SYNTHESIS AND PHARMACOLOGICAL INVESTIGATION OF 3-HYDROXY- AND 3-AMINOQUINUCLIDINE DERIVATIVES

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The alkaloid quinidine is one of the most effective antiarrhythmic agents. The bicyclic quinuclidine system is a structural fragment of the quinidine molecule. This fact prompted us to carry out a search for antiarrhythmic agents among a number of quinuclidine derivatives with a simpler structure than quinidine. As a result of an investigation carried out earlier, it has been established that 3-benzoyloxyquinuclidine hydrochloride (I, oxylidine) displays antiarrhythmic action on various forms of experimental arrhythmia [1].

It would be expedient to follow the variation in antiarrhythmic activity when different substituents are introduced into the benzene nucleus of I, and also to study 3-aroylaminoquinuclidines having elements of structural similarity with Novocainamid in the same direction.

For this purpose, the 3-aroyloxy-, 3-aroylamino- and 3-aralkylamino-quinuclidines shown in Tables 1 and 2 were synthesized.

Esters II, III and V-X were obtained by reacting 3-hydroxyquinuclidine with the hydrochlorides of the substituted benzoic acids in pyridine at 20° or 100°C, and ester IV, with an amino group in the benzene ring, was obtained by reducing nitro derivative III. The 3-acylaminoquinuclidines (XIV-XVIII) were synthesized by reacting 3-aminoquinuclidine with the hydrochlorides of the acids, and 3-(4-aminobenzoylamino)quinuclidine was synthesized by reducing the corresponding nitro derivative XXI.

Two methods were used to synthesize the 3-alkyl- and 3-aralkyl-aminoquinuclidines: the reduction of the 3-acylaminoquinuclidines with lithium aluminum hydride, and the reductive alkylation of 3-aminoquinuclidine with various carbonyl compounds or of the corresponding amines with 3-ketoquinuclidine. By the first method, 3-[N-(γ-phenylpropyl)amino]-quinuclidine (XX) was obtained from XV, and 3-methylaminoquinuclidine (XXIII) was obtained from 3-formylaminoquinuclidine (XXII). Amines XIX, XXIV and XXV were prepared by hydrogenation of the azamethines synthesized from 3-ketoquinuclidine and β-phenethylamine or ethanolamine and also from 3-aminoquinuclidine and veratraldehyde.

Compounds XXVI-XXXIV were synthesized in the following way. 3-[N-(β-hydroxyethyl)amino]-quinuclidine (XXIV) was converted into 3-[N-methyl-N-(β-hydroxyethyl)amino]quinuclidine (XXVI) by reaction with formalin and formic acid, and the esters XXVII and XXVIII were obtained from the latter. The dihydrochloride of 3-[N-(β-chloroethyl)amino]quinuclidine (XXIX) was formed by reaction of the dihydrochloride of XXIV with thionyl chloride, and amines XXX and XXXI were obtained by subsequent reaction of XXIX with morpholine and N-methylpiperazine. Cyanoethylation of amine XXIII led to 3-[N-methyl-N-(β-cyanoethyl)amino]quinuclidine (XXXII), the cyano group of which was reduced to aminomethyl, and amine XXXIV was obtained from 3-[N-methyl-N-(γ-aminopropyl)amino]quinuclidine (XXXIII).

The antiarrhythmic activity of compounds II-XX was studied. The investigations were carried out using I for comparison. We determined the effect on the refractory period of isolated rabbit cardiac auricle by the method of [2]; the effect on arrhythmia induced by electrical stimulation of the right cardiac auricle of urethane-narcotized cats under artificial respiration [3]; and the effect on arrhythmia in rats induced with aconite (30 μg/kg, intravenously) [4].

