SYNTHESIS AND ANTIARRHYTHMIC ACTIVITY OF DERIVATIVES OF 3-AMINOQUINUCLIDINE AND 2-(AMINOMETHYL)QUINUCLIDINE

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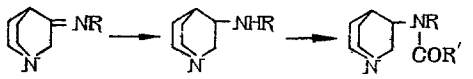
UDC 615.22:547.834.4

3-Benzoyloxyquinuclidine hydrochloride (oxylidine) displays antiarrhythmic activity in various forms of experimental arrhythmia [1]. The experimental results were substantiated by clinical evaluation [2]. Subsequently antiarrhythmic activity was also detected in 3-hydroxyquinuclidine esters with different substituents in the phenyl nucleus [3].

We decided to synthesize analogous N-acyl derivatives of 3-aminoquinuclidine and screen them for antiarrhythmic activity. 3-(Acylamino)quinuclidines are both analogs of 3-benzoyloxyquinuclidine and ethylenediamine derivatives in which one of the nitrogen atoms is incorporated in the quinuclidine ring. N,N'-Disubstituted ethylenediamines and their alkanoyl derivatives are known to have antiarrhythmic activity [4, 5].

We synthesized 3-[N-aryl(aralkyl)amino]quinuclidines and their acyl derivatives (I)-(XX) by reaction of 3-quinuclidinone with aromatic and aliphatic aromatic amines followed by reduction of the N-substituted 3-iminoquinuclidines with sodium borohydride or by catalytic reduction in the presence of platinum oxide to 3-[N-aryl(aralkyl)amino]quinuclidines (I)-(XII).* These were converted by reaction with benzoyl chloride and acetic anhydride to compounds (XIII)-(XX).



I-*XII* *XIII*-*XIX*

I, *XIII*: R=R'=C_6H_5
II, *XIV*: R=$C_6H_5CH_2$, R'=C_6H_5
III, *XV*: R=4-ClC_6H_4, R'=C_6H_5
IV, *XVI*: R=2-C_5H_4N, R'=CH_3
V, *XVII*: R=3-C_5H_4N, R'=CH_3
XVIII: R=3-C_5H_4N, R'=C_6H_5
VI, *XIX*: R=2-$CH_3OC_6H_4$, R'=C_6H_5
VII: R=4-$H_5C_2OOCC_6H_4$
VIII: R=$(C_6H_5)CH$; *IX*: R=2-ClC_6H_4
X: R=2-$CH_3C_6H_4$; *XI*: R=4-$CH_3C_6H_4$
XII, *XX*: R=2-$ClC_6H_4CH_2$, R'=CH_3

We examined the reduction of some N-acyl derivatives of 3-(N-phenylamino)quinuclidine with lithium aluminum hydride. We found that under the reaction conditions 3-(N-phenyl-N-benzoylamino)quinuclidine (XIII) underwent reductive cleavage to 3-(N-phenylamino)quinuclidine (I) and benzyl alcohol, whereas 3-(N-phenyl-N-acetylamino)quinuclidine was converted to 3-(N-phenylethylamino)quinuclidine.

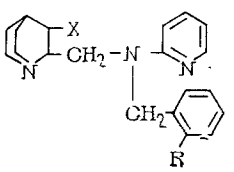
Together with the substituted 3-aminoquinuclidines we synthesized compound (XXI)-(XXIII), in which two methylene units are interpolated between the nitrogen atoms. We prepared these compounds by addition of N-(2-pyridyl)-N-benzylamines to 2-methylene-3-quinuclidinone. Reduction of ketone (XXI) with sodium borohydride gave two diastereomeric forms of alcohol

*Compounds (I), (II), and (XIII) were previously described in [6].

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 12, No. 11, pp. 56-60, November, 1978. Original article submitted April 5, 1978.

 0091-150X/78/1211-1452$07.50

(XXIII), which were separated by crystallization into the single isomers (XXIIIa) and (XXIIIb).



XXI: X=O, R=H
XXII: X=O, R=Cl
XXIII: X=(OH)H, R=H

EXPERIMENTAL PHARMACOLOGICAL PART

The antiarrhythmic effect of the synthetic compounds was assayed against aconitine arryhthmia in rats [7]. Experiments were carried out on male rats of weight 100-170 g under urethane anesthesia (1 ml of a 10% solution per 100 g weight, intraperitoneally). The electrocardiogram was recorded at lead II. Arrhythmia was induced by intravenous administration of aconitine (30 μg/kg). The preparations were tested for antiarrhythmic action in doses of 0.1, 0.2, and 0.5 LD_{50}. The toxicity was evaluated in white mice by intravenous injection; LD_{50} was calculated by Kärber's method.

