The studies involved determination of acute toxicities, local anesthetic (terminal anesthesia), analgesic, anticonvulsant, and psychotropic activity.

Acute toxicities were determined by a standard method [2], terminal anesthesia was determined in the rabbit eye by the Regnier—Valeeta method [3], analgesic activity by the hot plate method (t = +55°C) [7], and anticonvulsant activity by means of the effects of the compounds on convulsions modeled in mice by the administration of arecoline, corazole, and nicotine. Psychotropic activity was established from the effects of the drugs on the sedative effects of hexenal and chloral hydrate, the central effects of phenamine (hypothermia and motor excitation), 5-hydroxytryptophan (5-HT, hypothermia), and apomorphine (hypothermia and stereotypy). Motor activity was measured using an actometer [1], and the rectal temperature with a TPEM-1 electrical thermometer. To determine analgesic activity, the ED_{50} of the compounds was determined (i.e., the dose causing the pain threshold to be raised by a factor of two in 50% of the animals), and the breadth of analgesic activity (BAA). The latter was calculated by dividing the LD_{50} by the ED_{50}. All these studies, with the exception of the determination of local anesthetic activity, were carried out in mice. Thirty minutes after the administration of (I), (IIIα, β), or (IVα, β), the mice were treated subcutaneously with a single dose of arecoline (15 mg/kg), corazole (80 mg/kg), nicotine (25 mg/kg), phenamine (7.5 mg/kg), or apomorphine (25 mg/kg), or intraperitoneally (i/p) with 5-HT (50 mg/kg). Analgesic activity was measured in comparison with that of dicaine and promedol.

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SYNTHESIS AND STUDY OF QUATERNARY AMMONIUM DERIVATIVES OF dl-1-ARYLAMINO-2-HYDROXY-3-AMINOPROPANES

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We have previously shown that modification of the structure of the amino-group in β-adrenoblockers affords compounds with high antiarrhythmic properties [5, 6], and the side effects typical of β-adrenoblockers almost completely disappear. The most promising compounds, both from the chemical and pharmacological points of view, are quaternary derivatives of inderal. Quaternization of the amino-group in inderal by a variety of alkylating agents enabled us to establish the most effective cationic terminal groups in respect to antiarrhythmic activity [7]. Continuing these studies, we have replaced the ester grouping in β-adrenoblockers by arylamino, and quaternized the alkylamino-group with the previously selected alkylating agents.

The 1-arylamino-2-hydroxy-3-dimethylaminopropanes (I-III) required as starting materials were obtained by alkylating the arylamines with epichlorohydrin, followed by reaction with dimethylamine. Quaternization of the aliphatic amino-group with an equimolar amount of the alkylating agent in ethyl methyl ketone commenced even at room temperature, and was completed by heating.

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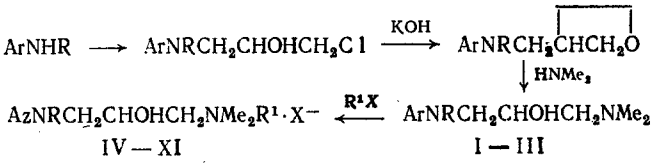
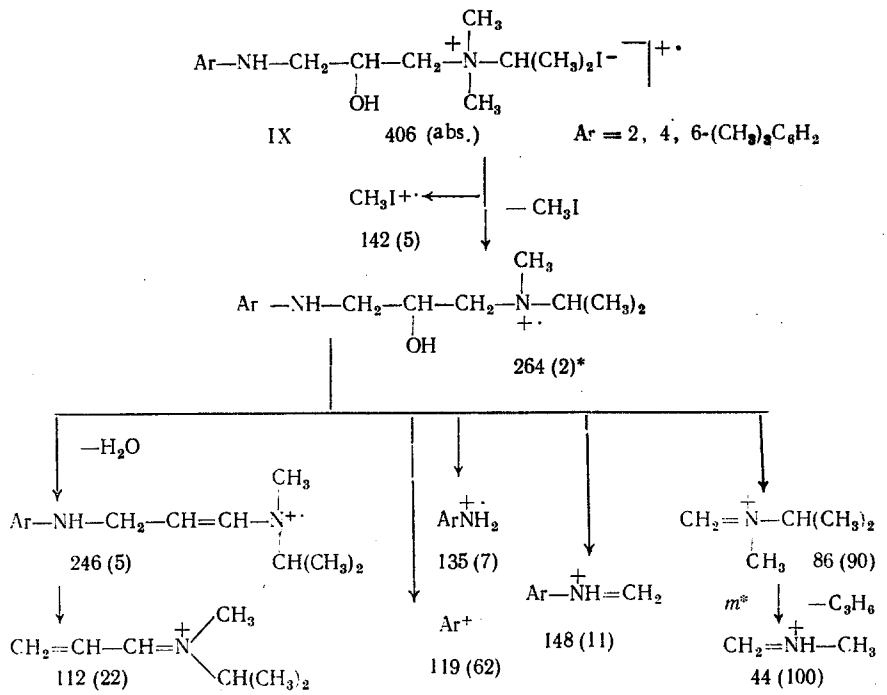


