CHEMICAL PECULIARITIES OF QUINUCLIDINE COMPOUNDS (REVIEW)

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Primarily recent studies of the peculiarities of the structures and chemical behavior of quinuclidine compounds that distinguish them from aliphatic and monocyclic amines and other azabicycloalkanes with angular nitrogen atoms are correlated.

Quinuclidine (1-azabicyclo[2.2.2]octane) (I) is of substantial interest not only as a structural fragment of a number of natural physiologically active substances and synthetic medicinal preparations but also from the point of view of theoretical organic chemistry as a peculiar heterocyclic system characterized by special chemical properties [1-3].

I

In contrast to tertiary aliphatic amines and N-substituted piperidines, quinuclidine is characterized by a quite rigidly fixed structure. Each of the six-membered rings that form this structure has a fixed "boat" form, and the considerable conformational changes in the rings that in other classes of compounds are due to the relative free rotation are impossible for quinuclidine and its derivatives. In addition, the fixed "boat" configuration leads to the appearance of shielded conformations in the quinuclidine system, and this is the reason for the certain distortion of the geometry of the molecules with deviation of the symmetry of the bicyclic system from C_{3v} symmetry.

The $J_{2,3}^{cis}$ spin–spin coupling constants in the PMR spectra of unsubstituted and 4-monosubstituted quinuclidines (9.7-10.3 Hz)[4-9] are in good agreement with the values calculated from the Karplus equation. In addition, the experimental $J_{2,3}^{trans}$ values of 5.3-5.6 Hz differ by more than 1 Hz from the values calculated for dihedral angle $\varphi = 120°$, which constitutes evidence for an increase in the H–C–H valence angles of quinuclidine as compared with the tetrahedral angles.

The introduction of substituents in the 3 position of the bicyclic system induces a change in the $J_{2,3}$ values. Inasmuch as the J value is only slightly sensitive to a change in φ for $\varphi \approx 0$, the decrease in $J_{2,3}^{cis}$ as a result of the successive introduction of carbon-, nitrogen-, and oxygen-containing substituents in the 3 position in place of hydrogen reflects only the effect of the electronegativity of the latter. On the other hand, the increase in the $J_{2,3}^{trans}$ value on introduction of substituents in which the first atom is carbon is not explained only by the electronegativity effect but constitutes evidence for an increase, as compared with unsubstituted quinuclidine, of the dihedral angle between the $H-C_2-C_3$ and $H-C_3-C_2$ planes, which is $\sim 4°$ when $\Delta J_{2,3}^{trans} = 1$ Hz. In 3-substituted quinuclidines in which the first atom of the substituent is oxygen or nitrogen, the $J_{2,3}^{trans}$ value is reduced as compared with unsubstituted quinuclidine, and this reduction is greater than for $J_{2,3}^{cis}$, which constitutes evidence for the existence in this case, in addition to the electronegative effect of the substituents, of distortion of the geometry of the bicyclic system due to a decrease in the dihederal angle between the $H-C_2-C_3$ and $H-C_3-C_2$ planes. Thus, depending on the character of the first atom of the substituent in 3-monosubstituted quinuclidines, the bridged conformation with an increase (a) or decrease (b) in dihedral angle φ predominates.

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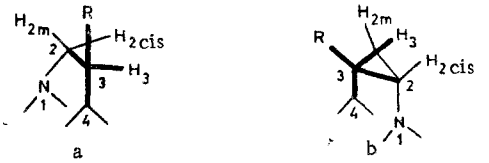
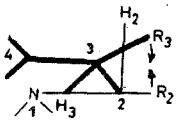


