All of the amino esters obtained were devoid of antiarrhythmic properties; Only VIIIa showed activity on the level of procainamide.

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SYNTHESIS AND ANTIARRHYTHMIC PROPERTIES OF QUATERNARY DERIVATIVES OF 1-[α-NAPHTHOXY]-2-HYDROXY-3-DIMETHYLAMINOPROPANE

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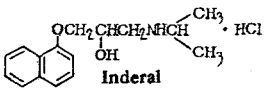
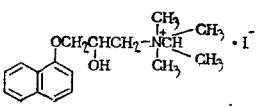
Beta-adrenergic blockers such as anaprilin (inderal) are used in conjunction with membrane stabilizers and potassium antagonists in the prevention and treatment of cardiac arrhythmia.

Side effects are associated with the clinical use of β-adrenergic blockers as antiarrhythmic agents [1]. Attempts by several researchers to eliminate these side effects by modifying the functional groups on the aromatic ring have had only marginal success [2, 3], but replacement of the amino group by ethylenediamine increased the antiarrhythmic activity [4, 5]. We have previously shown that replacement of the amino group in the aryloxypropanolamines by a guanidine group, or replacement of the ether group by an NH group, strengthens the antiarrhythmic properties and almost eliminates β-adrenergic-blocking and other effects [6, 7]. Subsequently, it was reported [8] that analogs of propanolol — ICI-46035 and UM-272 — in which the amino group was quaternized, increased the duration of the effective refractory period in dogs, and after occlusion of the coronary artery, prevented its contraction in the ischemic area, thereby retaining the functional homogeneity of the myocardium and preventing the occurrence of an ectopic beat [8]. The toxicity of these compounds was low, and the β-adrenergic-blocking action and other pharmacological effects associated with them were very weak [9, 10].



Inderal



UM-272

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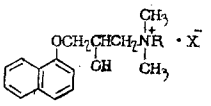
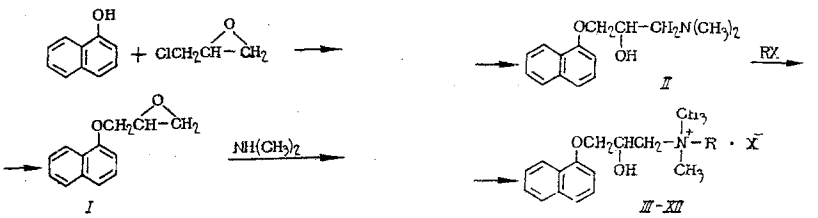
As there is no data on the effect of the structure of substitutents on the nitrogen atom on the antiarrhythmic action of quaternary propranolol derivatives, we have prepared a number of quaternary propranolol analogs of general formula by alkylation of 1-(α-naphthoxy)-2-hydroxy-3-dimethylaminopropane.



According to [11], the quaternary derivative of propranolol — UM-272 — is synthesized by the methylation of the base propranolol. This base is obtained by the reaction of the glycidic ester of α-naphthol (I) with isopropylamine; however, this reaction does not always stop after one of the amino hydrogens has been replaced [12]. Compounds III-XII were therefore synthesized by another route:



(R; X are as follows) III: $CH(CH_3)_2$; I; IV: $CH_2CONHC_6H_3(CH_3)_2$-2,6; Cl; V: $CH_2CONHC_6H_4Cl$-2; Cl; VI: $CH_2COC_6H_4Br$-4; Br; VII: $CH_2COOC_2H_5$; Br; VIII: $CH_2C_6H_4Br$-2; Br; IX: $CH_2CH{=}CH_2$; Br; X: $CH_2CONHC_6H_3(CH_3)_2$-2,4,6; Cl; XI: $CH_2CH_2N(CH_3)_2CH_2CH(OH)CH_2OC_{10}H_7$-1; 2 Br; XII: $CH_2CH(CH_3)COOC_2H_5$; Br.

This method avoids the difficulties associated with the preparation of the base propranolol. In order to explain the effect of groups in the cation on the properties of the molecule, we alkylated 11 examples of various classes of organic compounds. The quaternary analogs of propranolol are shown in Table 1 (compounds III-XII).

The structure and purity of the compounds were confirmed by elemental analysis and by chromatography, and in individual cases also by UV spectroscopy.

