SYNTHESIS AND CHOLINOLYTIC PROPERTIES OF ESTERS OF 3-HYDROXYQUINUCLIDINE

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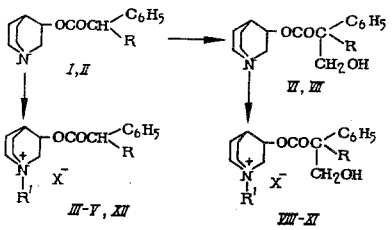
The esters of 3-hydroxyquinuclidine with aliphatic, aliphatic–aromatic, and aromatic acids, which have been synthesized, display marked pharmacological activity the character of which is determined by the structure of the acylating residue. Esters of the lower aliphatic acids proved to have cholinomimetic action, esters of aromatic and aliphatic–aromatic acids are characterized by cholinolytic properties [1].

With the aim of continuing the search for substances with high cholinolytic activity we have synthesized a series of new esters of 3-hydroxyquinuclidine and aliphatic–aromatic acids and esters containing a hydroxymethyl group together with aryl radicals in the acid portion of the molecule.

Synthesis of substances of the indicated structure was effected by reaction of 3-hydroxyquinuclidine with the acid chlorides of α-phenylbutyric and diphenylacetic acids with subsequent hydroxymethylation of 3-(α-phenylbutyryloxy)quinuclidine (I) and 3-(diphenylacetyloxy)-quinuclidine (II) with paraformaldehyde in dimethylformamide (DMF) in the presence of catalytic amounts of sodium ethylate



I, VI: R = C_2H_5; II, VII: R = C_6H_5; III, VIII: R = C_2H_5, R′ = H, X = Cl; IV, IX: R = C_2H_5, R′ = CH_3, X = I; V, XI: R = C_6H_5, R′ = CH_3, X = I; X: R = C_6H_5, R′ = H, X = Cl; XII: R = CH_3, R′ = H, X = Cl (aprolidine)

Ester (VI) was obtained in the form of a mixture of two diastereoisomers (VIa, VIb). The mixture was separated by fractional crystallization into the individual isomers from which the hydrochlorides (VIIIa, VIIIb) and methiodides (IXa, IXb) were obtained for biological study. Ester (VII) was also converted into the hydrochloride (X) and methiodide (XI).

It should be mentioned that ester (I) is a homolog of the previously studied hydrochloride of 3-(α-phenylpropionyloxy)quinuclidine (aprolidine) and the hydrochlorides (VIII) and (IX) have elements of structural similarity to atropine. Both compounds are characterized by strong cholinolytic activity.

In view of the above, pharmacological properties and primarily the influence of cholinoreactive systems of the organism have been studied for esters (III–XI) in comparison with aprolidine.

EXPERIMENTAL PHARMACOLOGICAL

Peripheral cholinolytic activity was studied according to the following effects: 1) by the reduction of the depressor reaction caused in urethane-anesthetized cats on intravenous injection of acetylcholine (0.1 μg/kg) and stimulation of the vagus; 2) by the weakening and prevention of spasm of the isolated rabbit intestinal section caused by acetylcholine ($2 \cdot 10^{-6}$ g/ml); 3) by the prevention of bronchoconstrictor action of acetylcholine in anesthetized guinea pigs [2]; doses of preparations were determined which prevented bronchospasm in 75% of

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animals on intravenous injection of acetylcholine 3-5 min before the investigated substances; 4) by the increase in pupil diameter of white mice on injection of preparations into the abdominal cavity. The action on central cholinergic systems was studied in white mice by the influence of preparations injected into the abdominal cavity on the duration and outcome of the convulsive action of arecoline (15 mg/kg subcutaneously) and nicotine (10 mg/kg subcutaneously). The LD_{50} was determined in mice on intravenous injection and calculated by the method of Kerber [3].

In a portion of the experiments the investigated compounds were compared with atropine and with aprolidine, a quinuclidine compound possessing marked cholinolytic activity [4].

