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SYNTHESIS OF 2-HYDROXY-3-DIETHYLAMINOPROPYL ESTERS OF SUBSTITUTED ACETIC ACIDS AND THEIR PHARMACEUTICAL ACTIVITY

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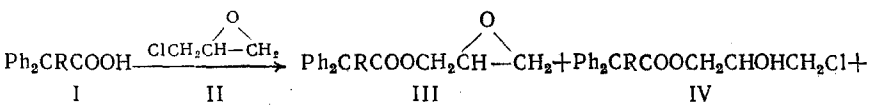
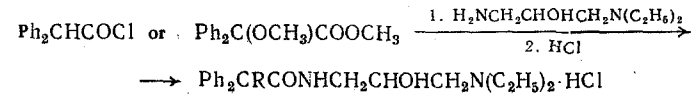
The present work is a continuation of earlier studies [1, 2], and was carried out to show the influence of a hydroxyl group in the amino-alcohol chain on the pharmaceutical activity of dialkylaminopropyl esters and amides of substituted acetic acids. The syntheses of hydrochlorides of the 2-hydroxy-3-diethylaminopropyl esters of diphenylacetic and α-alkoxydiphenylacetic acids (VIa-i) were therefore carried out (Table 1):



VIa: R=H; VIb: R=OCH_3; VIc: R=OC_2H_5; VId: R=OC_3H_7; VIe: R=OC_3H_7-iso; VIf: R=OC_4H_9; VIg: R=OC_4H_9-iso; VIh: R=OC_5H_{11}; VIi: R=OC_5H_{11}-iso.

According to this scheme, the hydrochlorides VIa-i were synthesized by amination of a mixture of III-V with excess diethylamine, followed by treatment with HCl. The mixture of III-V was obtained by the reaction of the substituted acetic acids (I) [3] with epichlorohydrin (II) in the presence of benzyltrimethylammonium chloride [4]. The formation of III-V was confirmed by TLC in the system ether–petroleum ether (12:8), visualized with iodine vapor.

The interaction of diphenylacetyl chloride or methyl α-methoxydiphenyl acetate with 2-hydroxy-3-diethylaminopropylamine (VII) [5], followed by treatment with HCl, gave the hydrochlorides of 2-hydroxy-3-diethylaminopropyl amides of diphenylacetic acid and α-methoxydiphenylacetic acids (VIIIa, b).



VIIIa: R=H; VIIIb: R=OCH_3

The compounds obtained were identified by IR and PMR spectroscopy, as well as by elemental analysis. In the IR spectra, characteristic absorptions were observed at 1700-1800 cm^{-1} (ester C=O), 3200-3600 cm^{-1} (OH), and 2400-2800 cm^{-1} ($R_4N^+Cl^-$). In the PMR spectra of VIa-i and VIIIa, b proton signals from the following fragments were observed: C_6H_5 (7.1-7.3 ppm), $COOCH_2CH$ (3.63-4.13 ppm), $N-CH_2$ (2.23-2.46 ppm), $(C_6H_5)_2CH$ (4.7 ppm), and $N(C_2H_5)_2$ (0.8-1.2 ppm).

EXPERIMENTAL CHEMISTRY

The melting points of the hydrochlorides of VIa-i and VIIIa, b were obtained on a Boethius micro-hot stage. IR spectra were determined on a UR-20 spectrometer (GDR) in vaseline oil. The PMR spectra were determined in $CDCl_3$ with a Varian T-60 instrument, using tetramethylsilane as internal standard. TLC of compounds I-VIIIa, b was carried out on a stationary

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TABLE 1. Hydrochlorides of 2-Hydroxy-3-diethylaminopropyl Esters of α-Alkoxydiphenylacetic Acids (VIa-i)

Compound VIa-i	Yield, %	mp, °C (from acetone)	R_f	Found, %				Calculated, %			
				C	H	N	Cl	C	H	N	Cl
a	66,5	129—30	0,64	66,31	7,58	4,11	9,81	66,75	7,41	3,70	9,40
b	57,4	114—5	0,66	65,00	7,16	3,87	9,02	64,78	7,36	3,43	9,71
c	53,4	120—1	0,71	65,83	8,04	3,75	8,10	65,48	7,59	3,32	8,42
d	47,0	100—2	0,70	66,30	7,80	3,75	8,66	66,13	7,80	3,21	8,15
e	57,9	146—7	0,74	66,54	7,41	3,04	8,19	66,13	7,80	3,21	8,15
f	44,4	114—5	0,64	66,44	7,60	2,80	7,75	66,74	8,00	3,11	7,89
g	51,7	133—4	0,68	66,44	7,66	2,89	7,80	66,74	8,00	3,11	7,89
h	37,1	128—9	0,63	67,20	8,10	3,58	8,03	67,31	8,19	3,02	7,65
i	47,2	131—2	0,70	67,87	7,87	3,29	7,45	67,31	8,19	3,02	7,65

phase of KSK silica gel with a gypsum binder. Solvent systems: A = n-butanol—ethanol—acetic acid—water (8:2:1:3); B = petroleum ether—ether (8:12); C = ethanol—water—ammonia (80:15:5). Visualization was with iodine vapor for system B, bromcresol purple for system C, and Dragendorf's reagent for system A.