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TABLE 1. 3-Hydroxyquinuclidine Esters

Compound	R'	R''	R'''	Yield (in %)[1]	Melting point (degrees C)	Found (in %)				Empirical formula	Calculated (in %)			
						C	H	Cl	N		C	H	Cl	N
II	OH	H	H	53,2	243—5	59,36	6,26	12,44	4,68	$C_{14}H_{17}NO_3 \cdot HCl$	59,36	6,39	12,49	4,93
III	NO_2	H	H	83,2	228—230	53,45	5,40	11,13	8,69	$C_{14}H_{16}N_2O_4 \cdot HCl$	53,77	5,48	11,11	8,96
IV	NH_2	H	H	83,5	225—7	52,46	6,32	21,89	8,61	$C_{14}H_{18}N_2O_2 \cdot 2HCl$	52,63	6,31	22,16	8,77
V	CH_3	H	H	52,8	209—1	64,27	7,02	12,62	4,72	$C_{15}H_{19}NO_2 \cdot HCl$	63,93	7,15	12,57	4,97
VI	H	CH_3	H	56,4	168—170	—	—	12,67	4,86	$C_{15}H_{19}NO_2 \cdot HCl$	—	—	12,57	4,97
VII	H	H	CH_3	58,7	220—2	64,25	7,06	12,55	4,79	$C_{15}H_{19}NO_2 \cdot HCl$	63,93	7,15	12,57	4,97
VIII	Cl	H	H	75,5	222—4	56,01	5,70	22,92	4,52	$C_{14}H_{16}ClNO_2 \cdot HCl$	55,64	5,70	23,13	4,64
IX	Cl	H	Cl	72,7	203—5	49,86	4,57	31,67	4,32	$C_{14}H_{15}Cl_2NO_2 \cdot HCl$	49,96	4,79	31,6	4,16
X	Br	H	H	37,5	220—2	42,72	4,46	—	3,62	$C_{14}H_{16}BrNO_2 \cdot HBr$[2]	42,98	4,38	—	3,58
XI[3]	H	H	Cl	—	198—200	—	—	—	—		—	—	—	—

[1]Compounds II, VIII and X were prepared at 100°C, the rest at 20°C.
[2]Found, %: Br 41.10. Calculated %: Br 40.88.
[3]Constants and analysis results are given in [5].

It was established that I in a concentration of $3 \cdot 10^{-6}$ g/ml lengthens the refractory period by 25%. At doses of 1-10 mg/kg (intravenously) it appreciably reduces or prevents arrhythmia induced in cats by electrical stimulation of the cardiac auricle. In the case of aconite-induced disturbances of the cardiac rhythm in rats, I has a diluting effect when administered by various routes. To judge from the data obtained, I is similar to Novocainamid and quinidine in the characteristics of its action. It is active at lower doses than Novocainamid, but the ratio of effective and lethal doses (i.e., the "therapeutic breadth") is approximately the same for both compounds. In some experiments (with aconite-induced arrhythmia), I has a longer-lasting effect than Novocainamid.

Several of the esters of 3-hydroxyquinuclidine approach I in their ability to lengthen the refractory period, especially those esters containing OH, CH_3 or chlorine groups in the phenyl nucleus (II, V, VII, VIII). These compounds, however, are considerably inferior to I in the other forms of experimental arrhythmia. The remaining 3-hydroxyquinuclidine esters have only slight antiarrhythmic properties.

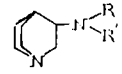
The 3-aroylamino- and 3-aralkylaminoquinuclidines (see Table 2), including XIII, which can be regarded as a cyclic analog of Novocainamid, do not possess antiarrhythmic activity.

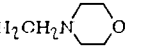
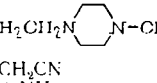
In addition to the antiarrhythmic effect of the 3-hydroxy- and 3-aminoquinuclidine derivatives, we also studied other aspects of their pharmacological activity. The hydrochloride of 3-benzoylaminoquinuclidine (XII) occupies a special place among the substances studied. Injection of XII into the veins of urethane-narcotized cats in doses of 0.5-1 mg/kg and above causes a sharp increase in arterial pressure, stimulation of respiration and contraction of the third eyelid. These reactions are suppressed by the administration of ganglion-blocking agents (1 mg/kg of hexonium), which indicates that this compound has a stimulating action on the ganglia of the vegetative nervous system and related formations. Tachyphylaxia is characteristic of compound XII, the effect decreasing on subsequent administrations.