Compounds (VIII), (XIII), (XV), (XVI), (XIX), and (XX) displayed antiarrhythmic action. This was most pronounced in compound (XV), which restored the disturbed rhythm of the heart in doses of 0.1-0.2 LD_{50}. However, the duration of this effect was short, lasting from 1 to 5 min, after which the rhythm was again disturbed. The antiarrhythmic action of the other compounds had an even shorter duration (several seconds). Compounds (VII), (XIV), (XVII), (XVIII), (XXI), (XXII), and (XXIII) had no effect on the experimental arrhythmia.

Thus some of these compounds do have antiarrhythmic activity, but they are less active than oxylidine.

EXPERIMENTAL CHEMICAL PART

3-(4'-Chlorophenylamino)quinuclidine (III). To a stirred solution of 3-(4'-chlorophenylamino)quinuclidine (15.15 g, 64 mmole) in ethanol (250 ml) was added under cooling with water sodium borohydride (8 g) over a period of 30 min. The mixture was left at room temperature for 20 h, whereupon alcohol was evaporated under vacuum. Water (50 ml) was added to the residue, which was extracted with chloroform. The extract was dried over magnesium sulfate. Chloroform was evaporated and the residue was distilled under vacuum or crystallized.

Compounds (VI)-(XII) were prepared in the same way.*

3-(3'-Pyridylamino)quinuclidine (V). A solution of 3-(3'-pyridylamino)quinuclidine (15 g, 74 mmole) [8] in absolute ethanol (180 ml) was stirred under hydrogen in the presence of platinum oxide (0.5 g) at room temperature. When 1 equivalent of hydrogen had been absorbed, the platinum black was filtered off. Ethanol was stripped under vacuum. Heptane (50 ml) and ether (300 ml) were added to the residue and the mixture was kept at 4°C for 48 h. The precipitate of (V) was filtered off and recrystallized.

Compound (IV) was prepared in the same way.*

3-(N-Benzyl-N-benzoylamino)quinuclidine (XIV). A mixture of 3-(N-benzylamino)quinuclidine (3 g, 14 mmole) and benzoyl chloride (15 ml) was heated at 130-140°C for 3 h. Excess benzoyl chloride was stripped under vacuum; 2 N hydrochloric acid (200 ml) was added to the residue, which was extracted with chloroform. The chloroform solution was evaporated. The residue was triturated with heptane and recrystallized.

Compounds (XV), (XIX), and (XX) were prepared in the same way.

3-[N-(3'-Pyridyl)-N-benzoylamino]quinuclidine (XVIII). A solution of (V) (2 g, 10 mmole) and benzoyl chloride (1.4 g, 10 mmole) in pyridine (25 ml) was heated at 100°C for 6 h. The reaction mixture was then evaporated under vacuum. The residue was triturated with ether and recrystallized from acetone–alcohol to give the hydrochloride of (XVIII).

*The starting 3-(arylamino)quinuclidines have been described.

TABLE 1. Properties of Compounds (III)-(XX)

Compound	Yield, %	Boiling point, °C (mm Hg) or melting point of base, °C	Melting point of salt, °C	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
III	59	109—11[a]		66,1	7,4	11,7	$C_{13}H_{17}ClN_2$	66,0	7,2	11,8
IV	77	108—10[b]		70,6	8,4	20,8	$C_{12}H_{17}N_3$	70,9	8,4	20,7
V	88	100—2[c]		65,0	8,5	19,1	$C_{12}H_{17}N_3$	65,2	8,7	19,0
VI	86	164—6 (1,7)		72,5	8,9	12,1	$C_{14}H_{20}N_2O$	72,4	8,7	12,1
VII	84	105—6[d]		70,3	8,2	10,2	$C_{16}H_{22}N_2O_2$	70,1	8,1	10,2
VIII	36	85—6[a]		82,1	8,4	9,6	$C_{20}H_{24}N_2$	82,2	8,3	9,5
IX	66	102—3[b]		63,7	7,6	11,1	$C_{13}H_{17}ClN_2 \cdot 0{,}5H_2O$	63,5	7,4	11,4
X	65	137—9 (0,8)		77,5	9,6	12,8	$C_{14}H_{20}N_2$	77,8	9,3	12,9
XI	73	149—50 (0,6)		77,6	9,6	12,8	$C_{14}H_{20}N_2$	77,8	9,3	12,9
XII	74	164—5 (1,3)		67,1	7,7	11,1	$C_{14}H_{19}ClN_2$	67,0	7,6	11,1
XIV	75	106—8[a]	209—211[g]	78,7	7,7	8,6	$C_{21}H_{24}N_2O$	78,7	7,5	8,7
XV	30	110—12[a]	130—132[g]	70,5	6,2	8,3	$C_{20}H_{21}ClN_2O$	70,5	6,2	8,2
XVI	79	104—6[a]	180—181[e]	50,0	6,9	12,7	$C_{14}H_{19}N_3O \cdot 2HCl \cdot H_2O$	50,0	6,9	12,5
XVII	75	160—2 (0,5)	78—79[f]	48,5	6,1	—	$C_{14}H_{19}N_3O \cdot 2C_4H_6O_6$	48,4	5,7	—
XVIII	57		169—170[g]	66,4	6,7	12,3	$C_{19}H_{21}N_3O \cdot HCl$	66,4	6,4	12,2
XIX	90		207—208[g]	67,5	6,5	7,8	$C_{21}H_{24}N_2O_2 \cdot HCl$	67,6	6,7	7,5
XX	63		209—210[g]	58,4	6,9	8,3	$C_{16}H_{21}ClNO \cdot HCl$	58,4	6,7	8,5

