UDC 547.834.4

SYNTHESIS OF DERIVATIVES OF 3-AMINO- AND 3-AMINOMETHYLQUINUCLIDINE

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 2, No. 2, pp. 243-249, 1966

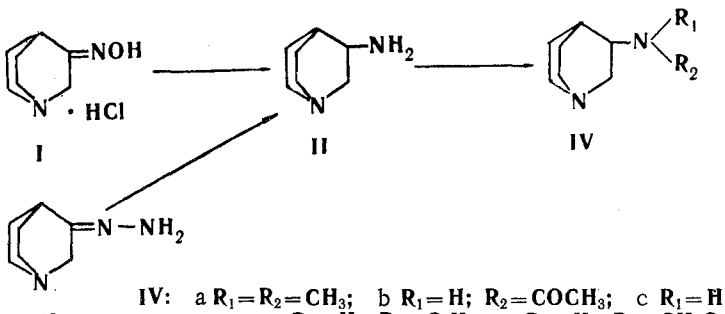
Various methods of preparing 3-aminoquinuclidine from quinuclid-3-one oxime and hydrazone are developed. Quinuclidine derivatives with a substituted amino group at position 3 are synthesized.

Researches on the synthesis and biological investigation of 3-substituted quinuclidine, mainly ethers of 3-hydroxyquinuclidine and bisquaternary salts of quinuclidine, made it possible to bring to light some pharmacologically active compounds in this series [1, 2]. In this connection we thought it of interest to continue the search for biologically active compounds among other 3-substituted quinuclidines, in particular, compounds where position 3 in the quinuclidine ring is substituted by an amino group.

The present paper gives results relating to synthesis of 3-aminoquinuclidine, 3-alkyl(aryl) aminoquinuclidines, and some related compounds.

3-Aminoquinuclidine was first prepared by reducing quinuclid-3-one (I) oxime in hydrochloric acid solution in the presence of a platinum catalyst [3]. As our research showed, under these conditions, and as the result of hydrogenolysis, a considerable amount of 3-hydroxyquinuclidine is formed along with 3-aminoquinuclidine (II).

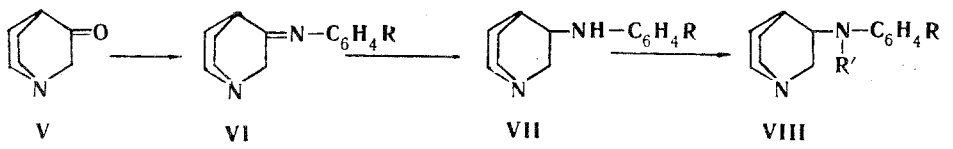
Reduction of the oxime of quinuclid-3-one with zinc dust in hydrochloric acid also gives a mixture of 3-hydroxyquinuclidine and II, the yield of the latter (19.6%) being somewhat higher than when using the first variant. When I is reduced catalytically in neutral solution with Raney nickel, hydrogenolysis of the oxime and formation of 3-hydroquinuclidine is also observed, but it proceeds to a considerably less extent than in the hydrochloric acid reduction. In this method the yield of 3-aminoquinuclidine amounted to 46.2%.



IV: a $R_1=R_2=CH_3$; b $R_1=H$; $R_2=COCH_3$; c $R_1=H$; $R_2=COC_6H_5$; d $R_1=H$; $R_2=C_2H_5$; e $R_1=H$; $R_2=CH_2C_6H_5$.

We also prepared 3-aminoquinuclidine by reducing the hydrazone of quinuclid-3-one (III) with lithium aluminum hydride (28% yield), as well as catalytically, in the presence of Raney nickel catalyst, at 100°C and under 30 atm hydrogen pressure. In this latter case the yield of II reached 75%. Interesting results were obtained by heating the hydrazone of quinuclid-3-one in solution in ethanol or benzyl alcohol, with Raney nickel catalyst. Under those conditions, reduction of the C=N bond, and hydrogenolysis of the N—N one, took place, to the accompaniment of alkylation of the amino group by the alcohol in which the reaction was run. The structures of the resultant 3-ethyl(benzyl) aminoquinuclidines were demonstrated by their identity with the compounds, formed by reducing 3-acetyl(benzoyl) aminoquinuclidines with lithium aluminum hydride.

