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REACTION OF 2-METHYLENE-3-OXOQUINUCLIDINE WITH NUCLEOPHILIC REAGENTS

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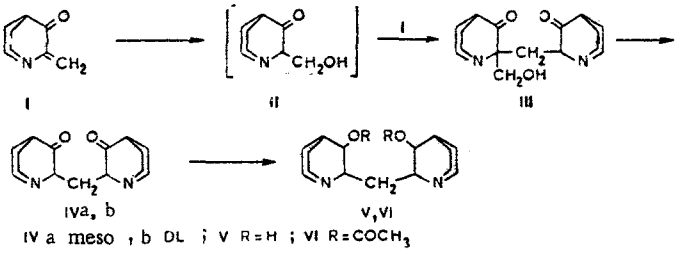
The salts and quaternary derivatives of 2-methylene-3-hydroxyquinuclidine readily add nucleophilic reagents because of the high polarity and polarizability of the carbon–carbon double bond, which are due to the overall electron-acceptor effect of the positively charged nitrogen atom and the carbonyl group. The double bond is substantially deactivated in the base, and the addition of nucleophilic reagents is hindered.

The quinuclidine molecule is a rigidly fixed bicyclic system with a fixed orientation of the free electron pair of the nitrogen atom, as a result of which $p\pi$ electron interactions are sterically impossible in Δ^2-dehydroquinuclidines and quinuclidine derivatives with a semicyclic double bond attached to the α carbon atoms, and, in contrast to ordinary enamines, only the inductive effect of the nitrogen atom is exerted on the double bond vis-a-vis the absence of a +M effect [1].

We have previously shown [2] that in the case of 2- and 3-carboxyl derivatives of quinuclidine with an endocyclic Δ^2-double bond the above-indicated steric and electronic effects are responsible for the rather high polarization of the double bond and that under the conditions of the Michael reaction strong nucleophilic agents add to it to give 2,3-disubstituted quinuclidines.

The present research was devoted to a study of the effect of migration of the double bond from the endocyclic position to the semicyclic position on the reactivities of unsaturated oxoquinuclidine compounds. We used 2-methylene-3-oxoquinuclidine I as the subject of study in reactions with nucleophilic agents. Because of the absence of $p\pi$ conjugation, the polarizability of the carbon–carbon double bond in I is reduced, and, as noted in [3], the addition of nucleophilic reagents such as alcohols to it is hindered. In addition, we showed that when ketone I is heated with an aqueous solution of potassium hydroxide, it is converted to a mixture of meso- and DL-bis(3-oxo-2-quinuclidyl)methanes IVa and IVb.



It may be assumed that IV are formed as a result of a subsequent series of transformations. 2-Hydroxymethyl-3-oxoquinuclidine II, which is formed as a result of the addition of water to the double bond of I, subsequently reacts with a second molecule of olefin I to give 2-hydroxymethylbis(3-oxo-2-quinuclidyl)methane III, which loses a molecule of formaldehyde to give diketone IV. Hydroxy ketone III was isolated when I was

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heated with sodium 2-methoxyphenoxide in xylene with subsequent treatment of the reaction mixture with water. When hydroxy diketone III is refluxed with aqueous sodium hydroxide solution, a molecule of formaldehyde is split out to give diketone IV. These transformations confirm the scheme proposed above for the reaction of ketone I with aqueous alkalis.

According to the PMR spectral data, diketone IV is formed in all cases as a mixture of approximately equal amounts of meso (IVa) and DL (IVb) isomers. This is confirmed both by the position and intensity of the signals of the protons of the quinuclidine rings and by the type of spectrum of the protons of the interannular CH_2 group. The chemical shifts of the protons of this group coincide in the spectrum of the DL form but differ in the spectrum of the meso form (see Table 1). This was displayed particularly graphically for the 2,2-dideuterated derivatives: two doublets for isomer IVa and a singlet for the IVb isomer.