a

b

a R = CH_3, $CH_2COOC_2H_5$, $COOCH_3$; b R = NH_2, OH, $OCOCH_3$

When a second substituent is introduced in the 2 position with a cis orientation relative to the substituent already present, the PMR data do not make it possible to estimate the character and degree of distortion of the geometry of the bicyclic system, inasmuch as $\varphi \simeq 0$: the $J_{2,3}^{cis}$ values differ only slightly for the cis-2,3-di- and 3-monosubstituted quinuclidines. On the other hand, when the second substituent has a trans orientation, the $J_{2,3}^{trans}$ values change substantially. Proceeding from the difference in the trans constant of trans-2, 3-dicarboxyquinuclidine and unsubstituted quinuclidines (2.8 Hz) and from the value $\partial J/\partial\varphi \simeq 0.24$ Hz/deg (when $\varphi \approx 120°$), the magnitude of the distortion of the dihedral angle in this case can be estimated to be 10-12°. In this case the angle between the $H-C_2-C_3$ and $H-C_3-C_2$ planes increases, and the angle between the $R_3-C_3-C_2$ and $R_2-C_2-C_3$ planes decreases, i.e., the R_2 and R_3 substitutents approach one another.

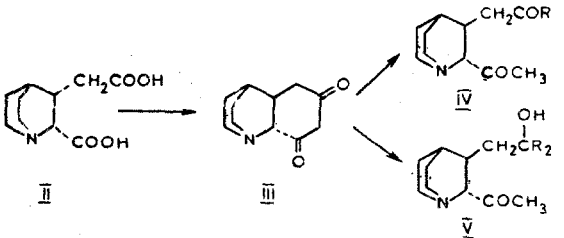


It is apparent that the conformational distortions described above are not of considerable magnitude, particularly in compounds with unsubstituted bridge carbon atoms.

Unsubstituted quinuclidine is characterized by higher symmetry and less strain in the cyclic system than other saturated 1-azabicycloalkanes. The relatively high melting point (158°) and the considerable volatility of I are manifestations of these features. Disruption of the symmetry of the quinuclidine molecule by the introduction of substituents or transition to condensed systems brings about a decrease in the melting point and reduces the vapor tension [10-14].

The rigidly fixed structure of the quinuclidine ring also determines the specific properties of some trans-2,3-disubstituted quinuclidines [15]. Thus, for example, 7,9-dioxocyclohexano[b]quinuclidine (III), the properties of which differ sharply from the properties of cyclic β-diketones [16], is formed instead of the anhydride of (trans-2-carboxy-3-quinuclidyl)acetic acid (II) on reaction of II with acetic anhydride.

The trans fusion of the cyclohexanedione and quinuclidine systems hinders enolization of diketone III; III does not undergo the Knoevenagel condensation with aromatic aldehydes and does not react with acrylonitrile.

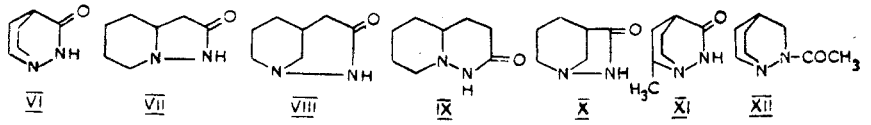


II III IV V

IV R = OH, OC_2H_5, NC_5H_{10}; V R = CH_3, C_6H_5

In addition, substances that have a labile hydrogen atom (water, alcohols, and amines) readily cleave diketone III to (2-acetyl-3-quinuclidyl)acetic acid or its derivatives (IV). Under the influence of a Grignard reagent, diketone III is converted with opening of the dioxocyclohexane fragment to keto alcohol V.

The hindered character of the conformational changes of the quinuclidine system is apparently also responsible for the anomalous basicity of 3-oxo-2-azaquinuclidine (VI) [17]. In contrast to all of the other 3-oxo-1,2-diazabicycloalkanes (VII-X), which have close pK_a values (2.2-2.8), 3-oxo-2-azaquinuclidine (VI) is a considerably weaker base, with pK_a 0.81.