It is evident from Table 1 that the investigated compounds show peripheral m-cholinolytic action. At a dose of 0.1 mg/kg, preparations prevented the development of the depressor reaction on injection of acetylcholine. They also inhibited the development of stimulation of the cardiac branch of the vagus in cats and reduced experimental bronchospasm in guinea pigs. The compounds were close in activity to aprolidine in the characteristics mentioned. Like aprolidine all tertiary derivatives at a concentration of $5 \cdot 10^{-7}$ g/ml reduced spasm of isolated rabbit intestinal sections caused by acetylcholine ($1 \cdot 10^{-6}$ g/ml) and they were significantly more active than their quaternary analogs.

All preparations showed strong mydriatic action. Compound (III), as the most active in this series, was subjected to a more detailed study of mydriatic activity in comparison with aprolidine and atropine. The mentioned compounds were injected into the abdominal cavity of white mice (0.1 ml of 0.001 % solution). As is evident from Table 1 compound (III) approached aprolidine but was two times less active than atropine in mydriatic activity.

Preparations also showed central m-cholinolytic action, however aprolidine superseded them them in this respect. Thus the most active compounds (III) and (VIIIa), in doses equal to 1/20 LD_{50} on intraperitoneal injection to white mice (5 and 15 mg/kg, respectively), completely prevented the convulsive action of arecoline. Aprolidine showed similar action at a dose of 0.4 mg/kg (LD_{50} was 122 mg/kg on injection into the abdominal cavity).

Compound (VIIIb) being an isomer of (VIIIa) was, like (X), superseded by (III), (VIIIa), and aprolidine in activity. At a dose of 1/10 LD_{50} they reduced the convulsive action of arecoline in mice and only at a dose of 1/5 LD_{50} did they prevent it completely. It was not possible to plot any dependence of central m-cholinolytic activity on the character of the acyl residues. Quaternary derivatives of the investigated 3-hydroxyquinuclidine esters were significantly less active and at doses of 1/3 LD_{50} by intraperitoneal injection did not reduce the convulsive action of arecoline. Like aprolidine no marked central n-cholinolytic action was shown. At doses of 1/3 LD_{50} injected into the peritoneal cavity lessening of the hyperkinesis caused by nicotine was not observed.

All the studied substances at toxic doses caused dyspnea, light tremor, and convulsions strengthening with increasing dose in white mice. As is evident from Table 1 the quaternary derivatives were significantly more toxic than their tertiary analogs. There was a relationship of toxicity to the change in structure of the acid portion of the molecule. Replacement of an ethyl radical by phenyl increased the toxicity of a compound. Preparaion (V) was more toxic than compound (IV) its ethyl analog. Preparation (X) was more toxic than compounds (VIIIa, VIIIb). Introduction of a hydroxymethyl radical led to a reduction of toxicity. The hydroxymethyl derivatives (VIIIa) and (VIIIb) were less toxic than (III). Compounds (V, IXb) were less toxic than (IV) and (XI) than (VIIIa). Toxicity did not correlate with the cholinolytic activity of preparations.

The carried out investigation has shown the peripheral and central cholinolytic activity of the new esters of 3-hydroxyquinuclidine which correspond basically to aprolidine, the hydrochloride of 3-(α,α-diphenylpropionyloxy)quinuclidine.

EXPERIMENTAL (CHEMICAL)

3-(α-Phenylbutyroyloxy)quinuclidine (I). A solution of α-ethylphenylacetic acid chloride (18.25 g: 0.1 mole) in chloroform (50 ml) was added with cooling to a solution of 3-hydroxyquinuclidine (12.7 g: 0.1 mole) in chloroform (100 ml). The reaction mixture was stirred while boiling for 18 h, (I) hydrochloride was filtered off, and recrystallized from isopropanol.