The 3-aminoquinuclidine derivatives XIV-XX are similar to one another in pharmacological properties. At doses of 5-10 mg/kg, they have a depressant effect on the ganglia of both the parasympathetic and sympathetic nervous systems. At relatively high concentrations ($1 \cdot 10^{-5}$-$1 \cdot 10^{-5}$)*, they all achieve acetylcholine-induced spasms of an isolated section of rabbit intestine either completely or by 50%. Compared with known ganglion-blockers and cholinolytics, these compounds are of relatively low activity. The substances under investigation possess a moderate hypotensive action: in doses of 2.5-5-10 mg/kg, they reduce the arterial pressure of urethane-narcotized cats by 20-40 mm, the hypotensive effect lasting for 5-30 min; they have no effect on the central m- and n-choline-reactive systems.

*As in Russian original – Publisher.

TABLE 2. 3-Aminoquinuclidine Derivatives



Compound	R	R′	Yield (%)	Boiling or melting point of base (in deg C)[1]	Melting point of hydrochlorides (in degrees)	Found (in %)				Empirical formula	Calculated (in %)			
						C	H	Cl	N		C	H	Cl	N
XII	H	COC_6H_5	78,3	149–150[2]	256–258	—	—	13,37	10,62	$C_{14}H_{18}N_2O \cdot HCl$	—	—	13,29	10,50
XIII	H	$COC_6H_4NH_2$-4′	81,2	—	297–298	59,25	7,32	12,46	14,59	$C_{14}H_{19}N_3O \cdot HCl$	59,46	7,47	12,61	14,86
XIV	H	$COCH_2C_6H_5$	48,7	128–9[2]	—	73,77	8,48	—	11,53	$C_{15}H_{20}N_2O$	73,74	8,25	—	11,46
XV	H	$COCH_2CH_2C_6H_5$	57,4	118–9[2]	182–184	74,27	8,51	—	10,68	$C_{16}H_{22}N_2O$	74,38	8,58	—	10,83
XVI	H	$COCH(C_6H_5)_2$	68	—	252–254	67,09	7,30	9,53	7,66	$C_{21}H_{24}N_2O \cdot HCl \cdot H_2O$	67,27	7,26	9,45	7,47
XVII	H	$COCH_2OC_6H_4Cl$-4′	83,2	—	228–230	54,68	5,73	21,16	8,32	$C_{15}H_{19}ClN_2O_2 \cdot HCl$	54,39	6,07	21,41	8,45
XVIII	H	$COC_6H_3Cl_2$-2′, 4′	93,4	—	277–278	47,54	5,55	30,33	8,04	$C_{14}H_{16}Cl_2N_2O \cdot HCl \cdot H_2O$	47,55	5,41	30,07	7,92
XIX	H	$CH_2CH_2C_6H_5$	87,2	130–2(0,2)	60–62[3]	57,45	7,70	—	6,65	$C_{15}H_{22}N_2 \cdot C_4H_6O_6 \cdot H_2O$	57,27	7,59	—	7,03
XX	H	$CH_2CH_2CH_2C_6H_5$	84,8	152–4 (0,3)	242–244	60,75	8,05	21,95	8,55	$C_{16}H_{24}N_2 \cdot 2HCl \cdot 2H_2O$	60,57	8,26	22,34	8,86
XXI	H	$COC_6H_4NO_2$-4′	73,2	—	264–266	50,57	5,92	10,55	12,55	$C_{14}H_{17}N_3O_3 \cdot HCl \cdot H_2O$	50,95	6,12	10,78	12,72
XXII	H	CHO	56,8	145–6 (0,6)	—	62,15	9,34	—	18,28	$C_8H_{14}N_2O$	62,31	9,15	—	18,11
XXIII	H	CH_3	76,5	135–7 (20)	—	68,83	11,5	—	20,26	$C_8H_{16}N_2$	68,52	11,5	—	19,97
XXIV	H	CH_2CH_2OH	91	138–140 (3)	—	63,49	10,70	—	16,55	$C_9H_{18}N_2O$	63,49	10,65	—	16,45
XXV	H	$CH_2C_6H_3(OCH_3)_2$-3′, 4′	75,2	200–1 (2)	234–236[4]	69,33	8,71	—	10,15	$C_{16}H_{24}N_2O_2$	69,53	8,72	—	10,13
XXVI	CH_3	CH_2CH_2OH	87,5	131–3 (3)	—	65,25	10,90	—	15,36	$C_{10}H_{20}N_2O$	65,17	10,94	—	15,20
XXVII	CH_3	$CH_2CH_2OCOCH_3$	91,5	117–8 (0,8)	—	63,74	9,54	—	11,97	$C_{12}H_{22}N_2O_2$	63,68	9,79	—	12,37
XXVIII	CH_3	$CH_2CH_2OCOC_6H_5$	72,8	167–9 (0,5)	—	70,61	8,86	—	10,04	$C_{17}H_{24}N_2O_2$	70,79	8,38	—	9,71
XXIX	H	CH_2CH_2Cl	76	—	240–241[4]	39,77	7,56	38,9	10,30	$C_9H_{17}ClN_2 \cdot 2HCl$	39,79	7,78	39,14	10,31
XXX	H		31,6	135–7 (0,7)	193–195[5]	64,91	10,15	—	17,78	$C_{13}H_{25}N_3O$	65,23	10,52	—	17,55
XXXI	H		36,3	165–7 (2)	105–107[5]	66,41	11,38	—	22,41	$C_{14}H_{28}N_2$	66,62	11,18	—	22,19
XXXII	CH_3	CH_2CH_2CN	97,8	133–4 (0,7)	—	68,50	9,85	—	21,63	$C_{11}H_{19}N_3$	68,34	9,90	—	21,73
XXXIII	CH_3	$(CH_2)_3NH_2$	74,5	104–6 (0,6)	—	67,30	12,0	—	21,49	$C_{11}H_{23}N_3$	66,96	11,70	—	21,29
XXXIV	CH_3	$(CH_2)_3N(CH_3)_2$	65	95–7 (0,5)	—	69,35	11,71	—	—	$C_{13}H_{27}N_3$	69,27	12,07	—	—