Legend. a) From heptane; b) from heptane—ether; c) from ethyl acetate; d) from ether; e) from dihydrochloride; f) from ditartrate; g) from hydrochloride.

3-[N-3'(Pyridyl)-N-acetylamino]quinuclidine (XVII). A solution of amine (V) (2 g, 10 mmole) in acetic anhydride (25 ml) and pyridine (50 ml) was heated at 100°C for 6 h. The mixture was then evaporated under vacuum. Residual pyridine was removed by vacuum distillation with xylene. The residue was made alkaline with 25% potassium carbonate solution and extracted with chloroform. The solvent was evaporated and the residue was distilled under vacuum.

Compound (XVI) was prepared in the same way.

The physical constants, yields, and analyses of compounds (III)-(XII) and (XIV)-(XX) are summarized in Table 1.

2-[N-(2'-Pyridyl)-N-benzylaminomethyl]-3-quinuclidinone (XXI). A mixture of 2-methylene-3-quinuclidinone (3.95 g, 29 mmole) and 2-(benzylamino)pyridine (5.35 g, 29 mmole) in methanol (40 ml) was refluxed for 25 h. The solution was then evaporated under vacuum. Ether was added to the oily residue until it dissolved and then heptane was added until the solution become cloudy. After standing at 4°C for 48 h the residue was filtered off and recrystallized from ethanol. The yield was 6.1 g (65.5%), mp 144-146°C. Found, %: C 75.06; H 7.26; N 13.28. $C_{20}H_{23}N_3O$. Calculated, %: C 74.86; H 7.21; N 13.08. The dihydrochloride had mp 209-211°C. Found, %: C 60.74; H 6.55; N 10.64. $C_{20}H_{23}N_3O \cdot 2HCl$. Calculated, %: C 60.92; H 6.41; N 10.70.

2-[N-(2'-Pyridyl)-N-(2'-chlorobenzyl)aminomethyl]-3-quinuclidinone (XXII) was prepared like compound (XXI), mp 152-153°C (from ethanol). Found, %: C 67.27; H 6.22; N 9.72; Cl 12.19. $C_{20}H_{22}ClN_3O$. Calculated, %: C 67.47; H 6.25; Cl 11.82; N 10.0.

2-[N-(2'-Pyridyl)-N-benzylaminomethyl]-3-hydroxyquinuclidine (XXIIIa) and (XXXIIIb). To a suspension of (XXI) (2.5 g, 7.8 mmole) in methanol (50 ml) was added sodium borohydride (1.85 g). The mixture was left at room temperature for 20 h. The resulting precipitate was filtered off and washed with ethanol to give diastereomer (XXIIIa) (0.9 g), with mp 181-183°C (from ethanol). Found, %: C 74.47; H 7.78; N 12.92. $C_{20}H_{25}N_3O$. Calculated, %: C 74.20; H 7.78; N 12.92. The mother liquor after removal of isomer (XXIIIa) was evaporated. Water (20 ml) was added to the residue, which was extracted with chloroform. The oily residue after removal of the chloroform was triturated with heptane, the precipitate was filtered off and recrystallized from acetone to give the second isomer (XXIIIb) (0.96 g) with mp 146-148°C. The total yield of both isomers (XXIII) was 1.86 g (74.4%). Found, %: C 74.49; H 7.63; N 12.83. $C_{20}H_{25}N_3O$. Calculated, %: C 74.20. H 7.78; N 12.92.

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