Quinuclid-3-one (V) readily undergoes reaction with aromatic amines in the presence of catalytic amounts of glacial acetic acid, or p-toluenesulfonic acid. Under those conditions there is no reaction with piperidine or pyrrolidine. The Schiff's bases are decomposed even at room temperature by ethanolic hydrogen chloride; they do not react with Grignard reagents. Reduction of VI with lithium aluminum hydride or catalytically in the presence of platinum, gives 3-arylaminoquinuclidines (VII).



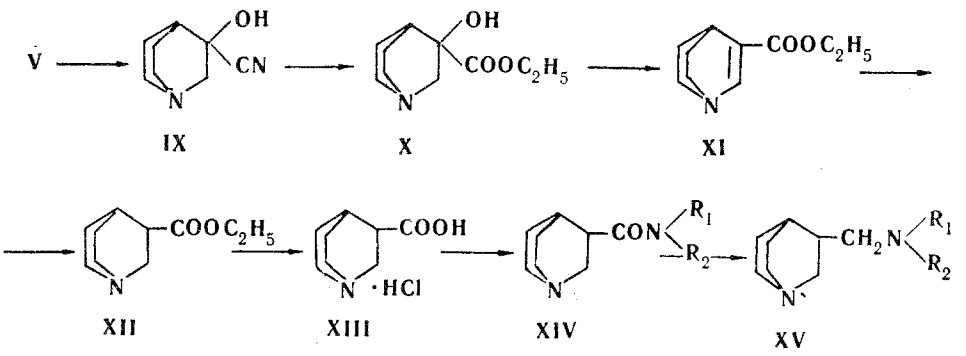
V VI VII VIII

VI and VII: a R=H; b R=2-CH_3; c R=4-CH_3:
VIII: a R=H; R^1=$COCH_3$; b R=H; R^1=COC_6H_5.

Reaction of 3-phenylaminoquinuclidine (VIIa) with acetic anhydride and benzoyl chloride gave 3-[N-acetyl (benzoyl) phenylamino]-quinuclidines (VIIIa, b).

3-Aminomethylquinuclidine derivatives (XV) are formed by lithium aluminum hydride reduction of amides of quinuclidine-3-carboxylic acid (XIV), which in their turn are prepared from quinuclidine-3-carboxylic acid (XIII), via the acid chloride.

Acid XIII is synthesized thus [4]:



IX X XI XII XIII XIV XV

We synthesized the starting compound, 3-hydroxy-3-cyanoquinuclidine (IX), utilizing the reaction of quinuclid-3-one (V) with acetonecyanohydrin instead of potassium cyanide, used in the paper mentioned. The hydroxynitrile IX was further converted to the ethyl ester of 3-hydroxyquinuclidine-3-carboxylic acid (X), which, according to our observations, is more stable (does not give a betaine structure under the reaction conditions) and is obtained in better yield than the corresponding methyl ester. The scheme described was used to synthesize quinuclidine-3-carboxylic acid (XIII) and its ethyl ester (XII) from X.

Investigation of the biological properties of the derivatives of 3-amino- and 3-aminomethylquinuclidine failed to reveal compounds with marked pharmacological activities.

Experimental

Synthesis of 3-aminoquinuclidine from quinuclid-3-one oxime. a) 3.18 g (0.056 mole) KOH and 2 g Raney Ni catalyst were added to a suspension of 10 g (0.056 mole) quinuclid-3-one oxime hydrochloride (I) in 100 ml dry ethanol, and the mixture hydrogenated in an autoclave at 100°, under 30 atm hydrogen pressure. After hydrogen uptake had ceased, the catalyst was filtered off, the filtrate evaporated under reduced pressure, and the solid residue extracted with ether. The ether solution was dried over K_2CO_3, filtered, and treated with ethanolic hydrogen chloride. The precipitate of 3-aminoquinuclidine dihydrochloride was recrystallized from dry MeOH. Yield 5.1 g (46.2%) colorless crystals, readily soluble in water, sparingly soluble in acetone and ether, mp 285–287° C (decomp). Found: C 42.25; H 8.24; Cl 35.68; N 14.00%. Calculated for $C_7H_{14}N_2 \cdot 2HCl$: C 42.21; H 8.09; Cl 35.61; N 14.07%.

