SYNTHESIS OF 3-ALKYL(ARYL)-3-AMINOQUINUCLIDINES

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A series of 3-alkyl(aryl)-3-aminoquinuclidines was synthesized by means of the interaction between 3-alkyl(aryl)-3-oxyquinuclidines and acetonitrile in the presence of concentrated sulfuric acid with subsequent hydrolysis of the 3-alkyl(aryl)-3-acetaminoquinuclidines. It was shown that in addition to acetamino derivatives 3-alkyl- Δ^2 dehydroquinuclidines and 3-alkylidenequinuclidines are formed, the structure of which was established by the method of NMR.

In order to synthesize derivatives of quinuclidine, which contain an amino group in the third position of the ring in addition to the alkyl(aryl) substitute, the Ritter reaction was used [1]—the interaction between 3-alkyl-3-oxyquinuclidines and nitriles in the presence of conc H_2SO_4 with subsequent hydrolysis of the acylamino derivatives to the 3-alkyl(aryl)-3-aminoquinuclidines.



3-Benzyl-3-oxyquinuclidine (Ia) was subjected to interaction with acetonitrile, acrylonitrile, and benzyl cyanide with the components present in various ratios and under different temperature conditions. Only in that case in which acetonitrile was used was 3-benzyl-3-acetaminoquinuclidine (IIa) obtained with a yield of 17.5% in addition to a significant quantity of 3-benzilidinequinuclidine (VIIIa), 68%. During the interaction between 3-phenyl-3-oxyquinuclidine (Ib) and acetonitrile in the presence of conc H₂SO₄, a mixture of 3-phenyl-3-acetaminoquinuclidine (IIb), 60%, and 3-phenyl- Δ^2 -dehydroquinuclidine (VIIa), 38%, is also formed. During the reaction between compound Ib and acrylonitrile and subsequent saponification of the products of the reaction, only a small yield of the amide IIIb was isolated. The poorly defined course of the Ritter reaction was also encountered in the case of 3-methyl- (Ic) and 3-butyl-3-oxyguinuclidines (Id). Under the above-mentioned conditions, compound Ic was converted into 3-methyl-3-acetaminoquinuclidine (IIc), 50%, and a mixture of 3-methyl- Δ^2 -dehydroquinuclidine (VIIb) and 3-methylenequinuclidine (VIIIb), 3%. 3-Butyl-3-acetaminoquinuclidine (IIId), 10%, and

3-butylidenequinuclidine (VIIIc), 50%, were isolated from compound Ic. In addition to the above-mentioned compounds, a small quantity of acetamide was invariably formed.

The structures of the unsaturated compounds, formed under the conditions of the Ritter reaction, were studied by means of NMR* spectra (see Table 1).

It follows from Table 1 that the spectra of the 3substituted quinuclidine can essentially be distinguished in relation to whether the double bond is endo-(VIIa, VIIb) or exocyclic (A, VIIIa, VIIIc).

1. The proton in a double bond $(C_2 - H)$ in compounds with an endocyclic bond is situated in a weaker field than the analogous proton $(C_9 - H)$ in compounds with an exocyclic double bond (VIIa and VIIIa; VIIb and A). This can probably be explained by the induction effect of the nitrogen atom.

2. In compounds with an exocyclic bond, all four protons at positions C_6 and C_7 differ very insignificantly in relation to the chemical displacements. Thus, the spectrum of these protons has the appearance of a nonsymmetrical triplet with widened lines, and the distance between the outer peaks is 15–17 Hz. On the other hand, in compounds with an endocyclic double bond, the spectrum of the protons at positions C_6 and C_7 extends to 60–65 Hz, which indicates the significant inequivalence of the two protons in each of the groups C_6 —H₂ and C_7 —H₂ as a consequence of the difference in orientation of these protons in relation to the diamagnetically anisotropic endocyclic bond, C=C.

3. The signal from the C_2 - H_2 protons, representing the widened peak in the region, $\delta \approx 3.5$ ppm, is also extremely characteristic for the compounds with an exocyclic double bond.

On the basis of the above-mentioned data, one might conclude that the unsaturated compound, obtained from compound Ia by the Ritter reaction, is a mixture of two geometric isomers of 3-benzilidenequinuclidine (VIIIa).

By comparing the values of chemical displacements of protons into positions C_4 and C_9 in compound VIIIa, with corresponding values for the 3-ethylidenequinuclidines and derivatives [3], one may conclude that in the isomer with $\delta_{C_4H} = 2.40$ ppm the substitute at C_9 is situated in the trans position in relation to C_4 . The relative content of this isomer is approximately 40-45%. The isomer with $\delta_{C_4H} = 2.95$ ppm corresponds to the cis-isomer.