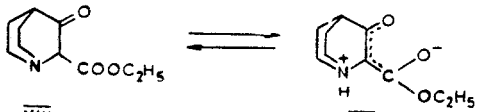
VI VII VIII IX X XI XII

The introduction of a carbonyl function in 1,2-diazabicyclic systems, which entails conversion from sp^3 to sp^2 hybridization of the C_3 atom, apparently leads to a certain distortion of the valence angles of the angular nitrogen atom. This distortion of the angles is compensated through a certain freedom of the conformational transitions in bicyclic compounds VII-X; disruptions of the valence angles are retained and are manifested in an appreciable reduction in basicity only in VI, in which the molecular conformation is quite rigidly fixed. This same effect is also observed in the case of C-methyl-substituted XI but vanishes on removal of the carbonyl groups attached to C_3 or on passing to N-acylated bicyclic compounds XII, which have a carbonyl group in the side chain rather than in the ring (pK_a = 2.20-2.29 for 2-acetyl-, 2-trimethoxybenzoyl-, and 2-nitroso-2-azaquinuclidines) [17].

An important feature of the structure of quinuclidine molecules is the specific character of the nonbonded electron pair of the nitrogen atom, which is practically unshielded by the adjacent hydrogen atom. N-Substituted piperidines and piperazines have characteristic absorption bands at 2700-2800 cm^{-1} due to the interaction of the free pair of electrons of the nitrogen atoms with the adjacent axial C–H bonds [18]. Quinuclidine does not absorb in this region [19], and this constitutes evidence for the absence of cis interaction; bands at 2430, 2915, and 3405 cm^{-1} are characteristic in this case.

The high degree of deshielding of the nonbonded pair of electrons attached to the quinuclidine nitrogen atom is also responsible for the considerably greater ease of its reaction with electrophilic agents as compared with the analogous reactions of tertiary aliphatic or monocyclic amines. For example, kinetic investigations [20] have shown that quinuclidine reacts with methyl iodide and isopropyl iodide 50 and 700 times faster, respectively, than triethylamine. The adducts at the nitrogen atom of this bicyclic system are also more stable. Thus the adduct of quinuclidine with trimethylborane is considerably more stable than the analogous trialkyamine derivatives [20].

The high basicity of the quinuclidine nitrogen atom in the case of 2-ethoxycarbonyl-3-oxoquinuclidine (XIII) on conversion of this compound to the enol form brings about transfer of a proton from the oxygen atom to the nitrogen atom to give dipolar ion XIV [21], the development of which is unknown for other ketone–enol systems containing an amino group. The primary existence of keto ester XIII in dipolar form XIV in hydroxyl-containing solvents was shown by means of PMR, IR, and UV spectroscopy and potentiometric titration [21, 22].



XIII XIV

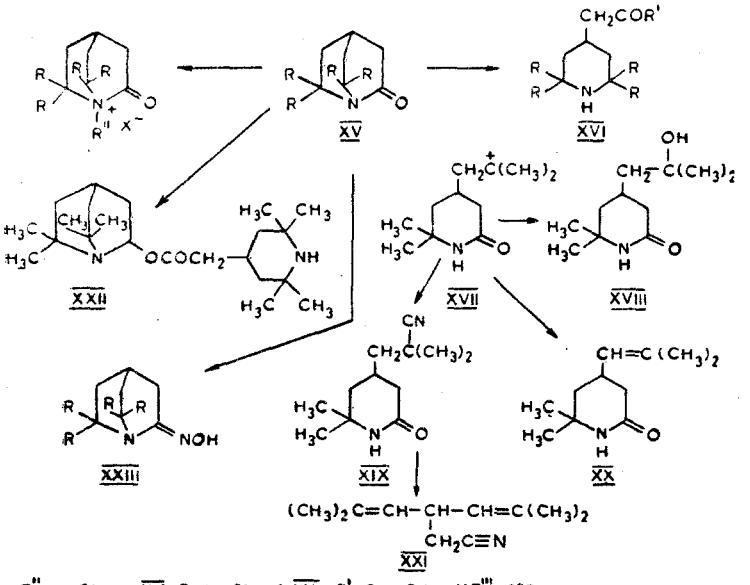
The tendency of diverse quinuclidine derivatives to undergo reactions with the corresponding electrophilic centers of biochemical receptors is also apparently associated with the high reactivity of the deshielded free pair of electrons of the nitrogen atom of the quinuclidine ring [23]. The considerably higher pharmacological activity of quinuclidine preparations as compared with the analogous derivatives of piperidines or acyclic amines and the recently discovered [24] possibility for the creation of effective medicinal agents of the quinuclidine series are explained by this possibility.