b) 20 g (0.3 g at) Zn dust was added over 5 hr to a solution of 5 g (0.028 mmole) I in 20 ml 17% hydrochloric acid with stirring, the temperature being held at 25–30° C. The reaction products were held at 20–25° for 20 hr, made alkaline with 50% NaOH, and extracted with ether. Acidification of the ether solution gave a precipitate which was a mixture of 3-hydroxyquinuclidine hydrochloride and II dihydrochloride. Recrystallization from MeOH gave 1.1 g (19.6%) II dihydrochloride, mp 285–287° C (decomp).

c) 5 ml concentrated hydrochloric acid and 0.5 g Pt oxide were added to a solution of 5 g (0.028 mole) I and 83 ml water. The mixture was shaken in hydrogen at a pressure of 40–60 cm water, and room temperature. After the

Table 1

Derivatives of 3-Aminoquinuclidine

Compound No.	R_1	R_2	Bp, °C (mm Hg) or Mp, °C	Mp of salts, °C	Formula	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N	Yield, %
IVa	CH_3	CH_3	77—78 (7)	253—254c	$C_9H_{18}N_2 \cdot 2HCl$	47.26	8.73	12.30	47.58	8.87	12.33	68
IVб	H	$COCH_3$	172—173 (3)	—	$C_9H_{16}N_2O$	63.90	9.60	16.22	64.25	9.58	16.65	59.2
IVв	H	COC_6H_5	159—160	—	$C_{14}H_{18}N_2O$	72.99	7.80	12.22	73.01	7.88	12.16	47.6
IVг	H	C_2H_5[a]	100—101 (11)	—	$C_9H_{18}N_2$	70.07	11.84	18.34	70.12	11.75	18.16	74
IVд	H	$CH_2C_6H_5$[b]	156—157 (2)	240—242c	$C_{14}H_{20}N_2$	77.48	9.43	12.94	77.73	9.32	12.95	62.4
VIIa	H	C_6H_5	112—114	205—207d	$C_{13}H_{18}N_2 \cdot C_7H_6O_3$	69.98	7.15	7.85	70.56	7.08	8.23	63.3
VIIб	H	$C_6H_4CH_3$-2	128—130 (0.6)	115—116d	$C_{14}H_{20}N_2 \cdot C_7H_6O_3$	71.15	7.43	8.16	71.16	7.39	7.91	73.5
VIIв	H	$C_6H_4CH_3$-4	77—78	180—181d	$C_{14}H_{20}N_2$	77.88	9.06	13.08	77.73	9.32	12.95	64.5
VIIIa	$COCH_3$	C_6H_5	228—230 (1)	—	$C_{15}H_{20}N_2O$	—	—	11.93	—	—	11.47	87.5
VIIIб	COC_6H_5	C_6H_5	112—114	—	$C_{20}H_{22}N_2O$	78.12	7.15	9.25	78.40	7.23	9.14	55.5

a) Prepared by reducing IVb. b) Prepared by reducing IVc.
c) Hydrochloride; d) Salicylate.

required quantity of hydrogen had been absorbed, the platinum black was filtered off, and the filtrate evaporated under reduced pressure. Then the solid residue was triturated with Me_2CO, and the insoluble material filtered off. The insoluble material was treated with ethanolic KOH (amount of alkali calculated on the Cl content of the precipitate), the KCl filtered off, the EtOH solution evaporated under reduced pressure, and the residue extracted with benzene. After evaporating the benzene, the 3-aminoquinuclidine distilled over at 35–40° C/0.3 mm. Yield 0.7 g material, from which was obtained II dihydrochloride, mp 285–287° C (decomp).

From the Me_2CO solution was isolated 3-hydroxyquinuclidine hydrochloride, mp 300–302° C.