[1]Residual pressure given in brackets (in mm)
[2]Melting point
[3]Tartrate
[4]Dihydrochloride
[5]Ditartrate

EXPERIMENTAL

3-(2-Hydroxybenzoyloxy)quinuclidine (II). Salicylyl chloride (3.3 g) is added to a solution of 2.7 g of 3-hydroxyquinuclidine in 30 ml of dry pyridine at 0°C. The solution is left for 24 h at 20°C, andthen heated for 3 h at 100°C, cooled, treated with 20 ml of a 50% potash solution, and extracted with benzene. The benzene and pyridine are distilled off under vacuum and the residue triturated with ether. The ether-insoluble residue is filtered off and the ether solution treated (until acid to Congo) with a 20% alcoholic solution of hydrogen chloride. The hydrochloride of II is obtained.

Esters III and V-X are prepared analogously to II at 20°C or with heating. The constants, analysis results, synthesis conditions and yields of esters II-X are given in Table 1.

3-(2-Aminobenzoyloxy)quinuclidine (IV). Alcohol (100 ml) and 0.3 g of platinum oxide are added to 3.45 g of 3-(2-nitrobenzoyloxy)quinuclidine (III) and the mixture shaken with hydrogen. After hydrogen absorption has ceased, the catalyst is filtered off, and the filtrate is acidified with a 20% alcoholic solution of hydrogen chloride and evaporated under vacuum. The residue is triturated with ether and the dihydrochloride of IV filtered off.

3-(4-Nitrobenzoyloxy)quinuclidine (XXI). Caustic soda (1.2 g) is added to a suspension of 3 g of 3-aminoquinuclidine dihydrochloride in 60 ml of methanol, the mixture carefully stirred, the sodium chloride filtered off, and the methanol distilled off under vacuum. Then 30 ml of anhydrous benzene is added to the residue, and a solution of 2.8 g of 4-nitrobenzoyl chloride is added with stirring and cooling. The reaction mass is boiled for 4 h, cooled, and the hydrochloride of XXI filtered off.

The 3-aroylaminoquinuclidines (XIV-XVIII) are prepared in analogous manner.

3-(4-Aminobenzoylamino)quinuclidine (XIII). Methanol (100 ml) and 0.15 g of platinum oxide are added to 3.3 g of the hydrochloride of XXI and the mixture is shaken with hydrogen. The necessary amount of hydrogen is absorbed in 10 min. The catalyst is filtered off, the methanol distilled off under vacuum, the residue triturated with acetone, and the hydrochloride of XIII isolated.