The rigidly fixed structure of the quinuclidine bicyclic system is responsible not only for the deshielding of the nonbonded electron pair of the angular nitrogen atom but also for its definite sterospecificity with respect to the axis of symmetry of the molecule. A manifestation of this characteristic is the peculiarity of the chemical behavior of compounds with multiple bonds in the α, β positions with respect to the angular nitrogen atom. The free p electrons of the nitrogen atoms in compounds of this type are practically orthogonal to the π electrons of the multiple bonds, and this excludes the possibility of a mesomeric effect, and the nitrogen atom has only an inductive effect on the adjacent grouping with multiple bonds.

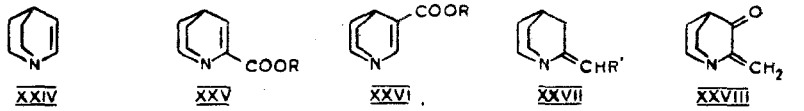
As an example one may cite the pecualiarities of the chemical behavior of 2-oxoquinuclidines (XV) [25-29], which are formally bicyclic amides. However, the absence of amide conjugation is responsible for the peculiarity of these compounds, the properties of which approach those of amino ketone. 2-Oxoquinuclidines XV are readily protonated and alkylated at the nitrogen atom; normal amides and lactams are

protonated at the oxygen atom. Compounds XV have high basicities; their pK_a values are 5.3-5.6, i.e., more than five orders of magnitude higher than the pK_a values of normal amides (for example, N-acetylpiperidine has pK_a 0.4). The frequency of the stretching vibrations of the C = O bond in their IR spectra is, on the average, 80 cm^{-1} higher than in the spectra of normal lactams, and the integral intensity of the carbonyl band is almost half the normal value. The absorption maxima in the UV spectra of 2-oxoquinuclidines occupy an intermediate position between the maxima of amides and ketones. The absence of amide mesomerism leads to an increase in the reactivity of XV. Thus in reactions with various proton nucleophilic agents (water, alcohols, amines, etc.), 2-oxoquinuclidines act as effective acylating agents in which stabilization of the initially formed intermediate adducts occurs with cleavage of the $N-C_2$ bond of the quinuclidine ring, and the final products of the transformations are 4-piperidylacetic acids (XVI) and derivatives. The hydrolysis, alcoholysis, and aminolysis of 2-oxoquinuclidine proceed at high rates, and their kinetics can be investigated by polarography, whereas normal amides and lactams are not reduced polarographically. In the case of 2-oxo-6,6,7,7-tetramethylquinuclidines (XIII, R = CH_3) [28,29] the reactions with nucleophilic agents in aprotic media (phenyllithium in ether, phosphorus pentachloride in benzene, lithium aluminum hydride in ether, and acetone cyanohydrin in an excess of this reagent) are also accompanied by cleavage of the C–N bond of the quinuclidine ring. However, in contrast to reactions with proton nucleophilic agents, the reactions in this case proceed at the $N-C(CH_3)_2$ bond rather than at the N–CO bond with subsequent stabilization of the intermediately formed unstable carbonium ion XVII either by addition of nucleophilic agents to give piperidones XVIII or XIX or as a result of splitting out of a proton with the development of unsaturated XX; in the case of the reaction with PCl_5 subsequent opening of the piperidone ring to give aliphatic dienonitrile XXI also occurs.