Synthesis of 3-aminoquinuclidine from quinuclid-3-one hydrazone. a) 5 g (0.036 mole) quinuclid-3-one hydrazone (III) was added to a suspension of 2.74 g (0.072 mole) lithium aluminum hydride in 70 ml ether and 70 ml benzene, and the mixture stirred and refluxed for 18 hr. The reaction products were cooled, treated with 6 ml H_2O, the inorganic salts filtered off, and carefully washed with benzene. After distilling off the solvents, the residue was distilled under reduced pressure. Yield 2 g (28%) II dihydrochloride, mp 284–285° C (decomp). Found: C 42.55 H 7.80; Cl 36.06; N 14.16%. Calculated for $C_7H_{14}N_2 \cdot 2HCl$: C 42.21; H 8.09; Cl 35.61; N 14.07%.

b) A mixture of 10 g (0.072 mole) III, 3 g Raney Ni catalyst, and 100 ml dry EtOH was subjected to reduction in an autoclave at 100° and 30 atm hydrogen. The products were worked up in the way described above, to give 12 g of precipitate, which was recrystallized from MeOH. Yield of II dihydrochloride, 10.2 g (75%), mp 284–286° (decomp).

c) 3-Benzylaminoquinuclidine (IVe). 4g (0.029 mole) III, 40 g Raney Ni catalyst, and 100 ml dry benzyl alcohol were refluxed together for 6 hr. Then the catalyst was filtered off, and washed with benzyl alcohol. The total filtrate was extracted with 17% hydrochloric acid. Evaporation of the hydrochloric acid solution under reduced pressure gave 7.5 g (90.5%) IVe dihydrochloride, as colorless crystals mp 240–242° C (ex MeOH + Me_2CO). Found: C 54.96; H 7.90; Cl 23.09; N 9.50%. Calculated for $C_{14}H_{20}N_2 \cdot 2HCl$: C 54.72; H 7.87; Cl 23.08; N 9.12%. Mixed mp with a specimen prepared from IVc undepressed. 3-Aminoquinuclidine (II). 1 g (0.0046 mole) IVe, prepared as described above, 0.2 g Pd chloride, and 20 ml 4% hydrochloric acid were shaken together in an atmosphere of hydrogen at room temperature. Yield 0.9 g (98.5%) II dihydrochloride, mp 284–285° C (decomp).

3-Ethylaminoquinuclidine (IVd). 7.4 g (0.053 g) III, 70 g Raney Ni catalyst, and 200 ml dry EtOH were refluxed together for 15 hr. Continuous evolution of NH_3 was observed. 70 g catalyst was added, and the mixture refluxed for 15 hr further. The catalyst was filtered off, the filtrate evaporated to dryness under reduced pressure, the residue treated with 50% K_2CO_3 solution, and then extracted with benzene. Yield 5 g (90.2%) IVd, colorless mobile liquid, bp 97–99° (10 mm). Dipicrate, yellow crystals, mp 192–194° C (Me_2CO + EtOH). Found: N 18.00%. Calculated for

$C_9H_{18}N_2 \cdot 2C_6H_3N_3O_7$: N 18.28%. Undepressed mixed mp with a specimen prepared from IVb.

3-Acetylaminoquinuclidine (IVb). 3.2 g (0.025 mole) 3-aminoquinuclidine and 20 ml Ac_2O were heated together for 1 hr at 100°C. The solution was evaporated under reduced pressure, made alkaline with K_2CO_3, and extracted with $CHCl_3$, to give 2.5 g (59.2%) IVb.

Yield, constants, and analytical data for the compound and for other derivatives of 3-aminoquinuclidine are given in Table 1.

3-Benzoylaminoquinuclidine (IVc). 1.96 g (0.049 mole) NaOH was added to a solution of 3 g (0.015 mole) II dihydrochloride in 20 ml water, and with ice cooling, 2.12 g (0.015 mole) benzoyl chloride added over 30 min. After that the mixture was stirred for a further 30 min, and the reaction products then extracted with $CHCl_3$. After distilling off the latter, the solid residue was recrystallized from benzene.

$LiAlH_4$ reduction of compounds IVa and IVb as described above gave 3-ethyl (benzyl) aminoquinuclidines (IVc and IVd).

