate of NaCl was separated by filtration and the filtrate was evaporated. The residue was initially purified by chromatography ($Al_2O_3/CHCl_3$) and then recrystallized from an appropriate solvent to obtain esters IIIa – IIIe in the base form. Note that the yields of the target esters decrease if the reaction is conducted in a two-phase benzene – 50% KOH solution system.

Method B. To a boiling suspension of 7 mmole of 3-trichloroacetylimidazo[1,2-a]benzimidazole VIIIa or VIIIb in 30 ml of absolute benzene was added dropwise a solution of sodium alcoholate prepared by dissolving 0.5 g sodium and 20 mmole of dialkylaminoalkyl alcohol in 40 ml of benzene. The mixture was boiled until complete vanishing of the yellow crystals of the initial ketone. Then the solvent was evaporated and the residue was treated with 20 ml of water and extracted with $CHCl_3$ (3 × 10 ml). The extracts were combined, evaporated to a residual volume of 10 ml, and purified by chromatography ($Al_2O_3/CHCl_3$). Dihydrochlorides III and IV were obtained by treating the ester base solutions in acetone or diethyl ether with HCl solutions in diethyl ether or isopropyl alcohol. Dihydrobromides were obtained using analogous reactions with concentrated HBr.

EXPERIMENTAL PHARMACOLOGICAL PART

The hypotensive action was studied in acute tests on narcotized (pentobarbital sodium, 50 mg/kg, i.p.) white mongrel rats weighing 180 – 220 g. Aqueous solutions of the test compounds were injected intravenously at a gradually increasing dose. The arterial pressure was monitored with a mercury manometer in a carotid artery. The hypotensive activity was estimated by the ED_{20} values representing a dose producing a 20% reduction in the arterial pressure, which were determined graphically from dose – effect plots. The reference drug was dibazole, a well-known benzimidazole derivative.

The antiarrhythmic activity was assessed by the ability of a test compound to influence the excitability of myocardium in rats. The experiments were conducted on isolated rat auricles immersed into a continuously oxygenated Locke's solution at 25°C as described in [4]. The activity was evaluated by the minimum effective concentration (MEC) at which the test compound prevented the auricle from adaptation to the induced rhythm over a 15-sec electrostimulation (at a frequency of 3 Hz, a pulse duration of 0.5 msec, and a voltage equal to the doubled threshold value)

The acute daily toxicity was studied on white mongrel mice weighing 18 – 20 g upon intraperitoneal injection of the test compounds. The LD_{50} values we recalculated according to Miller and Teinter [5]. The effective therapeutic breadth was evaluated as the ratio of the acute toxicity to antiarrhythmic activity parameters (LD_{50}/MEC).

RESULTS AND DISCUSSION

As is seen from Table 4, esters I – IV exhibit more or less pronounced hypotensive activity. Effects of the most active compounds (Ie, IIIa, IIId) exceed that of the reference drug dibazole.

Most of the compounds studied increase the threshold of myocardial excitability, their absolute activities being comparable to that of quinidine but lower than the activity of ethmozine (Table 4). However, the therapeutic breadth

(LD_{50}/MEC) of some compounds (Ib, Ic) exceeds the corresponding ratios of both quinidine and ethmozine.

Thus, introduction of the dialkylaminoalkyl groups containing both nitrogen atoms with unshared electron pairs and alkyl groups favors manifestations of a rather high pharmacological activity in the synthesized series of esters.

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