Thermal instability of diketones IV was observed during a mass spectroscopic investigation. Ions with m/e 42, 55, 68, 69, 82, 96, 97, and 110, which are characteristic for 3-oxoquinuclidine derivatives [4, 5], are observed in addition to a maximum mass peak with m/e 234 (28 au less than the molecular weight of IV) in the mass spectra of IV emerging from a gas-chromatographic column. A low-intensity peak with m/e 262, which corresponds to the molecular weight of IV and constitutes 0.22% of the total intensity of all of the ions in the spectrum, is observed in the mass spectrum of diketones IV introduced directly into the ion source. When the ionizing electron energy is reduced to 12 eV, the intensity ratio of the peaks with m/e 234 and 262 remains practically unchanged. Thus thermal decomposition of IV also occurs under milder conditions (at 50°C and $5 \cdot 10^{-7}$ mm in the mass spectrometer as against 250°C in the chromatograph vaporizer), and a fragmentation product with m/e 234 is primarily recorded.

The catalytic reduction of isomeric diketones IV or reduction with sodium borohydride leads to a mixture of at least three diastereomers of bis(3-hydroxy-2-quinuclidyl)methane V; this is confirmed by the presence in the PMR spectrum of bis(3-acetoxy-2-quinuclidyl)methane VI of six singlets of protons of the acetyl groups.

TABLE 1. Chemical Shifts of the Protons (δ, ppm)

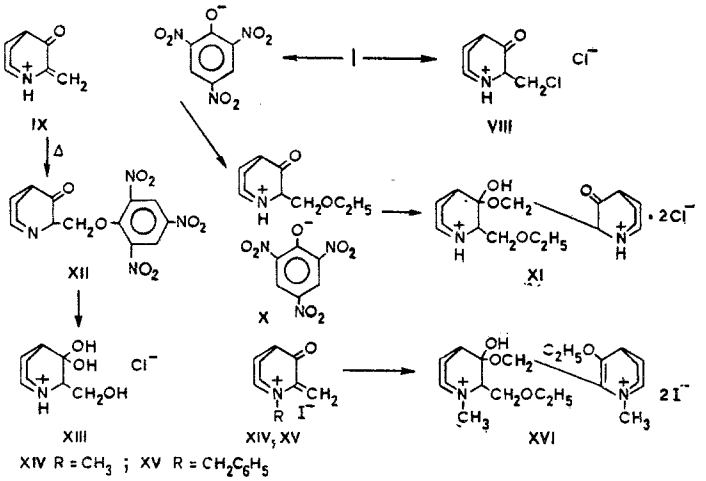
Compound	2H	6,7 H_2	3H	5,8 H_2	4H	Substituents	Solvent
I		3,12		1,98	2,62	5,28; 5,88	$CDCl_3$
IVa*	3,38					2,03	$CDCl_3$
IVb*	3,60	2,8—3,2		1,9—2,1	2,42	1,70 (A); 2,36 (B); J_{AB}=14 Hz	$CDCl_3$
VI*	2,6—3,4			1,25—2,0		2,6 (CH_2); 2,03; 2,05; 2,08; 2,09; 2,11; 2,12 (OCH_3)	$CDCl_3$
X	4,70	3,7—4,0		2,2—2,5	2,78	1,13 CH_3 (C_2H_5); 3,54 CH_2 (C_2H_5); 8,69 C_6H_5; 4,05 2-CH_2	d_6-DMF
XI	3,21	3,9		1,9—2,5	2,86	4,0, 4,15 2-CH_2, 2'-CH_2; 1,14 CH_3 (C_2H_5); 3,65 CH_2 (C_2H_5)	D_2O
XII						5,35 CH_2; 8,64 (C_6H_5)	D_6-DMSO
XVI	3,3—3,8			1,8—2,2	2,38 2,62	2,98, 3,07 N—CH_3 1,16, 1,19 CH_3 (C_2H_5); 3,55, 3,57 CH_2 (C_2H_5)	D_2O
XVII	2,96	2,8—3,2		1,96	2,30	1,23, J=7,2 Hz	CCl_4
XVIII* cis	2,68	2,7—3,3	3,83; J_{23}=8 Hz J_{34}=4,5 Hz	1,4—2,1	1,82	1,20, J=7,5 Hz	$CDCl_3$
XVIII* trans			3,30; J_{23}=5 Hz J_{34}=3 Hz				$CDCl_3$
XX* cis	2,70	2,5—3,1	4,85; J_{23}=8 Hz J_{34}=4,2 Hz	1,1—1,8	1,85	1,03, J=7,5 Hz	CCl_4
XX* trans			4,30; J_{23}=4,4 Hz J_{34}=3,2 Hz				CCl_4

Compound	2,6a	2,6e	3, 1, 5	7	8	9	Solvent
XIX	2,54	3,08	1,0—2,0	3,77	5,91	5,1—5,8	$CDCl_3$

*This compound was studied in the form of a mixture of isomers.