^{*}NMR spectra were determined in the apparatus JNM-4H-100 with a working frequency of 100 MHz. Tetramethylsilane was used as the internal standard.

Table 1

NMR	Snectra	\mathbf{of}	3-Alkylideneguinuclidineg	and	Λ^2 -Dehydroquinuclidines
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		isplacen	lacements δ, ppm					
Com- pound	Structural formula	C ₅ —H ₂ ; C ₈ —H ₂	C ₆ —H ₂ ; C ₇ —H ₂	С₄—Н	C ₂ —H ₂	C2-H or C9-H	Sol- vent	
VIIa	C ₆ H ₅	1.25—1.90	2.35—3.00	3.07		6.65	CCl₄	
VIIb*	CH3		2.402.97	2.35		6.16	CDCl₃	
A**	H H C C H ₃	1.50—1.75	2.75-2.90	2.25	3.43	5.13	CDC13	
	H CH ₃			2.65	2.35			
VIIIa	$ \begin{array}{c} H \\ 4 \\ 5 \\ 6 \\ 7 \\ 1 \\ 2 \\ 6 \\ 7 \\ 1 \\ 2 \\ 6 \\ 6 \\ 7 \\ 1 \\ 2 \\ 6 \\ 6 \\ 1 \\ 1 \\ 2 \\ 6 \\ 1 \\ 5 \\ 1 \\ 1 \\ 1 \\ 2 \\ 1 \\ 6 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1$	1.55—1.85	2.702.85	2.40	3.57	6.10	CCI4	
	$ \begin{pmatrix} H & C_6 H_5 \\ I & I \\ I & I \\ I & H \end{pmatrix} $			2.95	3.47			
VIIIc	$ \begin{array}{c} \begin{array}{c} 4 \\ 5 \\ 6 \\ 7 \\ N \end{array} \begin{array}{c} H \\ C \\ C \\ S \\ S$	1.62	2.75	2.21	3.32	5.03	CCl4	

*In a mixture with 3-methylenequinuclidine [2]. **Studied by L. N. Yakhontov et al., [3].

Table 2 \mathcal{R}'

Com	R	R′	R″	Bp (pressure, mm), °C	Empirical formula	Found, %			Calc. %			Yield	Mp of salts,
pound						С	H	N	С	H	N	%	°C
IIIa	CH₂C ₆ H₅	Н	Н	145—146 (1)	C14H20N2	77.80	9.30	_	77.73	9.32		57	110—111ª
ШЬ	C ₆ H ₅	н	Н	131-132 (2)	$C_{13}H_{18}N_2$	76.87	8.70	13.50	77.18	8.97	13.85	97	
IIIc	CH3	Н	Н	5860	$C_8H_{16}N_2\cdot 2HCl$	44.80	8.39	13.00	45.08	8.51	13.14	92.2	·320—322 b
IIId	n-C₄H9	Н	н	82-83 (0,4)	$C_{11}H_{22}N_2$	72.27	11.89	15.59	72,47	12.16	15.36	47.5	
lVa	CH ₂ C ₆ H ₅	CH₃	CH3	140-141 (2) 26-28	$C_{16}H_{24}N_2$.	78.63	9.74	11.59	78.63	9.90	11.46	74	5760 °
IVb	C ₆ H ₅	CH₃	CH₃	104—106	$C_{15}H_{22}N_2$	78.50	9,40	12.26	78.21	9.63	12.12	78.6	45—47 d
IVc	CH3	CH3	CH3	71-72 (2)	$C_{10}H_{20}N_2$	70.97	11.63	16.50	71.37	11.98	16.64	82.3	76—78℃
Va	CH2C6H5	C ₂ H ₅	н	132-134 (2)	$C_{16}H_{24}N_2$	78,39	9.99	11.25	78.63	9.90	11.46	50.6	62—64 °
Vc	CH3	C ₂ H ₅	н	140-141 (10)	$C_{10}H_{20}N_2$	71.18	11.68	16.92	71,37	11.98	16.64	53.2	101—102°
VIa	CH ₂ C ₆ H ₅	C ₂ H ₅	CH3	140-141 (1)	$C_{17}H_{26}N_2$	_		10.70		-	10.84	76.8	78—80 °
VIc	CH ₃	C ₂ H ₅	CH₃	61-63 (1)	$C_{11}H_{22}N_2$	72.60	12.30	15.56	72.47	12.16	15.36	81.5	-
IX	C ₆ H ₅	СНО	Н	$\begin{array}{c} 275-280 \\ 52-54 \end{array}$ (0,8)	C ₁₄ H ₁₈ N ₂ O	_	-	12.17	-	-	12.16	58.5	-
х	C ₆ H ₅	CH₃	н	127—129 (1)	$C_{14}H_{20}N_2$	77.68	9.57	12.95	77.73	9.32	12.94	64	-
XI	C ₆ H ₅	CH ₃	COCH3	180—192 (1)	$C_{16}H_{22}N_2O \cdot C_6H_3N_3O_7$	53.92	5,15		54.21	5.17	-	63.4	95—97f
VIb	C ₆ H ₅	CH3	C ₂ H ₅	128—130 (1,5)	$C_{16}H_{24}N_2$	78.45	10.04	-	78.63	9.90	-	29.5	-