TABLE 1. Pharmacological Activity of Compounds (III–XI), Aprolidine, and Atropine

Compound	m-Cholinolytic activity					LD_{50} on injection to mice	
	concentration removing acetylcholine spasm of rabbit intestinal section g/ml	dose removing the depressor reaction in cats on stimulation of the vagus mg/kg	dose removing the depressor reaction on intravenous injection of acetylcholine to cats mg/kg	dose preventing bronchoconstrictor action of acetylcholine in 80% guinea pigs mg/kg	increase of pupil diameter on injection of 0.1 ml 0.001% solution to white mice	intravenously	into the abdominal cavity
III	$5 \cdot 10^{-7}$	0,1	0,1	0,1	by 1.5-fold	35	115
IV	$1 \cdot 10^{-5}$	0,1	0,1	0,1	—	11,8	57
VIIIa	$5 \cdot 10^{-7}$	0,1	0,1	0,1	—	126	285
VIIIb	$5 \cdot 10^{-7}$	0,1	0,1	—	—	94	242,5
IXa	$1 \cdot 10^{-5}$	0,1	0,1	—	—	18,5	85
IXb	$1 \cdot 10^{-5}$	0,1	0,1	—	—	18,5	78
V	$1 \cdot 10^{-5}$	0,1	0,1	0,1	—	6,6	20
X	$5 \cdot 10^{-7}$	0,1	0,1	0,1	—	58	182,5
XI	$1 \cdot 10^{-5}$	0,1	0,1	0,1	—	17,7	97,5
XII	$1 \cdot 10^{-6}$	0,1	0,05	0,05 (cats)	by 2-fold	38,7	122
Aprolidine	$5 \cdot 10^{-8}$	0,005	0,005	0,005	by 3-fold	—	—
Atropine							

TABLE 2. Esters of 3-Hydroxyquinuclidine

Compound	Yield, %	mp, °C	Found, %				Empirical formula	Calculated, %			
			C	H	N	Hal		C	H	N	Hal
III	92	131	65,98	7,65	4,62	11,34	$C_{17}H_{23}NO_2 \cdot HCl$	65.9	7,8	4,52	11,44
IV	86	126	52,71	6,45	3,55	30,28	$C_{18}H_{26}INO_2$	52.54	6,3	3,36	30,56
V	75	184	57,17	5,38	3,12	27,12	$C_{22}H_{26}INO_2$	57.0	5,65	3,02	27,37
VIIIa	95	176	63,62	7,88	4,25	10,27	$C_{18}H_{25}NO_3 \cdot HCl$	63.58	7,7	4,12	10,43
VIIIb	93	192	63,38	7,37	3,93	10,36	$C_{18}H_{25}NO_3 \cdot HCl$	63.58	7,7	4,12	10,43
IXa	84	177	51,32	6,42	3,02	28,36	$C_{18}H_{26}INO_3$	51,24	6,3	3,14	28,5
IXb	85	128	51,45	6,03	3,07	28,18	$C_{18}H_{26}INO_3$	51,24	6,3	3,14	28,5
X	89	167	67,93	6,62	3,36	8,86	$C_{22}H_{25}NO_3 \cdot HCl$	68,1	6,75	3,6	9,14
XI	78	197	55,77	5,57	2,93	25,6	$C_{23}H_{26}INO_3$	56,0	5,76	2,84	25,75

Constants, yields, and analytical results are given in Table 2.

Diastereomeric 3-(α-Hydroxymethyl-α-phenylbutyroyloxy)quinuclidine (VIa, VIb). An alcohol solution of sodium ethylate obtained from sodium (0.1 g) and ethanol (1 ml) was added as catalyst during 20 min to a stirred mixture of (I) (13.7 g: 0.05 mole) and paraformaldehyde (2 g: 0.067 mole) in dry DMF (50 ml) at 20°C. The mixture was stirred for 2 h then paraformaldehyde (1 g: 0.033 mole) and catalyst (0.5 ml) were added. The mixture was left at 20°C for 2 h, cooled with ice water, and treated with concentrated hydrochloric acid to acid reaction. The reaction mixture was evaporated in vacuum, the residue made alkaline with potassium carbonate, andextracted with chloroform. After distilling off the solvent the residue was rubbed with heptane. The solid insoluble in heptane was recrystallized from ether. Isomer (VIa) (6.3 g: 42%) was obtained mp 141–142°C. Found, %: C 71.32; H 8.45; N 4.38. $C_{18}H_{25}NO_3$. Calculated, %: C 71.26; H 8.31; N 4.61.