Values of Ar, R, R′, X. IV: Ph, Ph, $CH_2COC_6H_4Br$-4, Br; V: Ph, Ph, Pr-*i*, I; VI: C_6H_4Cl-2, H, Pr-*i*, I; VII: C_6H_4Cl-2, H, $CH_2COC_6H_4Br$-4, Br; VIII: C_6H_4Cl-2, H, $CH_2C_6H_4Cl$-2, Br; IX: $C_6H_2Me_3$-2, 4, 6, H, Pr-*i*, I; X: $C_6H_2Me_3$-2, 4, 6 H, $CH_2C_6H_4Cl$-2, Br; XI: $C_6H_2Me_3$-2, 4, 6, H, $CH_2COC_6H_4Br$-4, Br.

The structures and homogeneity of the compounds obtained (IV-XI) were confirmed by elemental and chromatographic analysis, and in several cases by their UV and mass spectra. All the compounds had similar UV spectra with three absorption bands at 205-207, 237-245, and 285-298 nm, typical of substituted anilines [8]. Only in the UV spectra of (IX) and (XI) was the band at 237 nm absent, evidently as a result of the isolation of the aryl residue from conjugation with the amino-group by the two ortho-methyl substituents. The location of the isopropyl group introduced into (IX) (on the aliphatic nitrogen) was confirmed by examination of the mass spectrum of this quaternary salt. The spectrum showed peaks for the ions $(M-CH_3I)^{+\cdot}$ (m/z 264), characteristic of the mass spectra of quaternary salts of amines, but no $(M-HI)^+$ ions were present [10]. Further fragmentation of this ion, shown below, is similar to the fragmentation of β-ethanolamines [12, 13].



*m/z values shown (relative intensity, %).

The peak for the metastable ion with apparent mass m* = 22.4 (calculated 22.45) confirms the additional presence of the isopropyl group in the ion m/z 86.

EXPERIMENTAL CHEMICAL PART

TLC was carried out on Silufol UV-254 plates in the solvent system n-butanol–ethanol–acetic acid–water (8:2:1:3). The spots were visualized with iodine vapor. UV spectra were recorded on a Specord UV-VIS instrument in 93% ethanol (for V, VI, and IX) or 93% ethanol with an equimolar amount of HCl (for I-III) at a concentration of 10^{-4} mole/liter. Mass spectra were obtained on a MAT-112S mass spectrometer, ionization energy 70 eV, with direct introduction of the sample into the ion source.

d,l-1-Diphenylamino-2-hydroxy-3-dimethylaminopropane (I). To 169 g (1 mole) of diphenylamine was added 92.53 g (mole) of epichlorohydrin and 10 ml of glacial acetic acid, and the mixture kept at ambient temperature for three days. To complete the reaction, the mixture was kept for 30 h at 45-50°C. To the resulting oily mixture was added (portionwise with stirring) 500 ml of 40% KOH cooled to ambient temperature, the mixture was stirred for 5-6 h, and kept