The mass spectrum of diacetate VI [molecular peak with m/e 350 and subsequent fragmentation through the acetyl groups: m/e 307 ($M^{+\cdot} - CH_3\dot{C}O$), 291 ($M^{+\cdot} - CH_3\dot{C}O_2$), 247 ($M^{+\cdot} - CH_3\dot{C}O - CH_3COOH$), 231 ($M^{+\cdot} - CH_3CO_2 - CH_3COOH$)] and subsequent cleavage of the bonds at the methylene group (m/e 182, 168, 152, 126) confirm its structure. When diol V is heated with 70% sulfuric acid, it loses two molecules of water to give bis(Δ^2-dehydro-2-quinuclidyl)methane VII.

The transition from the 2-methylene-3-oxoquinuclidine base to its salts and quaternary derivatives, which entails a considerable increase in the proton-acceptor effect of nitrogen and consequently an increase in the polarity and polarizability of the olefinic bond, substantially changes the reactivity of I. This was demonstrated thoroughly by the reactions of the hydrochloride, picrate, and methiodide of 2-methylene-3-oxoquinuclidine with nucleophilic reagents. Thus 2-chloromethyl-3-oxoquinuclidine hydrochloride (VIII) is formed when dry hydrogen chloride is bubbled into a solution of base I in methylene chloride.



The picrate of 2-methylene-3-oxoquinuclidine IX, obtained by treatment of an acetone solution of ketone I with picric acid, adds a molecule of alcohol at room temperature to give the picrate of 2-ethoxymethyl-3-oxoquinuclidine (X). In the PMR spectrum of picrate X (see Table 1) the signals of all of the protons of the quinuclidine ring, particularly the α protons (2,6,7H) are observed at weaker field than in the case of the nonprotonated compounds, apparently because of the inductive effect of the positively charged nitrogen atom.

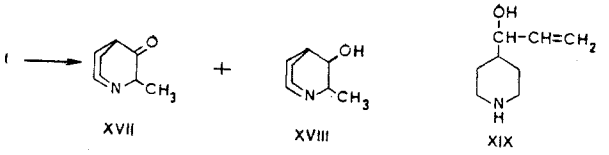
2-Ethoxymethyl-3-hydroxy-3-(3'-oxo-2'-quinuclidylmethyloxy)quinuclidine dihydrochloride (XI) was obtained instead of the expected 2-ethoxymethyl-3-oxoquinuclidine hydrochloride when salt X was treated with concentrated hydrochloric acid. The formation of XI was evidently a consequence of two successive reactions: hydrolysis of 2-ethoxymethyl-3-oxoquinuclidine to carbinol II and addition of it to the carbonyl group of base X. Signals of the protons of two quinuclidine rings, two groups of CH_2 substituents, and one ethyl group are observed in the PMR spectrum of XI. The weak-field shift of the signal of the 4H proton of one of the quinuclidine rings relative to the 4H signal of the other ring attests to the presence of a C = O group in the first ring in the 3 position, whereas the C_3 atom in the second ring has sp^3 hybridization.

When picrate IX is heated to the boiling point in dimethylformamide (DMF) or to 100°C in phenol, it undergoes rearrangement to give 2-(2',4',6'-trinitrophenyloxymethyl)-3-oxoquinuclidine (XII). The IR spectrum of picrate IX contains, in addition to a carbonyl band at 1730 cm^{-1}, a characteristic $\overset{+}{N}H$ salt band at 2560 cm^{-1}. The absorption of a carbonyl group (1750 cm^{-1}) is retained in the spectrum of ether XII, but the band at 2560 cm^{-1} vanishes. The position of the signals of the protons of the CH_2 group of the side chain in the PMR spectrum (see Table 1) also confirms the structure of this compound. Ether XII is an unstable substance and is converted to 2-hydroxymethyl-3,3-dihydroxyquinuclidine hydrochloride (XIII) when it is treated with an alcohol solution of hydrogen chloride. The formation of triol XIII is the result of cleavage of ether XII and the addition of two molecules of water to the liberated 2-methylene-3-oxoquinuclidine hydrochloride. Ketone I is also converted to triol XIII when it is treated with hydrochloric acid.