2-Hydroxy-3-diethylaminopropyl α-Alkoxydiphenylacetate Hydrochlorides (VIa-i). A mixture of 0.05 mole of I and 0.4 mole of II was heated to boiling, 0.0013 mole of benzyltrimethylammonium chloride was added, and the heating was continued for an additional 30 min. The excess II was removed in vacuum in a stream of nitrogen, and 30 ml of toluene was added and distilled three times. TLC in system B showed three spots corresponding to III-V. The mixture was heated for 8 h with diethylamine in the ratio of 1:2 and then treated with a solution of 9% hydrochloric acid, extracted with ether, and dried. The aqueous acidic layer was made alkaline with saturated potassium carbonate and extracted with ether. The extract was dried with sodium sulfate, the solvent was distilled, and the residue was treated with a solution of HCl in absolute ether to give VIa-i (cf. Table 1).

N-(2-Hydroxy-3-diethylaminopropyl)diphenylacetamide Hydrochloride (VIIIa). To 29.3 g (0.1 mole) of diphenylacetyl chloride in 100 ml of dry benzene was added with cooling 14.6 g (0.1 mole) of 2-hydroxy-3-diethylaminopropylamine (VII). The mixture was boiled for 6 h, the solvent was distilled, the residue was treated with a saturated solution of potassium carbonate, and extracted with ether. The extract was dried, the ether was distilled, and the residue was distilled under vacuum to give the aminoamide, 58.8% yield, bp 210-212°C (1 mm). Found, %: C 73.61; H 8.81; N 8.64. $C_{20}H_{28}N_2O_2$. Calculated, %: C 73.14; H 8.53; N 8.52.

Hydrochloride mp 95°C. R_f = 0.74 (system A). IR spectrum, ν, cm^{-1}: 2400-2800 $\left(\geq\overset{+}{N}H\,Cl^{-}\right)$, 3200 (OH).

N-(2-Hydroxy-3-diethylaminopropyl)-α-methoxydiphenylacetamide Hydrochloride (VIIIb). To 12.5 g (0.05 mole) of methyl α-methoxydiphenylacetate in 100 ml of dry benzene was added with cooling 14.6 g (0.1 mole) of VII. The mixture was boiled for 6 h and worked up analogously to VIIIa. After distillation of the solvent, the residue was distilled under vacuum to give the aminoamide, 54.3% yield, bp 220-224°C (1 mm). Hydrochloride mp 105-108°C (VIIb). R_f = 0.77 (system A). Found, %: C 65.06; H 7.94; N 8.05; Cl 8.53. $C_{22}H_{31}N_3O_3$. Calculated, %: C 64.93; H 7.66; N 7.88; Cl 8.70.

EXPERIMENTAL PHARMACOLOGY

The antispasmodic, cholinolytic, adrenoblocking, sympatholytic, and antiarrhythmic activity of compounds VIa-i and VIIIa, b were studied.

The antispasmodic activity was studied in white mice. Electroshock and pentylene tetrazole-, nicotine-, and arecholine-induced convulsions served as spasmodic agents for these studies. Cholinolytic action was studied in frog primary abdominal muscles, in which the concentration to relax the acetylcholine spasm by 50% was determined. The activity of the above compounds on the α-adrenoreceptors and on the passage of excitation through the sympathetic nerves was studied in experiments on the isolated spermatic ducts of rats [6]. This type of activity was judged by the decrease in the contraction of the spermatic ducts produced by transmural electrical stimulation and the introduction of nonadrenalin at a concentration of $1 \cdot 10^{-6}$ g/ml. The action of each compound was determined in experiments on 4 ducts, usually at a concentration of 0.05 mM, and the arithmetic mean was determined with confidence limits of P = 0.05 [7].