3-Dimethylaminoquinuclidine (IVa). 1.2 g (0.0095 mole) II, 1.8 g (0.022 mole) 37% formalin, and 2.64 g (0.057 mole) formic acid were heated together for 16 hr at 100° C. The reaction products were evaporated under reduced pressure, made alkaline with K_2CO_3, and then extracted with benzene. Methiodide, mp 224–226° C. Found: I 58.07%. Calculated for $C_{11}H_{24}I_2N_2$: I 57.99%.

3-Phenyliminoquinuclidine (VIa). 10 g (0.08 mole) V, 50 ml aniline, 100 ml dry toluene, and 10 drops glacial AcOH were heated together for 12 hr in a Dean and Stark apparatus. The solution was evaporated under reduced pressure, and the residue distilled, to give 13.24 g (82.8%) VIa, bp 130° C (1 mm), mp 78–79° C. Found: C 77.76; H 7.86; N 14.07%. Calculated for $C_{13}H_{16}N_2$: C 77.95; H 8.05; N 13.99%. Salicylate, mp 172–174° VIb and VIc were made similarly.

3-(o-Methylphenyl) iminoquinuclidine (VIb). Viscous liquid, bp 136–138° C (1.2 mm). Found: C 78.51; H 8.46; N 13.10%. Calculated for $C_{14}H_{18}N_2$: C 78.46; H 8.47; N 13.07%. Salicylate mp 200° C (decomp).

3-(p-Methylphenyl) iminoquinuclidine (VIc). Mobile yellow liquid, bp 132–134° C (2 mm). Salicylate, mp 200° C (decomp). Found: C 71.62; H 6.95; N 8.01%. Calculated for $C_{14}H_{18}N_2 \cdot C_7H_6O_3$: C 71.57; H 6.86; N 7.98%.

3-(β-Naphthyl) iminoquinuclidine (VId). 5g (0.04 mole) V, 10 g (0.07 mole) β-naphthylamine, 25 ml xylene, and a few crystals of p-toluenesulfonic acid were heated together for 25 hr in a Dean and Stark apparatus to give 6 g (60%) VId, bp 175–180°C (0.5 mm). Salicylate, mp 150–152° C. Found: C 74.10; H 6.43; N 6.88%. Calculated for $C_{17}H_{18}N_2 \cdot C_7H_6O_3$: C 74.20; H 6.23; N 7.21%.

3-Phenylaminoquinuclidine (VIIa). a) 2g (0.01 mole) VIa, 1 g (0.026 mole) $LiAlH_4$, 30 ml dioxane, and 30 ml ether were refluxed together for 20 hr. The products were worked up in the way described above.

b) 2 g (0.01 mole) VIa, 0.1 g Pt oxide, and 20 ml EtOH were shaken together in hydrogen at room temperature. After 1 mole of hydrogen had been absorbed, the Pt was filtered off, the filtrate evaporated under reduced pressure, and the solid residue recrystallized from ether. Compounds VIIb and VIIc were prepared similarly.

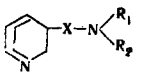
3-(N-Acetylphenylamino) quinuclidine (VIIIa). 5 g (0.025 mole) VIIa and 50 ml Ac_2O were refluxed together for 4 hr. The solution was then evaporated under reduced pressure, the residue made alkaline with K_2CO_3, and extracted with $CHCl_3$.

3-(N-Benzoylphenylamino) quinuclidine (VIIIb). 4 g (0.02 mole) VIIa and 8 ml benzoyl chloride were heated together for 4 hr at 100° C. 30 ml water was added to the reaction products after cooling, and excess benzoyl chloride extracted with benzene. Then the aqueous layer was made alkaline with K_2CO_3, and the VIIIb extracted with benzene.

3-Hydroxy-3-cyanoquinuclidine (IX). 24.6 g (0.29 mole) acetonecyanohydrin was added over 1 hr, with ice water cooling and stirring to a solution of 30 g (0.24 mole) V in 30 ml water. The mixture was stirred for 4 hr at room temperature, the precipitate formed filtered off, washed with water, and dried, yield 33 g (90.3%) IX, mp 168–170° C [4].