TABLE 1. Quaternary Ammonium Derivatives of d,l-1-Arylamino-2-hydroxy-3-aminopropanes

Compound	Yield, %	Decomposition temperature, °C	R_f	Found, %		Empirical formula	Calculated, %	
				N	halogen		N	halogen
IV	70	133—40	0.32	4.83	28.74	$C_{25}H_{28}BrN_2O_2 \cdot Br^-$	5.11	29.16
V	63	163—5	0.35	6.33	28.42	$C_{26}H_{29}N_2O \cdot I^-$	6.36	28.83
VI	68	105—7	0.38	7.32	Cl 8.45 I 31.58	$C_{14}H_{24}ClN_2O \cdot I^-$	7.03	Cl 8.90 I 31.85
VII	87	80—2	0.36	5.04	Cl 6.62 Br 31.15	$C_{19}H_{23}ClBr_2N_2O_2 \cdot Br^-$	5.53	Cl 7.00 Br 31.55
VIII	86	192—3	0.40	6.08	Cl 16.10 Br 18.73	$C_{16}H_{23}Cl_2N_2O \cdot Br^-$	6.45	Cl 16.34 Br 18.41
IX	62	166—7	0.37	6.51	30.92	$C_{17}H_{30}N_2O \cdot I^-$	6.89	31.26
X	52	137—9	0.32	6.04	Cl 24.67 Br 18.41	$C_{21}H_{30}ClN_2O \cdot Br^-$	6.34	Cl 25.10 Br 18.11
XI	88	190—1	0.30	4.96	31.44	$C_{22}H_{30}BrN_2O_2 \cdot Br^-$	5.45	31.13

Note. Compounds (IV), (VIII), and (IX) were recrystallized from ethanol, (V) from a mixture of ethanol and ethyl methyl ketone (1:1), (VI) and (X) from a mixture of ethanol and ether (1:1), (VII) from ethyl methyl ketone, and (XI) from water.

overnight. The epoxy-compound separated as an oily layer, and was isolated, washed several times with water, and ethanol added until the oil dissolved. There was then added 270 ml (1 mole) of 33% aqueous dimethylamine, the mixture kept for two days at ambient temperature, the solvent removed under reduced pressure, and the (I) distilled, bp 172-174°C (2 mm), mp 49-50°C. R_f 0.37, yield 19%. UV spectrum, λ_{max}, nm (log ε): 205 (3.23), 245 (2.84), 292 (2.90). This compound, obtained from N-(γ-chloro-β-hydroxy-propyl)diphenylamine and dimethylformamide in presence of base, had mp 48-49°C [3].

Similarly obtained, from 2-chloroaniline, was d,l-1-(2-chlorophenylamino)-2-hydroxy-3-dimethylaminopropane (II), viscous liquid, bp 144-146°C (2 mm), R_f 0.32, yield 52%. Found, %: Cl 15.12; N 11.86. $C_{11}H_{17}ClN_2O$. Calculated, %: Cl 15.57; N 12.25. UV spectrum, λ_{max}, nm (log ε): 207 (3.80), 245 (3.40), 298 (2.78). The use of mesidine gave d,l-1-(2,4,6,trimethylphenylamino)-2-hydroxy-3-dimethylaminopropane (III), viscous liquid, bp 160-162°C (2-3 mm), R_f 0.31, yield 20%. Found, %: N 11.45. $C_{14}H_{24}N_2O$. Calculated, %: N 11.86. UV spectrum, λ_{max}, nm (log ε): 207 (4.34), 237 (3.70), 285 (2.87).

d,l-1-(N-Isopropyl-N,N-dimethylamino)-3-diphenylaminopropan-2-ol Iodide (V). A mixture of 8.1 g (30 mmole) of (I), 5.1 g (30 mmole) of isopropyl iodide, and 10 ml of ethyl methyl ketone was boiled for 15 h. After cooling and keeping for several hours, the solid was filtered off and washed with ethyl methyl ketone. Crystallization from ethanol gave pure (V), UV spectrum, λ_{max}, nm (log ε): 208 (4.23), 243 (3.98), 292 (4.00). Similarly, alkylation of (I) with p-bromophenacyl bromide gave (IV). Data for (IV) and (V) are given in Table 1.