TABLE 2. Activity of the Preparations on Nerve Stimulation and the Adrenoreceptors of Rat Spermatic Ducts

Compound	Decrease in transmural stimulation-induced spermatic duct contraction, % of control		Diminished contraction of ducts produced by noradrenalin, % of control	
	10 min	60 min	10 min	60 min
VIa	98 (95,8—100,2)	70 (56,1—83,9)	8 (—2—18)*	70 (20—120)*
VIb	90 (75—10,5)	65 (49—81)	23 (—24—70)	1
VIc	78 (63,7—92,3)	74 (32,4—115,6)	89 (73,8—104,2)	88 (72,1—103,9)
VId	69 (41,7—96,3)	77 (57,3—96,7)	91 (89,2—100,8)	40 (15,2—64,8)
VIe	78 (53,2—102,8)	69 (41,7—96,3)	93 (89,2—96,8)	74 (44,2—103,8)
VIf	99	78 (48,4—107,6)	61 (—54,4—176,4)*	145 (43,3—256,7)*
VIg	90 (78,5—101,5)	96 (83,3—108,7)	85 (54,8—115,2)	88 (69,6—106,4)
VIh	84 (65,9—102,1)	8 (1,7—14,3)	53 (1,2—104,8)	13 (—5,7—31,7)
VIi	98 (94,8—101,2)	100	81 (67,7—94,3)	95 (85,8—104,2)
VIIIa	60 (32,1—87,9)	46 (29,5—62,5)	38 (14,2—61,8)	20 (1,3—38,7)
VIIIb	95 (89,3—100,7)	48 (—2,2—98,2)	13 (—26,1—52,1)	265 (94,3—435,7)*

*Increased contraction of ducts produced by noradrenalin, % of control.

Note. The limits of variation are given in parentheses.

For evaluation of antiarrhythmic activity, as experimental model of heart arrhythmia, the regeneration of electrical current in narcotized cats was used [8]. The activity of the compounds was evaluated by the increase of fibrillation threshold (in mA). The results obtained were worked up statistically by the Student—Fischer method [7]. Procainamide was used as a standard for comparison.

Inspection of the antispasmodic properties of these compounds shows that by intraperitoneal introduction in a dose of 50 mg/kg (toxic dose = 100-200 mg/kg), all compounds, independently of structure, do not influence convulsions produced by arecholine and electrical stimulation. In respect to convulsions produced by pentylene tetrazole, weak activity was shown by compounds VIb, d, e.

The studied compounds somewhat weakened the convulsions produced by nicotine.

Analysis of the cholinergic properties of compounds VIa-i and VIIIa, b showed that they possessed significant activity. The average effective concentrations of VIa-i was in the range of $1 \cdot 10^{-6}$ to $5 \cdot 10^{-6}$ g/ml. The most active compounds were VIa, e, for which the ED_{50} was $1 \cdot 10^{-6}$ g/ml. Compound VIIIa was an exception, since its activity was significantly lower ($ED_{50} = 1 \cdot 10^{-5}$ g/ml).

Investigation of adrenal blocking and sympatholytic properties revealed that all of the compounds showed significant ability to block the conduction of stimulation through sympathetic nerves. This activity was most pronounced for compound VIIg, which also strongly blocked the α-adrenoreceptors of spermatic ducts (Table 2).

Investigation of antiarrhythmic activity of compounds VI and VIII showed that compounds VI, introduced in a dose of 10 mg/kg, did not prevent experimental arrhythm. Antiarrhythmic activity was discovered only in VIIIa.

In a dose of 26 mg/kg, corresponding to one-sixth LD_{50} (LD_{50} = 162 mg/kg, intraperitoneal), VIIIa prevented arrhythm and increased the heat fibrillation threshold by three orders of magnitude (0.064 ± 0.007 and 0.204 ± 0.098; $P < 0.001$). However, at the indicated dose, the preparation gave a sharp reduction in arterial pressure and depressed the rate of heart contractions. Under similar conditions, experiments with procainamide showed similar activity at a dose of 50 mg/kg (LD_{50} = 312 mg/kg) (0.072 ± 0.001 and 0.248 ± 0.023; $P < 0.001$) [9]. However, hypotension and depressive effects on the contraction rate was weakly expressed.

The pharmacological test results have established that by comparison with Arpenal (γ-diathylaminopropyl diphenylacetate hydrochloride) [10] and γ-diethylaminopropyl α-alkoxydiphenyl acetate hydrochloride, including Eptanal [11], the new compounds VI and VIII, containing a hydroxyl group in the aminoalkanol chain, are distinguished by the absence of anti-inflammatory activity. Here, the action on the peripheral nicotine-sensitive cholinoreceptors is conserved. Further, compounds VI and VIII show adrenoreceptor blocking properties. This result indicates that phenyl esters are not necessary to influence the adrenoreceptors [12], and that it is possible to take advantage of ester derivatives of substituted acetic acids.

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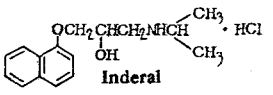
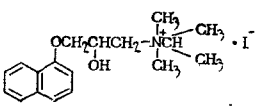
Beta-adrenergic blockers such as anaprilin (inderal) are used in conjunction with membrane stabilizers and potassium antagonists in the prevention and treatment of cardiac arrhythmia.

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



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