2-Methylene-3-oxoquinuclidine methiodide (XIV) was also found to be more reactive than the base. Methiodide XIV is formed in the reaction of base I with methyl iodide in acetone at room temperature. Under similar conditions but in ethanol, the reaction product is 2-ethoxymethyl-3-hydroxy(3'-ethoxy-Δ^2-dehydro-2'-quinuclidylmethyloxy)quinuclidine dimethiodide (XVI). Like XI, XVI is probably formed as a result of acetalization of the primary reaction product (in this case 2-ethoxymethyl-3-oxoquinuclidine methiodide) by its re-

action with the 2-hydroxymethyl-3-oxoquinuclidine methiodide present in the reaction mixture and subsequent enolization of the carbonyl group. The structure of XVI is in agreement with the IR spectral data: the absence of the characteristic bands for the carbonyl group and the presence of absorption in the region characteristic for hydroxyl groups. According to the PMR spectral data, the XVI molecule contains two quinuclidine rings with substitution that differs in character, two ethyl groups, and two N-methyl groups.

The reduction of ketone I under various conditions proceeds ambiguously. A mixture of 2-methyl-3-oxo- (XVII) and 2-methyl-3-oxoquinuclidine (XVIII) is formed in the case of hydrogenation in the presence of a platinum catalyst. Compound XVIII was isolated in the form of a single diastereomer. The catalytic reduction of the keto group in methyl ketone XVII to an alcohol group takes place only in hydrochloric acid solution, during which the same diastereomer of alcohol XVIII is formed. A mixture of two diastereomers of alcohol XVIII was obtained in the reduction of ketone XVII with sodium borohydride. The reduction of I with lithium aluminum hydride is a considerably more complex process. In this case, in addition to alcohol XVIII, we isolated vinyl(4-piperidyl)carbinol (XIX), which is formed as a result of cleavage of the quinuclidine ring at the $N-C_1$ bond. The structure of carbinol XIX was confirmed by its PMR spectrum (see Table 1).



XVII XVIII XIX

As in the case of other 3-oxoquinuclidines, a characteristic shift of the signal of the H_4 proton (a symmetrical quintet with $^3JH_\gamma H_\beta \approx 3$ Hz) to weak field relative to the signal of this proton in the spectrum of quinuclidine derivatives with an sp^3-hybridized C_3 atom is observed in the PMR spectrum of ketone XVII. The spectrum of carbinol XVIII, obtained by catalytic reduction of ketones I and XVII, is characterized by a single set of signals, whereas the spectrum of the product obtained by reduction of ketone XVII with sodium borohydride is characterized by two sets of signals. On the basis of the previously found ratios between the vicinal spin–spin coupling constants for isomeric 2,3-disubstituted quinuclidines ($^3JH_2H_3cis > {}^3JH_2H_3trans$; $^3JH_3H_4cis > {}^3JH_3H_4trans$) it can be concluded that the cis isomer of carbinol XVIII is formed in the catalytic reduction, whereas a mixture of the cis and trans isomers of the carbinols is formed in the reduction with sodium borohydride. The data from the PMR spectra of 2-methyl-3-acetoxyquinuclidines XX obtained by acetylation of a mixture of the isomeric carbinols confirm the above conclusion regarding the configuration of these compounds.

EXPERIMENTAL

The IR spectra of the compounds were recorded with a UR-10 spectrometer. The chromatograms and mass spectra were obtained with a Varian Matt 111 chromatographic mass spectrometer at 70 eV with helium as the carrier gas at a flow rate of 20 ml/min and with an MKh-1303 mass spectrometer equipped with a system for direct introduction of the samples into the ion source at 30 and 12 eV; the column was filled with 5% SE-30 on Chromosorb W and 5% XE-60 on Chromaton N. The PMR spectra of solutions of the compounds in D_2O were recorded with a TNM-4H-100 spectrometer with $(CH_3)_3COH$ ($\delta CH_3 = 1.23$ ppm) as the internal standard (tetramethylsilane was the standard for other solutions).