d l-(N-Isopropyl-NN-dimethylamino)-3-(2-chlorophenylamino)propan-2-ol Iodide (VI). To a solution of 11.40 g (50 mmole) of (II) in 20 ml of ethyl methyl ketone was added 8.5 g (50 mmole) of isopropyl iodide, and the mixture heated for 5 h at 50-60°C. After keeping for several hours at ambient temperature, the oily compound was precipitated out with ether, and crystallized from ethanol—ether (1:1). UV spectrum, λ_{max}, nm (log ε): 208 (4.45), 245 (4.03), 300 (3.25).

Similarly, alkylation of (III) with o-chlorobenzyl or isopropyl iodide gave respectively crystalline (X) and (IX). UV spectrum of (IX), λ_{max}, nm (log ε): 210 (4.36), 285 (2.90).

Addition to (II) of p-bromophenacyl bromide or o-chlorobenzyl bromide, or to (III) of p-bromophenacyl bromide resulted in exothermic reaction, and after a few minutes (VII), (VIII), and (XI) gradually separated, respectively. UV spectrum of (XI). λ_{max}, nm (log ε): 208 (4.28), 283 (2.78). For other data on compounds (VI-XI), see Table 1.

EXPERIMENTAL BIOLOGICAL PART

Acute toxicities of the quaternized arylaminopropanolamines were determined by the Litchfield and Wilcoxon method, in white mice by the intraperitoneal route [2]. The LD_{50} values of the compounds varied from 42.5 mg/kg (V) to 90 mg/kg (VI). The LD_{50} of quinidine was 225 mg/kg, and that of novocainamide 380 mg/kg (Table 2).

TABLE 2. Toxicity and Antiarrhythmic Activity of Quaternary Ammonium Salts of 1-Arylamino-2-hydroxy-3-dimethylaminopropanes

Compound	LD_{50} and confidence limits for mice following intraperitoneal administration, mg/kg	Calcium chloride arrhythmia			Aconitine arryhythmia	
		% survival	cause of death		onset, sec	duration, min
			fibrillation	asystole		
V	42,5 (35,4—51,0)	20	100	—	179,2±22,7	55,0±4,2
VI	90,0 (56,3—144,0)	30	100	—	245,0±34,7*	54,8±9,7
VII	54,2 (58,2—49,8)	30	100	—	150,5±7,5	68,6±7,2
VIII	80,0 (65,8—89,2)	10	100	—	141,7±25,7	60,7±3,5
IX	76,6 (65,9—87,4)	—	100	—	163,3±17,1	56,2±8,9
X	35,0 (27,2—42,8)	50*	100	—	130,0±8,9	78,3±7,3
Control		10	88,9	11,1	166,0±10,6	70,5±7,7
Quinidine	225,0 (193,0—261,0)	30	71,1	28;9	210,0±7,8*	46,7±6,5*
Novocainamide	380,0 (343,0—421,0)	30	71,1	28,9	223,3±28,5*	64,4±5,3*

*Statistically significant results.

Primary screening was carried out with calcium chloride [11] and aconitine [4] models of arrhythmia in rats, using doses of 5% of the LD_{50} for mice.

Nearly all the compounds were weakly active in the calcium chloride model arrhythmia, increasing the survival of the rats by 30% over the controls. The most active compound was (X), on treatment with which the survival of the animals was increased to 50%, although they were not protected against ventricular fibrillation. On treatment with quinidine and novocainamide, the survival of the rats was also 30% (Table 2).