Ethyl 3-hydroxyquinuclidine-2-carboxylate (X). a) 33 g (0.216 mole) IX, 330 ml concentrated HCl, and 660 ml glacial AcOH were refluxed together for 20 hr. The solution was then evaporated under reduced pressure, the residue dried, and esterified by heating with 300 ml 10% ethanolic HCl, to give 32 g (74%) X, mp 118–120° C (ex Me_2CO). The ester distils over on heating under reduced pressure. Found: C 60.22; H 8.64; N 7.37%. Calculated for $C_{10}H_{17}NO_3$: C 60.29; H 8.60; N 7.03%.

Table 2



3-Aminomethylquinuclidine Derivatives

X	R_1	R_2	Bp, °C (pressure mm), mp, °C	Dihydrochloride mp, °C	Formula	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N	Yield, %
CO	CH_3	CH_3	120 (1)	—	$C_{10}H_{18}N_2O$	—	—	15.70	—	—	15.37	63
CO	C_2H_5	C_2H_5	124 (1)	—	$C_{12}H_{22}N_2O$	—	—	13.08	—	—	13.32	68.4
CO	$R_1-R_2=(CH_2)_5$		172 (0.3)	—	$C_{13}H_{22}N_2O$	—	—	12.95	—	—	12.61	56.4
CO	H	$C_5H_4N=2$	166—167	—	$C_{13}H_{17}N_3O$	67.35	7.25	18.20	67.52	7.41	18.17	59.3
CH_2	CH_3	CH_3	97—98 (8)	266—268	$C_{10}H_{20}N_2 \cdot 2HCl$	49.79	9.37	11.73	49.79	9.19	11.61	65
CH_2	C_2H_5	C_2H_5	80 (1)	220—221	$C_{12}H_{24}N_2 \cdot 2HCl$	53.85	9.53	10.45	53.53	9.73	10.44	69.4
CH_2	$R_1-R_2=(CH_2)_5$		115 (1)	271—273	$C_{13}H_{24}N_2 \cdot 2HCl$	55.39	9.08	9.70	55.50	9.32	9.96	58.2

b) A current of dry HCl was passed for 5 hr into a boiling solution of 20 g (0.132 mole) IX in 200 ml EtOH. The products were evaporated under reduced pressure, made alkaline with K_2CO_3, and extracted with $CHCl_3$, to give 26.2 g (81%) X.

Ethyl quinuclidine-3-carboxylate (XII). 12.2 g (0.061 mole) X and 70 ml $SOCl_2$ were refluxed together for 24 hr. The solution was evaporated under reduced pressure, the residue made alkaline and then extracted with ether, to give 9 g (81.1%) 3-carboethoxy-1-azabicyclo [2.2.1] oct-2-ene (XI), a colorless liquid, bp 120–121° C (10 mm). 14 g (0.077 mole) XI, 200 ml 4% ethanolic HCl, and 0.5 g Pt oxide were shaken together in hydrogen, to give 11.7 g (82.3%) XII, a colorless liquid, bp 123–124° C (15 mm). Found: C 65.40; H 9.29%. Calculated for $C_{10}H_{17}NO_2$: C 65.54; H 9.35%.

Saponification of XII gave quinuclidine-3-carboxylic acid hydrochloride (XIII) mp 271–273° C (decomp).

N, N-dimethyl quinuclidine-3-carboxamide. 5 g (0.026 mole) XIII and 50 ml $SOCl_2$ were heated together for 10 hr at 65–70° C. The solution was evaporated under reduced pressure, and the residue added in portions of 100 ml 20% solution of Me_2NH in ether. The reaction products were treated with 50 ml 50% K_2CO_3 solution, the ether layer separated off, and the aqueous layer extracted with $CHCl_3$. The residue obtained from the extracts was distilled under reduced pressure. Other amides (XIV) of quinuclidine-3-carboxylic acid were prepared similarly. They were further reduced with $LiAlH_4$, as described above, to give substituted 3-aminomethylquinuclidines (XV).

Data for compounds XIV and XV are given in Table 2.

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21 December 1964

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