^aDipicrate, ^bDihydrochloride, ^cCitrate, ^dTartrate, ^eDicitrate, ^fPicrate.

In addition, by the method of NMR a study was made of the unsaturated compound VIIIc, formed from 3butyl-3-oxyquinuclidine (Id) during the Ritter reaction. The spectrum of the protons of the quinuclidine nucleus in compound VIIIc is basically similar to the spectrum of the nucleus of 3-ethylidenequinuclidine (A). The size of the chemical displacement of the proton at C_4 ($\delta = 2.21$ ppm) is close to that of the proton at C_4 for trans-3-ethylenequinuclidine ($\delta = 2.25$ ppm). On this basis one might conclude that the compound under investigation is 3-butylidenequinuclidine with the trans arrangement of the substitute at C_9 in relation to C_4 .

It has been mentioned above that, in all cases studied, in addition to the amino derivatives, the unsaturated compounds VII and VIII are also found. Formation of the latter is apparently not associated with the direct dehydration of the original tertiary alcohols I by H_2SO_4 . This is confirmed by the fact that 3-benzyl-3-oxyquinuclidine is unable to undergo dehydration by H_2SO_4 even during prolonged heating to 170° C, and under the conditions of the Ritter reaction it is mainly converted to compound VIIIa. On the contrary, 3-phenyl-3-oxyquinuclidine readily loses water on heating with H_2SO_4 , and in the case of the interaction with acetonitrile, in the presence of H_2SO_4 , it is converted mainly into the acetamino derivative **IIb.** The poorly defined course of the Ritter reaction for the compounds I is possibly associated with the fact that intermediate substances in this reaction, sulfoesters of 3-alkyl(aryl)-3-oxyquinuclidines, form 3-alkyl(aryl)quinuclidine cations, which are further stabilized by combination with acetonitrile with the formation of the acetamino derivatives II or by removal of the proton and conversion into the unsaturated compounds VII and VIII.

3-Alkyl(aryl)-3-acetaminoquinuclidines (II) are hydrolyzed by prolonged heating with 17% HClat180°C for compound IIa and at 100°C for the remaining compounds. The resulting 3-alkyl(aryl)-3-aminoquinuclidines (III) were converted into 3-alkyl(aryl)-3-dimethylaminoquinuclidines (IV) by interaction with formalin and formic acid. When the amino derivatives II were reduced with lithium aluminum hydride, 3-alkyl (aryl)-3-ethylaminoquinuclidines were synthesized (Va and Vc), from which 3-alkyl(aryl)-3-methylethylaminoquinuclidines (VIa and VIc) were obtained. Another scheme was used for the synthesis of 3-phenyl-3-methylethylaminoquinuclidines (VIb):



When 3-phenyl-3-aminoquinuclidine (IIIb) interacted with formic acid in the presence of acetic anhydride, it was converted into 3-phenyl-3-formylaminoquinuclidine (IX), from which 3-phenyl-3-methylaminoquinuclidine (X) was obtained on reaction with lithium alu-

When the biological properties of the obtained derivatives of 3-alkyl(aryl)-3-aminoquinuclidines were studied, no compounds were found with pronounced pharmacological activity.