Reaction of 2-Methylene-3-oxoquinuclidine (I) with Aqueous Potassium Hydroxide Solution. A solution of 20 g (0.145 mole) of I in 200 ml of 25% aqueous potassium hydroxide solution was refluxed for 20 h, after which it was cooled and extracted with chloroform. The chloroform was removed by vacuum distillation to give 14 g (73.2%) of a mixture of meso- and DL-bis(3-oxo-2-quinuclidyl)methanes (IV) with mp 206-207°C (from isopropyl alcohol) [6]. IR spectrum: 1720 cm^{-1} (C = O). Found: C 68.7; H 8.3; N 10.5%. $C_{15}H_{22}N_2O_2$. Calculated: C 68.7; H 8.5; N 10.7%.

2-Hydroxymethylbis(3-oxo-2-quinuclidyl)methane (III). A 10-g (0.073 mole) sample of I was added to sodium 2-methoxyphenoxide, obtained from 9.05 g (0.073 mole) of 2-methoxyphenol and 1.68 g (0.073 g-atom) of sodium in 200 ml of toluene, and the mixture was refluxed with stirring for 12 h. It was then cooled, treated with 200 ml of water, acidified (with respect to Congo Red) with concentrated hydrochloric acid, and extracted with benzene. The hydrochloric acid solution was alkalized with sodium hydroxide and extracted with chloroform. Removal of the chloroform by vacuum distillation and trituration of the residue with ether gave 1.7 g (16%) of a product with mp 180-182°C (from isopropyl alcohol). Found: C 65.6; H 8.1; N 9.1%. $C_{16}H_{24}N_2O_3$. Calculated: C 65.7; H 8.2; N 9.2%.

Meso and DL Isomers of Bis(3-oxo-2-quinuclidyl)methane (IV). A solution of 0.15 g (0.05 mmole) of III in 1.5 ml of 30% aqueous sodium hydroxide solution was heated at 100°C for 10 h, after which it was extracted with chloroform. Workup of the chloroform extract gave 0.1 g (74%) of a mixture of diketones IV with mp 206-207°C (from isopropyl alcohol). Found: C 68.6; H 8.4; N 10.9%. $C_{15}H_{22}N_2O_2$. Calculated: C 68.7; H 8.5; N 10.7%.

Bis(3-hydroxy-2-quinuclidyl)methane (V). A 3-g (0.079 mole) sample of sodium borohydride was added with stirring in the course of 1 h to a solution of 3 g (0.0114 mole) of a mixture of the meso and DL forms of diketone IV in 60 ml of methanol, and the mixture was allowed to stand at room temperature for 20 h. The solvent was removed by vacuum evaporation, and the residue was dissolved in 30 ml of water. The aqeuous solution was extracted with chloroform, and the extract was worked up to give the product, with mp 212-215°C (from a mixture of methanol and ethyl acetate), in quantitative yield (3 g). Diol V thus obtained was a mixture of four diastereomers. IR spectrum: 3100 cm^{-1} (NH). Found: C 67.4; H 9.8; N 10.8%. $C_{15}H_{26}N_2O_2$. Calculated: C 67.4; H 9.8; N 10.9%.

Bis(3-acetoxy-2-quinuclidyl)methane (VI). A solution of 3.75 g (0.142 mole) of diol V in 40 ml of acetic anhydride was refluxed for 5 h, after which the acetic anhydride was removed by vacuum distillation, and the residue was made alkaline with 25% potassium carbonate solution and extracted with chloroform. Workup of the extract gave 4 g (81.5%) of a product with bp 175-180°C (0.7 mm). Found: C 64.9; H 8.8; N 8.2%. $C_{19}H_{30}N_2O_4$. Calculated: C 65.1; H 8.6; N 8.0%. The ditartrate hap mp 85-87°C (dec.). Found: C 48.3; H 6.6%. $C_{19}H_{30}N_2O_4 \cdot 2C_4H_6O_6$. Calculated: C 48.5; H 6.6%.