EXPERIMENTAL CHEMISTRY

The purity of the quaternary analogs of propranolol was checked by chromatography using Silufol UV-254 plates in n-butanol—ethanol—acetic acid—water (8:2:1:3). Spots were visualized in iodine vapor. The UV spectra of the compounds in water (concentration 10^{-4} M) were obtained using an SF-16 instrument; all the compounds absorbed at 288 nm ($\log \varepsilon \sim 3.9$).

Glycidic Ester of α-Naphthol (I). To a stirred mixture of 1 mole of epichlorhydrin was added during the course of 1 h a solution of 1 mole of α-naphthol and 1 mole of sodium hydroxide in 300 ml of water. The mixture was stirred for 1 h, and allowed to stand overnight. The oily layer was separated, washed with water, and fractionally distilled in vacuum. The fraction with bp 145-148°C (1 mm) was collected [13]. Yield 67%.

1-(α-Naphthoxy)-2-hydroxy-3-dimethylaminopropane (II). A mixture of 0.5 mole of I and 1 mole of dimethylamine in 180 ml of ethanol when allowed to stand for 10 h at room temperature gave II, bp 165-167°C (1 mm) [14], in 65% yield.

1-(N-Isopropyl-N,N-dimethylamino)-3-(α-naphthoxy)propan-2-ol Iodide (III). A mixture of 0.1 mole of II, 0.1 mole of isopropyl idodie, and 30 ml of methyl ethyl ketone was heated for 10 h at 80-90°C. When cool, it was allowed to stand for several hours and the precipitated material suction filtered, and washed with methyl ethyl ketone. Recrystallization from ethanol gave pure III.

The quaternary derivatives (IV-XII, Table 1) were obtained in the same way using appropriate alkylating agents.

EXPERIMENTAL PHARMACOLOGY

The acute toxicity of the propranolol analogs was determined by the method of Miller and Tainter; mice were given intraperitoneal injections of the compounds (Table 2). The LD_{50} of these compounds varied from 50 ± 2.5 mg/kg (for compound VI) to 155 ± 2.9 mg/kg (for compound VII). The LD_{50} for inderal was 95 ± 1.3 mg/kg.

TABLE 1. Quaternary Derivatives of 1-(α-Naphthoxy)-2-hydroxy-3-dimethylaminopropane

Compound	Yield, %	Decomp. temp., °C	R_f^*	Found, %		Empirical formula	Calculated, %	
				N	halogen		N	halogen
III	69	155,5—156,5	0,30	3,07	30,10	$C_{16}H_{26}NO_2 \cdot I^-$	3,37	30,56
IV	81	185	0,41	6,59	8,34	$C_{25}H_{31}N_2O_3 \cdot Cl^-$	6,88	8,72
V	86	157—158	0,37	6,50	7,47	$C_{23}H_{26}ClN_2O_3 \cdot Cl^-$	6,23	7,90
VI	93	139	0,38	2,40	15,0	$C_{23}H_{25}BrNO_3 \cdot Br^-$	2,67	15,28
VII	82	145—146	0,41	3,14	19,02	$C_{19}H_{26}NO_4 \cdot Br^-$	3,40	19,39
VIII	87	115—119	0,35	2,63	15,68	$C_{22}H_{25}BrNO_2 \cdot Br^-$	2,82	16,14
IX	84	119—121	0,28	3,58	21,40	$C_{18}H_{24}NO_2 \cdot Br^-$	3,82	21,83
X	93	217—218	0,48	6,23	7,30	$C_{26}H_{33}N_2O_3 \cdot Cl^-$	6,14	7,79
XI	10	175—180	0,42	3,78	—	$C_{32}H_{42}N_2O_4 \cdot 2Br^-$	4,13	23,56
XII	25	182—185	0,40	2,99	18,84	$C_{21}H_{30}NO_3 \cdot Br^-$	3,30	18,75

*Compounds III, VI, VIII-X, and XII were recrystallized from ethanol, IV, V, and VII from a mixture of ethanol and methyl ethyl ketone (1:1), and XI from methyl ethyl ketone.
Note. Compound XI became very cloudy when titrated and this interfered with the determination.

The initial screening was carried out on arrhythmias induced by calcium chloride [15] and by aconite [16] in rats.

All the compounds exhibited an antiarrhythmic action on calcium chloride-induced arrhythmia, and prevented the development of ventricular fibrillation in rats. Compound IX was the most active, with an ED_{50} of 0.8 ± 0.28 mg/kg, and the therapeutic index, which gives the ratio of LD_{50} to ED_{50}, was 81.3. Compound IV was the least active with an ED_{50} of 7.1 ± 1.76 mg/kg, and a therapeutic index of 7.8. Propranolol had no preventive effect on calcium chloride-induced arrhythmia.