EXPERIMENTAL

3-Benzyl-3-Acetaminoquinuclidine (IIa). In the course of 40 min, 10 ml conc H_2SO_4 (d 1.84) was added to 5 g (0.027 mole) of 3benzyl-3-oxyquinuclidine (Ia) and 10 ml (0.19 mole) acetonitrile. During this procedure the temperature of the reaction mass was increased to 60° C. The mixture was maintained at room temperature for 48 hr and then, with mixing, was slowly poured onto 100 g of ice. The H_2SO_4 solution was treated with a 50% solution of potash and extracted with chloroform. The chloroform solution was evaporated under vacuum and the residue was ground with ether. A 1 g (17.5%) quantity of compound IIa was removed by filtration. The colorless crystals are readily soluble in alcohols, chloroform, water, and insoluble in ether and acetone, mp 218-219.5° C (from a mixture of acetone and alcohol). Found, %: C, 74.10; H, 8.25; N, 10.88. Calculated for $C_{16}H_{22}N_2O$, %: C, 74.42; H, 8.58; N, 10.84.

After separation of compound IIa the ethereal solution was evaporated and the residue was distilled under vacuum. At first, 0.4 g acetamide (mp 79° C) was sublimed, and then 2.95 g (64.5%) of 3-benzilidenequinuclidine (VIIIa), a mixture of geometric isomers, was distilled. A colorless mobile liquid, readily soluble in organic solvents and insoluble in water, mp 138-140° C (2 mm) [4]. Found, %: C, 84.46; H, 8.71. Calculated for C₁₄H₁₇N, %: C, 84.37; H, 8.59.

3 Phenyl-3-acetaminoquinuclidine (IIb). A 5 g quantity (0.0247 mole) of 3-phenyl-3-oxyquinuclidine (Ib) was treated with 10 ml (0.19 mole) acetonitrile and 10 ml H₂SO₄ in an analogous manner to that described above. A 3.6 g (58.5%) quantity of compound IIb was obtained in the form of colorless crystals, readily soluble in chloroform and water, and insoluble in ether, acetone, and benzene, mp 200-201° C (from water). Found, %: C, 64.60; H, 8.54; N, 10.06. Calculated for C15H20N2O · 2H2O, %: C, 64.26; H, 8.63; N, 9.99. Water of crystallization was removed on sublimation of the compound under vacuum (2 mm. 190° C), mp 200-201° C. Found, %: C, 73.99; H 8.21; N, 11.58. Calculated for C15H20N2O, %: C, 73.73; H, 8.25; N, 11.52. Hydrochloride, colorless crystals, mp 72° C (with decomp.). Found, %: Cl, 13.01; N, 10.01. Calculated for C15H20N2O . HCl, %: Cl, 12.62; N, 9.98. Picrate, yellow crystals, mp 254-255° C. Found, %: C, 53.10; H, 5.17; N, 14.88. Calculated for C15H20N2O • C6H3N3O7, %: C, 53.27; H, 4.89; N, 14.79. After separation of compound IIb from the ethereal solution 0.3 g acetamide and 1.7 g (38%) 3-pheny1- \triangle^2 -dehydroquinuclidine (VIIa) were obtained, bp $105-108^{\circ}$ C (0.35 mm), n_{D}^{20} 1.5843. Hydrochloride, mp 210-212° C[2].

3-Phenyl-3-aminoquinuclidine (IIIb). A 6 ml volume of H_2SO_4 was added to a solution of 3 g (0.015 mole) Ib in 6 ml (0.115 mole) acrylonitrile. The mixture was maintained at room temperature for 24 hr. The hydrochloride solution was concentrated under vacuum and the residue was treated with a 50% solution of KOH and extracted with benzene. A 0.9 g (30%) quantity of compound IIIb was obtained in the form of a colorless, mobile liquid, readily soluble in organic solvents and poorly soluble in water, bp 131-133° C (2 mm), n_D^{25} 1.5761. Found, %: C, 77.45; H, 9.07; N, 13.91. Calculated for $C_{13}H_{18}N_2$, %: C, 77.18; H, 8.97; N, 13.85.

3-Methyl-3-acetaminoquinuclidine (IIc). Four g (0.028 mole) 3-methyl-3-oxyquinuclidine (Ic), 8 ml (0.015 mole) acetonitrile, and 8 ml H₂SO₄ were treated in the manner described for the preparation of compound IIa. The chloroform extract of the reaction products was evaporated under vacuum and the residue was removed by distillation. At first, 0.56 g acetamide was sublimed and then compound IIc was removed by distillation. The compound crystallized on cooling. Yield, 2.5 g (48.5%), bp 138-140° C (2 mm), mp 112-114° C (from ether). Colorless crystals were readily soluble in organic solvents and water. Found,

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%: C, 65.44; H, 9.81; N, 15.46. Calculated for C₁₀H₁₈N₂O, %: C, 65.89; H, 9.95; N, 15.36.

