

Table 1

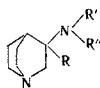
NMR Spectra of 3-Alkylidenequinclidines and Δ^2 -Dehydroquinclidines

Compound	Structural formula	Size of the chemical displacements δ , ppm						Solvent
		C ₅ -H ₂ ; C ₆ -H ₂	C ₆ -H ₂ ; C ₇ -H ₂	C ₄ -H	C ₂ -H ₂	C ₃ -H or C ₉ -H		
VIIa		1.25—1.90	2.35—3.00	3.07		6.65	CCl ₄	
VIIb*			2.40—2.97	2.35		6.16	CDCl ₃	
A**		1.50—1.75	2.75—2.90	2.25	3.43	5.13	CDCl ₃	
				2.65	2.35			
VIIIa		1.55—1.85	2.70—2.85	2.40	3.57	6.10	CCl ₄	
				2.95	3.47			
VIIIc		1.62	2.75	2.21	3.32	5.03	CCl ₄	

*In a mixture with 3-methylenequinclidine [2].

**Studied by L. N. Yakhontov et al., [3].

Table 2



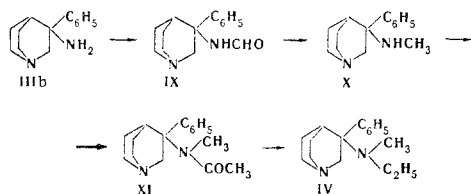
Compound	R	R'	R''	Bp (pressure, mm), °C	Empirical formula	Found, %			Calc. %			Yield %	Mp of salts, °C
						C	H	N	C	H	N		
IIIa	CH ₂ C ₆ H ₅	H	H	145—146 (1)	C ₁₄ H ₂₀ N ₂	77.80	9.30	—	77.73	9.32	—	57	110—111 ^a
IIIb	C ₆ H ₅	H	H	131—132 (2)	C ₁₃ H ₁₈ N ₂	76.87	8.70	13.50	77.18	8.97	13.85	97	—
IIIc	CH ₃	H	H	58—60	C ₈ H ₁₆ N ₂ · 2HCl	44.80	8.39	13.00	45.08	8.51	13.14	92.2	320—322 ^b
IIId	n-C ₄ H ₉	H	H	82—83 (0.4)	C ₁₇ H ₂₂ N ₂	72.27	11.89	15.59	72.47	12.16	15.36	47.5	—
IVa	CH ₂ C ₆ H ₅	CH ₃	CH ₃	140—141 (2) 26—28	C ₁₆ H ₂₄ N ₂	78.63	9.74	11.59	78.63	9.90	11.46	74	57—60 ^c
IVb	C ₆ H ₅	CH ₃	CH ₃	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	CH ₃	CH ₃	CH ₃	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 ^e
Va	CH ₂ C ₆ H ₅	C ₂ H ₅	H	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 ^e
Vc	CH ₃	C ₂ H ₅	H	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 ^e
VIa	CH ₂ C ₆ H ₅	C ₂ H ₅	CH ₃	140—141 (1)	C ₁₇ H ₂₆ N ₂	—	—	10.70	—	—	10.84	76.8	78—80 ^e
VIc	CH ₃	C ₂ H ₅	CH ₃	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	CHO	H	275—280 (0.8) 52—54	C ₁₄ H ₁₈ N ₂ O	—	—	12.17	—	—	12.16	58.5	—
X	C ₆ H ₅	CH ₃	H	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	COCH ₃	180—192 (1)	C ₁₆ H ₂₂ N ₂ O · C ₆ H ₃ N ₃ O ₇	53.92	5.15	—	54.21	5.17	—	63.4	95—97 ^f
VIb	C ₆ H ₅	CH ₃	C ₂ H ₅	128—130 (1.5)	C ₁₆ H ₂₄ N ₂	78.43	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 3-butyl-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 C₄ ($\delta = 2.21$ ppm) is close to that of the proton at C₄ 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 C₃ in relation to C₄.

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 H₂SO₄. This is confirmed by the fact that 3-benzyl-3-oxyquinuclidine is unable to undergo dehydration by H₂SO₄ 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 H₂SO₄, and in the case of the interaction with acetonitrile, in the presence of H₂SO₄, 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% HCl at 180° 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-

minum hydride. This compound was acetylated with acetic anhydride and the acetamine obtained (XI) was reduced to 3-phenyl-3-methylethylaminoquinuclidine (VIb) by means of lithium aluminum hydride.

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 H₂SO₄ (d 1.84) was added to 5 g (0.027 mole) of 3-benzyl-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 H₂SO₄ 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 C₁₆H₂₂N₂O, %: 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-benzylidenequinuclidine (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-phenyl- Δ^2 -dehydroquinuclidine (VIIa) were obtained, bp 105–108° 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 H₂SO₄ 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 C₁₃H₁₈N₂, %: 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,

%: C, 65.44; H, 9.81; N, 15.46. Calculated for $C_{10}H_{18}N_2O$, %: 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 (VIIIc). Yield, 0.15 g (3%), mp 240–243° C [2, 5]. Found, %: Cl, 22.01. Calculated for $C_8H_{13}N \cdot HCl$, %: Cl, 22.20.

3-Butyl-3-acetaminoquinuclidine (IIId). 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 $C_{11}H_{19}N$, %: 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 (IIId). 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% H_2SO_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% H_2SO_4 .

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 IVb, IVc, and 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.

3-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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