The heptane solution was evaporated and the residue was recrystallized from a mixture of ether and petroleum ether. Isomer (VIb) (2.4 g: 15.8%) was obtained mp 111–112°C. Found, %: C 71.48; H 8.43; N 4.55. $C_{18}H_{25}NO_3$. Calculated, %: C 71.26; H 8.31; N 4.61.

3-(α-Hydroxymethyldiphenylacetyloxy)quinuclidine (VII) was obtained in a similar manner by the reaction of 3-(diphenylacetyloxy)quinuclidine with paraformaldehyde.

Constants, yields, and analytical results for compounds (III–V, VIII–XI) are given in Table 2.

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SYNTHESIS AND ANTIARRHYTHMIC ACTIVITY OF 1,4-DIAZABICYCLO[4. m. 0]ALKANYL AMIDES OF p-NITRO- AND p-AMINOBENZOIC ACIDS

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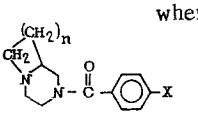
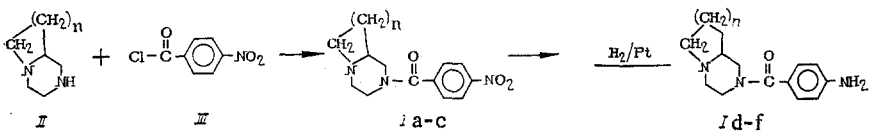
Compounds with psychotropic [1] and antianginal [2] actvity based on 1,4-diazabicyclo[4. m. 0]alkanes have been obtained previously. Data are presented in the present work on the synthesis and antiarrhythmic activity of previously unknown 1,4-diazabicyclo[4. m. 0]alkanyl amides of p-nitro- and p-aminobenzoic acids of general formula (Ia-f).



where a) X=NO$_2$, n=2
b) X=NO$_2$, n=3
c) X=NO$_2$, n=4
d) X=NH$_2$, n=2
e) X=NH$_2$, n=3
f) X=NH$_2$, n=4

Compounds (Id-f) may be considered as analogs of the antiarrhythmic preparation procainamide in which the diethylaminoethylamine residue is replaced by 1,4-diazabicyclo[4. m. 0]-alkanyl radicals. The synthesis of amides (I) was effected according to the scheme:



II III Ia-c Id-f

1,4-Diazabicyclo[4. m. 0]alkanes (II), obtained by methods described previously [3, 4], were converted into the corresponding amides (Ia-c) by acylation with p-nitrobenzoyl chloride (III). The reaction was carried out by boiling amines (II) with a small excess of acid chloride (III) in dichloroethane solution. Crystalline hydrochlorides of amides (Ia-c) were precipitated from the reaction mixture depending on the extent of heating. The bases of these amides, obtained by making alkaline aqueous solutions of the hydrochlorides with aqueous ammonia, were white crystalline substances soluble in organic solvents.

Amides (Ia-c) were reduced (the theoretical quantity of hydrogen was absorbed after 20-30 min) over a platinum catalyst in alcohol solution to the bases of the corresponding aminoamides (Id-f). These were obtained after removal of the catalyst and distilling off solvent as viscous oils crystallizing on rubbing with ether. The hydrochlorides of amides (Id-f) were very hygroscopic substances. The properties and yields of amides (Ia-f) are given in Table 1.

The obtained amides (Ia-f) were subjected to pharmacological study with the aim of clarifying their antiarrhythmic activity (procainamide was taken as standard). These compounds were tested as hydrochlorides and substances (Id-f) were prepared in dilute hydrochloric acid solution in order that the solution pH was within the limits 3.5-4.0.

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