In studies of protective antiarrhythmic activity in model aconitine arrhythmia in rats, (VI) was effective significantly delaying the development of arrhythmia and reducing its duration. All the compounds with the exception of (X) reduced the duration of aconitine arrhythmia. It will be seen from the results obtained that novocainamide and quinidine significantly reduced the duration of aconitine arrhythmia. It is, however, noteworthy that on treatment with quinidine and novocainamide, irreversible changes in the ECG occurred in 20 and 10% of the animals, respectively, to the extent of ventricular fibrillation (Table 2).

β-Adrenoblocking activity was examined as described in [1]. It was found that only (IX) showed a tendency to block β_1- and β_2-adrenoreceptors.

Despite the results reported in [9], indicating the absence of antiarrhythmic activity in substituted propanoldiamines, some of the monoquaternary ammonium derivatives of propanoldiamines synthesized here have shown a weak antirrhythmic effect. For this reason, a search for the optimum pairing of the cationic terminal group and the aromatic moiety in 1-arylamino-2-hydroxy-3-aminopropanes could lead to the synthesis of compounds with high antiarrhythmic activity.

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SYNTHESIS AND ANTICONVULSANT ACTIVITY OF BENZIMIDAZO[1,2-c]QUINAZOLINES

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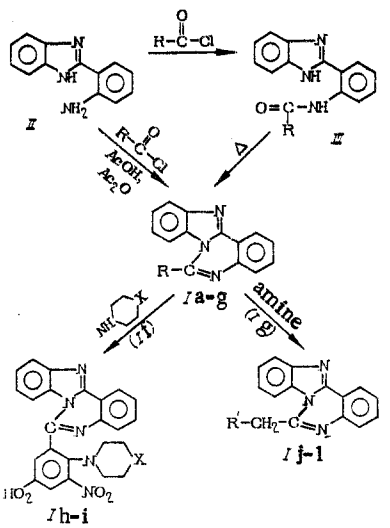
Imidazo[1,2-c]quinazolines display a number of interesting pharmacological properties [6]. With the aim of obtaining novel biologically active compounds, some benzimidazo[1,2-c]-quinazolines (I) have been synthesized and some of their properties examined.

These compounds (I) are usually obtained by acylating 2-o-aminophenylbenzimidazole (II) with carbonyl chlorides, followed by cyclization of the resulting benzimidazole amides (III). We have previously shown [2] that (I) can be obtained in high yields by the direct reaction of (II) with benzoyl chlorides or benzoic anhydrides mixed with acetic acid and acetic anhydride:



Ia: R = C_6H_5; Ib: R = o-ClC_6H_4; Ic: R = o-BrC_6H_4; Id: R = m-ClC_6H_4; Ie: R = p-ClC_6H_4; If: R = o-Cl-m, m'-$(NO_2)_2C_6H_2$; Ig: R = CH_2—Cl; Ih X = O; Ii: X = =N—CH_3; Ij: R′ = —$N(Et)_2$; Ik: R′ = —N O; Il: R′ = —N N—CH_3.

Using substituted benzoyl chlorides and chloroacetyl chloride, a number of 6-aryl-(Ia-f) and 6-chloromethyl-(Ig)-benzimidazo[1,2-c]quinazolines have been obtained. Compounds (If) and (Ig), which contain a reactive halogen atom, are highly reactive towards nucleophilic substitution by a variety of amine residues, namely morpholine, N-methylpiperazine, and diethylamine. The physicochemical properties of the compounds obtained are given in Table 1.

The IR spectra of the 6-substituted compounds (Ia-l) show strong absorption for the azomethine bond and benzene ring C=C at 1612-1626 cm^{-1}, and characteristic absorption for the benzimidazo[1,2-c]quinazoline ring at 1360-1388 cm^{-1} [4]. The absence of amide carbonyl absorption at 1663-1674 cm^{-1} and of stretching vibrations of amide NH at 3360-3380 cm^{-1} confirms the structure of these compounds. The UV spectra of (Ia-l) show an absorption maximum at 268-278 nm, typical of these structures, which appears to be due to $n \rightarrow \pi^*$ and $\pi-\pi^*$ electronic transitions of the conjugated system of the benzimidazo [1,2-c]quinazoline ring [2].

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