Effective as prophylactic agents were compounds III, VI, VIII, and IX; in doses of 2.5-10% of the LD_{50} for mice, they prevented the onset of destructive heart rhythm in 20-50% of experimental animals, and significantly ($P < 50\%$) retarded the development of arrhythmia and decreased its duration in the remaining cases. Propranolol was ineffective in these tests.

The effects of compounds III, VIII, and IX on ventricular arrhythmia, induced in dogs by strophanthin G (60 μg/kg, intravenously), was investigated. A single injection of 5-10% of the LD_{50} for mice of these compounds caused a significant (50-90%) decrease in the occurrence of ventricular ectopic beats, and in some cases, a temporary (for 10-30 min) restoration of the sinus rhythm. As demonstrated earlier in our laboratory [17, 18] in experiments on cats, propranolol exerted an antiarrhythmic effect lasting for 1-3 min on 50% of the experimental animals with strophanthin-induced arrhythmia.

Ventricular arrhythmia was induced in dogs by ligation of a branch of the coronary artery; all the test compounds, in doses corresponding to 2.5-15% of the LD_{50} for mice, possessed a weak antiarrhythmic action, reducing the rhythm of contraction and the occurrence of ectopic beats. Propranolol was ineffective in the treatment of ventricular arrhythmia and, moveover, in doses of 2 mg/kg it caused the death of a majority of experimental animals [17, 18].

The action of compounds III, VI, VIII, and IX on atrial fibrillation in cats, induced by the application of a 0.05% solution of aconite nitrate to the right atnium, was also studied. The test compounds were injected intravenously in doses of 0.5-1 mg/kg at intervals of 5-10 min until the normal rhythm was completely restored; all curtailed the atrial fibrillation and reduced the sinus rhythm (dosage 1.8 ± 0.54 to 3.0 ± 0.72 mg/kg). Propranolol under similar conditions exhibited an antiarrhythmic effect in some cases only, moveover, the accumulated dose reached 6.4 ± 0.45 mg/kg, i.e., it was 2-3 times greater ($P < 0.05$).

This study of the pharmacological properties of quaternized propranolol derivatives shows that in contrast to propranolol, the quaternary derivatives possess higher antiarrhythmic activity, a wider spectrum of antiarrhythmic action and a greater therapeutic index. The most effective compounds were those with isopropyl, p-bromophenacyl, o-bromobenzyl, and allyl groups on the quaternary nitrogen atom. It is concluded that quaternization and substi-

TABLE 2. Toxicity and Antiarrhythmic Activity of Quaternary Propranolol Derivatives for Several Ventricular and Atrial Arrthythmias

Compound	LD_{50} for mice on intraperitoneal injection, mg/kg	Effectiveness for calcium chloride arrhythmia in rats		Effective dose for aconite atrial fibrillation in cats, mg/kg
		ED_{50}, mg/kg	therapeutic index (LD_{50}/ED_{50})	
III	98±1,6 (94,9—101,4)	2,7±0,81 (1,03—4,37)	36,3	2,4±0,30 (1,5—3,23)
IV	56±2,7 (50,7—61,3)	7,1±1,76 (3,47—10,73)	7,8	—
V	68±1,8 (64,5—71,5)	4,2±1,04 (2,05—6,35)	16,2	—
VI	50±2,5 (45,1—54,9)	1,6±0,71 (0,12±3,08)	31,3	2,3±0,54 (0,17—4,43)
VII	155±2,9 (149,3—160,7)	4,7±1,77 (1,05—8,35)	32,9	—
VIII	90±4,4 (81,4—98,6)	2,0±0,88 (0,20—3,80)	45,0	3,0±0,72 (0,71—5,29)
IX	65±3,7 (57,7—72,3)	0,8±0,28 (0,21—1,39)	81,3	1,8±0,54 (0,08—3,52)
X	77±2,9 (71,3—82,7)	2,8±0,82 (1,09—4,51)	27,5	—
Propranolol	95±1,3 (92,5—97,5)	Ineffective	—	6,4±0;45 (5,15—7,65)

Note. Range of variation is given in parentheses.

tution of the propranolol nitrogen atom can lead to compounds which are of possible value in the treatment of cardiac arrhythmia.

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