The ability of the carbonyl group in these compounds, in contrast to the normal amides and lactams, to undergo reduction by lithium aluminum hydride only to CHOH rather than CH_2 (the reduction product is acylated by excess 2-oxoquinuclidine to ester XXII), to form oximes XXIII with hydroxylamines and to increase the lability of the protons of the adjacent CH_2 group to such an extent that they readily undergo the usual deuterium exchange is also associated with the absence of mesomerism in 2-oxoquinuclidines.



The peculiarities of the chemical behavior of unsaturated quinuclidine compounds such as Δ^2-dehydroquinuclidine (XXIV) [30,31] and its 2- and 3-alkoxycarbonyl-substituted derivatives (XXV, XXVI) [4] and quinuclidine derivatives with a semicyclic double bond in the 2 position (XXVII) [32] are also associated with the fixed spatial orientation of the free pair of electrons of the angular nitrogen atom.

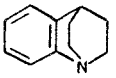


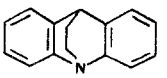
These compounds are formally bicyclic enamines. However, the absence of p π conjugation is responsible for their difference from ordinary tertiary α-vinylamines. Thus, for example, Δ^2-dehydroquinuclidines do not have the characteristic (for enamines) absorption maximum at 230 nm and are not hydrolyzed under mild conditions by dilute acids.

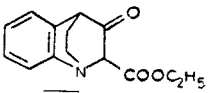
In addition, XXV and XXVI differ substantially from linear vinylogs of amides in reactions with nucleophilic agents with respect to the considerably lesser (due only to the inductive effect of nitrogen) deactivation of the double bond. Compounds XXVI are capable of adding strong nucleophiles such as alcohols, ethyleneimine, 1,3-dipolar agents, and isopropylmagnesium iodide [4, 30, 33] to the double bond, whereas XXV also adds substances with an active methylene group – nitromethane and malonic and cyanoacetic esters [4]. Δ^2-Dehydroquinuclidine (XXIV), in which both the mesomeric effect of the angular nitrogen atom and the activating effect of the alkoxycarbonyl group on the double bond are absent, reacts only with phenyl azide [30, 33].

The absence of enamine properties is also distinctly displayed in 2-methylene-3-oxoquinuclidine (XXVIII) [34, 36], which readily adds various nucleophilic reagents – water, alcohols, phenols, aromatic and aliphatic amines, hydrogen halides, and substances with an active methylene group – to the semicyclic double bond.

The spatial orientation of the free pair of electrons of the quinuclidine nitrogen atom also affects the properties of the condensed benzo[b]- and dibenzo[b, e]- quinuclidine systems (XXIX, XXX) [37-39]. Whereas the free pair of electrons of the nitrogen atom is conjugated with the π electrons of the aromatic system in N,N-dialkylanilines, 1,2,3,4-tetrahydroquinolines, or indolines, the pπ mesomeric effect is absent in benzoquinuclidines XXIX and XXX.


XXIX


XXX



XXXI

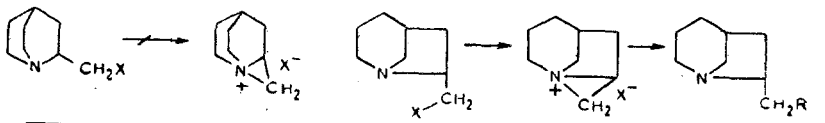
This changes the basicities of the compounds substantially. Whereas the pK_a values of N, N-diethylaniline [40] and diphenylamine [40] are 6.56 and 0.79, respectively, the pK_a values for XXIX and XXX are 7.79 and 4.46, respectively. The reactivity of the aromatic portion of the molecule is also reduced considerably [38, 41, 42]. Thus, for example, benzo[b]quinuclidine does not undergo diazo coupling with p-nitrobenzenediazonium chloride [38] and is not brominated in the benzene ring: only the perbromide or a molecular complex are formed in various solvents at various temperatures in the presence or absence of catalysts [42]. Substituents can be introduced in the benzene ring of benzo[b]quinuclidine with more active electrophilic reagents – a nitrating mixture or chlorosulfonic acid [41, 42]. However, in contrast to ordinary aromatic amines, the electrophilic substituent enters the meta position relative to the nitrogen atom rather than the ortho or para position: it was established by means of the PMR spectra and dipole moments that the products of nitration and chlorosulfonation of benzo[b]-quinuclidines are the 7-substituted derivatives [41, 42].