On acidification of the chloroform distillate with an alcoholic solution of HCl, crystals were obtained which were apparently a mixture of the hydrochlorides of 3-methylenequinuclidine (VIIIb) and 3-methyl- Δ^2 -dehydroquinuclidine (VIIc). Yield, 0.15 g (3%), mp 240-243° C [2, 5]. Found, %: Cl, 22.01. Calculated for C₈H₁₃N • HCl, %: Cl, 22.20.

3-Butyl-3-acetaminoquinuclidine (IId). Chloroform extract of the reaction products, obtained during the interaction between 5 g (0.027 mole) of 3-butyl-3-oxyquinuclidine (Id), 10 ml (0.19 mole) acetonitrile, and 10 ml H_2SO_4 were evaporated, and the residue was fractionated under vacuum. At first, 0.3 g acetamide was sublimated, and then two fractions were collected: 1-st fraction, bp 97-98° C (11 mm) is butylidenequinuclidine. According to NMR data in this case a single geometric isomer of compound VIIIc was obtained. Yield, 2.12 g (48%). Colorless, mobile liquid, readily soluble in organic solvents and water. Found, %: C, 79.94; H, 11.32; N, 8.26. Calculated for C₁₁H₁₉N, %: C, 79.94; H, 11.59; N, 8.47.

2-nd fraction, bp 140-141° C (2 mm), mp 125-127° C (from ethyl acetate). The compound is 3-butyl-3-acetaminoquinuclidine (IId). Yield, 0.6 g (10%). Colorless, hygroscopic crystals, readily soluble in alcohol, chloroform, acetone, and water, and insoluble in ether and benzene. Found, %: C, 60.28; H, 10.65; N, 10.81. Calculated for $C_{13}H_{24}N_2O \cdot 2H_2O$, %: C, 59.97; H, 10.84; N, 10.75.

3-Benzyl-3-aminoquinuclidine (IIIa). A solution of 2.3 g(8.9 mM) of compound IIa in 23 ml of $17\% \text{ H}_2\text{SO}_4$ was heated for 20 hr at 180° C in a sealed tube. The hydrochloride solution was evaporated under vacuum and the residue was treated with a 50% solution of potassium hydroxide and extracted with benzene. After removal of benzene the residue was distilled under vacuum.

The amines IIIb-d were obtained when the acetamino derivatives of compounds IIb-d were boiled for 40 hr with 17% H₂SO₄.

The yields, constants, and results of the analyses of these compounds and also of the other derivatives of 3-alkyl(aryl)-3-aminoquinuclidines (IV-VI, IX-XI) are presented in Table 2.

3-Benzyl-3-dimethylaminoquinuclidine (IVa). A 1.1 g quantity (5.7) mM) of compound **IIIa**, 1.02 g (34 mM) of 37% formalin, and 1.4 g (32 mM) of formic acid were heated for 20 hr at 100° C. The reaction mass was treated with a 50% solution of KOH and extracted with benzene.

Compounds $\ensuremath{\text{IVb}}$, $\ensuremath{\text{IVc}}$, and $\ensuremath{\text{VIc}}$ were obtained by an analogous method.

3-Benzyl-3-ethylaminoquinuclidine (Va). One g (0.0039 mole) compound IIa was added to a suspension of 1 g (0.026 mole) lithium aluminum hydride in a mixture of 15 ml ether and 15 ml dioxane. The reaction mass was boiled for 20 hr. On cooling, it was treated with 2 ml water and the inorganic salts were filtered and washed with chloroform. The combined extracts were evaporated and the residue was distilled.

By this method the amines **VIb**, **VIc**, and **X** were obtained which had been derived from the acyl derivatives **XI**, **IIc**, and **IX**, respectively.

3-Phenyl-3-formylaminoquinuclidine (IX). A mixture of 0.7 ml (0.016 mole) formic acid and 1.93 ml (0.0205 mole) acetic anhydride was heated for 2 hr at 50° C. A solution of 3 g (0.0194 mole) of compound IIIb in 10 ml chloroform was poured into the cooled mass and the mixture was maintained at room temperature for 50 hr. The mixture was then evaporated under vacuum and treated with a 50% solution of potash and extracted with chloroform.

8-Phenyl-3-methylacetaminoquinuclidine (XI). A mixture of 1.2 g (0.01 mole) of compound X and 15 ml acetic anhydride was boiled for 1 hr. Excess acetic anhydride was removed by distillation under vacuum, and the residue was treated with a 50% solution of potash and extracted with chloroform.

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