Bis(Δ^2-dehydro-2-quinuclidyl)methane (VII). A solution of 1 g (0.37 mmole) of diol V in 7 ml of 70% sulfuric acid was refluxed for 10 h, after which it was poured with cooling into 10 ml of water, and the resulting acid solution was made alkaline with 50% potassium hydroxide solution and extracted with ether. Workup of the extract gave 0.35 g (40.5%) of a product with bp 138-140°C (0.8 mm). The product was a light-yellow mobile liquid that gave a positive test for a double bond with potassium permanganate. Found: C 77.9; H 9.8; N 11.9%. $C_{15}H_{22}N_2$. Calculated: C 78.2; H 9.6; N 12.2%.

2-Chloromethyl-3-oxoquinuclidine Hydrochloride (VIII). A solution of 10 g (0.073 mole) of 2-methylene-3-oxoquinuclidine I in 100 ml of dry methylene chloride was saturated with hydrogen chloride until the mixture was acidic with respect to Congo Red. It was then allowed to stand for 20 h at room temperature, and the resulting precipitate was removed by filtration and washed with methylene chloride to give 15.5 g (100%) of product. IR spectrum: 1746 (C = O), 2480, 2550 cm^{-1} ($\overset{+}{N}H$). Found: Cl 32.9%. $C_8H_{12}ClNO \cdot HCl$. Calculated: Cl 33.8%.

2-Methylene-3-oxoquinuclidine Picrate (IX). A solution of 2.68 g (0.0117 mole) of picric acid in 50 ml of acetone was added to a solution of 1.6 g (0.0117 mole) of I in 20 ml of acetone, and the mixture was allowed to stand at room temperature for 20 h. The resulting precipitate was removed by filtration to give 3.6 g (84%) of a product with mp 237-238°C (dec.). IR spectrum: 1730 (C = O) and 2560 cm^{-1} ($\overset{+}{N}H$). Found: C 46.2; H 3.9; N 15.5%. $C_8H_{11}NO \cdot C_6H_3N_3O_7$. Calculated: C 46.6; H 3.9; N 15.4%.

2-Ethoxymethyl-3-oxoquinuclidine Picrate (X). A solution of 2.29 g (0.01 mole) of picric acid in 20 ml of ethanol was added to a solution of 1.37 g (0.01 mole) of I in 25 ml of ethanol, and the resulting precipitate was removed by filtration and recrystallized from a mixture of ethanol and acetone to give 3.8 g (90.3%) of a product with mp 242-243°C (dec.). IR spectrum: 1750 (C = O) and 2570 cm^{-1} ($\overset{+}{N}H$). Found: C 46.7; H 4.9; N 13.9%. $C_{10}H_{17}NO_2 \cdot C_6H_3N_3O_7$. Calculated: C 46.4; H 4.8; N 13.6%.

2-Ethoxymethyl-3-hydroxy-3-(3'-oxo-2'-quinuclidylmethyloxy)quinuclidine Dihydrochloride (XI). A suspension of 1 g (2.4 mmole) of picrate X in 20 ml of concentrated hydrochloric acid was extracted with benzene. After removal of the picric acid, the hydrochloric acid solution was vacuum evaporated, the residue was triturated with isopropyl alcohol, and the mixture was worked up to give colorless crystals with mp > 300°C. Found: C 52.8; H 7.5; Cl 17.4; N 6.9%. $C_{18}H_{28}N_2O_4 \cdot 2HCl$. Calculated: C 52.8; H 7.4; Cl 17.3; N 6.9%.

2-(2',4',6'-Trinitrophenyloxymethyl)-3-oxoquinuclidine (XII). A 2.5-g (0.068 mole) sample of picrate IX was dissolved in 25 ml of refluxing DMF, and the crystals that formed when the solution was cooled were removed by suction filtration and washed with boiling dioxane to give 1.6 g (64%) of a product with mp 256-258°C (dec.). IR spectrum: 1750 cm^{-1} (C = O). Found: C 46.7; H 4.0; N 15.1%. $C_{14}H_{14}N_4O_8$. Calculated: C 46.6; H 3.9; N 15.4%.