3-(γ-Phenylpropylamino)quinuclidine (XX). A portion of 3-(β-phenylpropionylamino)quinuclidine (XV) (3.45 g) is added with stirring to a suspension of 1.5 g of lithium aluminum hydride in a mixture of 50 ml of benzene and 50 ml of ether. The reaction mass is stirred while boiling for 20 h, cooled, and treated with 3 ml of water. The inorganic salts are filtered off and reextracted with benzene. The combined extracts are evaporated and the residue distilled under vacuum.

3-(β-Phenethylamino)quinuclidine (XIX). A mixture of 6.3 g of 3-ketoquinuclidine, 6.1 g of β-phenethylamine, and 100 ml of benzene is heated in an apparatus with a Dean-Stark attachment for 7 h. The benzene solution is evaporated under vacuum, the residue dissolved in 100 ml of absolute alcohol, and shaken with hydrogen in the presence of 0.2 g of platinum oxide. After the absorption of 1 g-eq of hydrogen the platinum is filtered off, the alcohol solution evaporated under vacuum, and the residue distilled.

XXIV and XXV are synthesized under analogous conditions by reaction of 3-ketoquinuclidine with ethanolamine and of 3-aminoquinuclidine with 3,4-dimethoxybenzaldehyde followed by reduction of the azamethines.

3-Formylaminoquinuclidine (XXII). A portion of formic acid (1.56 g) and 3.76 g of acetic anhydride are heated at 60°C for 2 h. The mixture is cooled to 0°C and 20 ml of benzene and 3 g of 3-aminoquinuclidine added. Two days later, the reaction mass is evaporated under vacuum, and the residue is treated with potash and extracted with chloroform.

3-Methylaminoquinuclidine (XXIII) is synthesized by reducing XXII with lithium aluminum hydride under the conditions described for the preparation of XX.

3-[N-methyl-N-(β-hydroxyethyl)amino]quinuclidine (XXVI). A portion of XXIV (8.65 g) 4.8 g of 35% formalin, 7 g of formic acid and 15 ml of water are heated at 100°C for 15 h. The reaction mass is evaporated under vacuum, and the residue treated with potash and extracted with chloroform.

3-[n-methyl-N-(β-acetoxyethyl)amino]quinuclidine (XXVII). A portion of XXVI (2 g) and 5 ml of acetic anhydride are heated at 100° for 3 h. The solution is evaporated under vacuum, and the residue made alkaline with potash and extracted with benzene.

3-[N-methyl-N-(β-benzoyloxyethyl)amino]quinuclidine (XXVIII). A portion of XXVI (2 g), 1.55 g of benzoyl chloride, and 20 ml of dry chloroform are boiled for 6 h. The reaction mass is evaporated under vacuum, and the residue dissolved in 15 ml of 10% hydrochloric acid and extracted with benzene. The acid solution is then made alkaline with potash and the reaction product extracted with benzene.

Dihydrochloride of 3-[N-(β-chloroethyl)amino]quinuclidine (XXIX). A portion of the dihydrochloride of XXIV (8.7 g) and 40 ml of thionyl chloride are boiled for 4 h. Excess thionyl chloride is distilled off under vacuum, the residue is triturated with acetone, and XXIX is filtered off.

3-[N-(β-N-morpholinoethyl)amino]quinuclidine (XXX). A portion of XXIX (3 g), 7 g of morpholine, and 20 ml of absolute alcohol are boiled for 6 h. The solution is evaporated under vacuum, and the residue stirred with 20 ml of a 25% potash solution and extracted with benzene.

Compound XXXI is obtained in an analogous manner from XXIX.

3-[N-methyl-N-(β-cyanoethyl)amino]quinuclidine (XXXII). A portion of XXIX (2 gl), 1.5 g of acrylonitrile, 2 ml of water, and 18 ml of alcohol is boiled for 5 h. The alcohol is distilled off under vacuum, and the residue treated with potash and extracted with ether.

3-[N-(γ-aminopropyl)amino]quinuclidine (XXXIII) is prepared by reducing XXXII with lithium aluminum hydride (see XX), and 3-[N-(γ-dimethylaminopropyl)amino]quinuclidine (XXXIV) is prepared by alkylating the amine XXXIII with formalin and formic acid (see XXVI).

The constants, analysis results, and yields of the 3-aminoquinuclidine derivatives (XII-XXXIV) are given in Table 2.

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