Treatment of XII with an alcohol solution of hydrogen chloride at room temperature precipitated colorless crystals of 2-hydroxymethyl-3,3-dihydroxyquinuclidine hydrochloride (XIII) [3] with mp 268-270°C (from

water). Found: C 45.7; H 7.6; Cl 17.0; N 7.0%. C 38.6; H 5.3; I 45.0; N 4.9%. $C_9H_{14}INO$. Calculated: C 38.7; H 5.1; I 45.5; N 5.0%.

2-Methylene-3-oxoquinuclidine Methiodide (XIV). A 5.18-g (0.0365 mole) sample of methyl iodide was added to a solution of 5 g (0.0365 mole) of I in 25 ml of acetone, and the mixture was allowed to stand at room temperature for 3 days. It was then filtered to give 9.8 g (95.5%) of methiodide XIV with mp 187-188°C. IR spectrum: 1633 (C = C) and 1727 cm^{-1} (C = O). Found: C 38.6; H 5.3; I 45.0; N 4.9%. $C_9H_{14}INO$. Calculated: C 38.7; H 5.1; I 45.5; N 5.0%.

2-Ethoxymethyl-3-hydroxy-3-(3'-ethoxy-Δ^2-dehydro-2'-quinuclidylmethyloxy)quinuclidine (XVI). A 5.18-g (0.0365 mole) sample of methyl iodide was added to a solution of 5 g (0.0365 mole) of I in 20 ml of ethanol, and the mixture was allowed to stand for 3 days. It was then filtered to give 9.3 g (91.3%) of a product with mp 217-218°C. IR spectrum: 3160 and 3420 cm^{-1} (OH). Found: I 38.6; N 4.2%. $C_{22}H_{40}I_2N_2O_4$. Calculated: I 39.0; N 4.3%.

2-Methylene-3-oxoquinuclidine Chlorobenzylate (XV). A mixture of 3 g (0.0218 mole) of I, 2.77 g (0.0218 mole) of benzyl chloride, and 10 ml of acetone was refluxed for 5 h, after which the acetone was decanted, and the residue was triturated with ether to give 5.6 g (97.3%) of a product with mp 185-186°C (dec.). Found: Cl 13.0%. $C_{15}H_{18}ClNO$. Calculated: Cl 13.4%.

Reduction of 2-Methylene-3-oxoquinuclidine (I). A) Catalytic Reduction. A solution of 10 g (0.073 mole) of I in 100 ml of benzene was shaken with hydrogen at 20°C in the presence of 0.5 g of platinum oxide [the hydrogen pressure was 20-30 cm (water column)] until hydrogen absorption ceased. The platinum black was removed by filtration, the alcohol was removed by vacuum distillation, the residue was diluted with 20 ml of hexane, and the mixture was allowed to stand at +4°C for 20 h. The hexane solution was decanted from the resulting precipitate, and the latter was triturated with ethyl acetate to give 3.2 g (31%) of cis-2-methyl-3-hydroxyquinuclidine (XVIII) with mp 105-107°C (from ethyl acetate). IR spectrum: 3100 cm^{-1} (OH). Found: C 67.8; H 10.4; N 10.2%. $C_8H_{15}NO$. Calculated: C 68.0; H 10.7; N 9.9%.

The hexane mother liquor after separation of XVIII was vacuum evaporated, and the residue was distilled to give 4.7 g (46.3%) of 2-methyl-3-oxoquinuclidine (XVII) with bp 106-108°C (8 mm). IR spectrum: 1725 cm^{-1} (C = O). Found: C 68.7; H 9.7; N 10.1%. $C_8H_{13}NO$. Calculated: C 69.0; H 9.4; N 10.1%.

B) Reduction with Lithium Aluminum Hydride. A solution of 2 g (0.0146 mole) of I in 20 ml of benzene was added to a suspension of 2 g (0.053 mole) of lithium aluminum hydride in 20 ml of ether, and the mixture was refluxed with stirring for 5 h. It was then cooled and treated with 4 ml of water, and the resulting precipitate was removed by filtration and washed with chloroform. The combined extracts were vacuum evaporated, and the residue was distilled to give 1.4 g of a viscous liquid, with bp 88-90°C (0.4 mm), that crystallized on standing. Recrystallization from 3 ml of ethyl acetate gave 0.4 g (19.4%) of vinyl(4-pyridyl)carbinol (XIX) with mp 105-108°C. IR spectrum: 3075 and 3248 cm^{-1} (OH, NH). Found: C 68.1; H 10.7; N 9.8%. $C_8H_{15}NO$. Calculated: C 68.1; H 10.7; N 9.9%.

The mother liquor after separation of carbinol XIX was vacuum evaporated, and the residue was identified from PMR data as a mixture of carbinols XVIII (cis isomer) and XIX.

2-Methyl-3-hydroxyquinuclidine (XVIII). A) A solution of 1.6 g (0.0107 mole) of ketone XVII in 30 ml of 1 N hydrochloric acid was shaken with hydrogen in the presence of 0.1 g of platinum oxide until 1 mole of hydrogen had been absorbed, after which the platinum was removed by filtration, and the filtrate was vacuum evaporated. The residue was made alkaline with potassium carbonate and extracted with chloroform to give 1.3 g (81%) of the cis isomer with mp 105-107°C. This product was identical to the product obtained in the reduction of I in neutral solution.

B) A 2-g (0.054 mole) sample of sodium borohydride was added to a solution of 2 g (0.0144 mole) of ketone XVII in 20 ml of methanol, and the mixture was allowed to stand at room temperature for 20 h. It was then evaporated, and the residue was triturated in 20 ml of water. The aqueous mixture was extracted with chloroform, and the extract was worked up to give 1.5 g (74.5%) of a mixture of diastereomeric carbinols XVIII.

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REACTION OF 2-METHYLENE-3-OXOQUINUCLIDINE WITH PHENOL AND NAPHTHOLS

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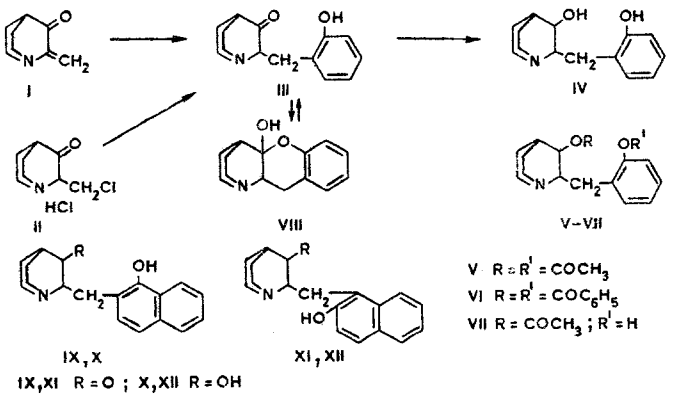
C-Alkylation in the ortho position of phenol and naphthols occurs in the reaction of 2-methylene-3-oxoquinuclidine with sodium phenoxide and sodium derivatives of naphthols. The structures of the products were confirmed by IR, PMR, and mass spectroscopic data.

In a previous communication we described the reaction of 2-methylene-3-oxoquinuclidine (I) and its salts and quaternary derivatives with some nucleophilic reagents (water and alcohols) [1], during which we discovered a substantial difference in the reactivities of base I and its salts.

In a continuation of this research we studied the reaction of I with aromatic hydroxy derivatives – phenol and α- and β-naphthols.

In the reaction of ketone I with sodium phenoxide and sodium derivatives of α- and β-naphthols, instead of the normal Michael reaction – addition of hydroxyl-containing compounds to the olefinic bond of I – we observed C-alkylation in the ortho position of phenol and the naphthols to give 2-(2'-hydroxybenzyl)-3-oxoquinuclidine (III), 2-(1'-hydroxy-2'-naphthylmethyl)-3-oxoquinuclidine (IX), and 2-(2'-hydroxy-1'-naphthylmethyl)-3-oxoquinuclidine (XI). Under similar conditions ketone I does not react with 3-hydroxypyridine. As a result of heating 2-chloromethyl-3-oxoquinuclidine hydrochloride (II) [1] with phenol we also obtained III. It is possible that in this case the initial step in the reaction is thermal dehydrohalogenation of chloride II and subsequent reaction of the resulting reactive 2-methylene-3-oxoquinuclidine hydrochloride with phenol.



The structures of III, IX, and XI were confirmed by chemical transformations and by IR, PMR, and mass spectral data. The IR spectra of these compounds contain, in addition to absorption in the region corresponding

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