It has also been shown by PMR spectroscopy that the quinuclidine ring in benzo[b]quinuclidine is more strained than in unsubstituted quinuclidine because of the different lengths of the bridge bond [4-7]. This factor is responsible, for example, for the considerable shift of the ketone–enol tautometric equilibrium of 2-ethoxycarbonyl-3-oxobenzo[b]quinuclidine (XXXI) to favor the ketone form as compared with 2-ethoxycarbonyl-3-oxoquinuclidine (XIII), inasmuch as the conversion to the enol form in benzoquinuclidine XXXI is associated with a further increase in the strained character of the bicyclic system [4].

Investigations of the thermodynamic equilibria of the diastereomeric 2-ethoxycarbonyl-3-oxobenzo-[b]quinuclidines and of the kinetics of deuterium exchange in these compounds showed [4] that steric interaction of the substituents with the protons of the adjacent (unsubstituted) bridge of the quinuclidine ring, as one should have expected, is substantially greater than with the benzene ring. This is also in agreement with the different reactivities of the substituents in the syn and anti positions relative to the benzene ring of various benzo[b]quinuclidine derivatives [4-7]. Thus, for example, in the reaction with thionyl chloride of diastereomers of 3-hydroxy-3-ethoxycarbonyl- and 3-hydroxy-3-cyanobenzo[b] quinuclidines having an anti orientation of the hydroxyl groups the reaction proceeds via an S_N^2 mechanism with attack by the reagent on the C_3 atom from the benzene ring side and formation of the corresponding syn-3-chloro deri-

vatives as the final products. In the case of isomers with a syn orientation of the hydroxyl group the reaction proceeds ambiguously, but the anti-3-chloro derivatives are not formed.

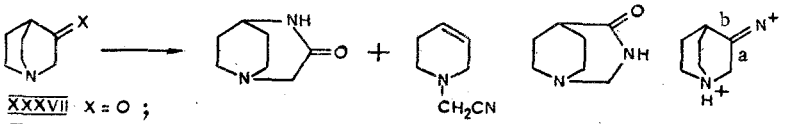
The chemical inertness of 2-halomethylquinuclidines (XXXII) is also associated with the fixed orientation of the free electron pair of the quinuclidine ring [43, 44].



XXXII XXXIII XXXIV XXXV XXXVI

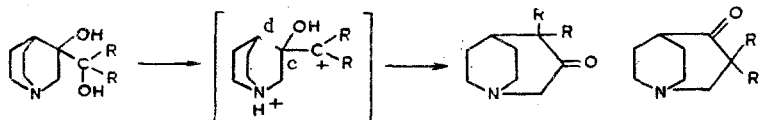
It is well known that the reactions of β-aminoalkyl halides with nucleophilic agents proceeds through intermediate aziridinium derivatives. This pathway activates the halogen atoms in various β-aminoalkyl halides in which the nitrogen atom is located in the aliphatic chain or is included in the mono- or 1-azabicyclic system. Halomethyl derivatives of 1-azabicyclo[3.2.1]octane (XXXIV) apparently react with nucleophilic agents via the indicated mechanism (XXXIV → XXXV → XXXVI). In the case of 2-halomethylquinuclidines XXXII the formation of the intermediate isomeric aziridinium salts (XXXIII) is sterically hindered, and XXXII are therefore characterized by extremely low reactivities. They either do not react with diverse nucleophilic agents (amines, alcohols, metal cyanides, sodiomalonic ester, etc.), or the reactions take place under severe conditions with formation of the products in low yield.

The effect of the angular nitrogen atom of the quinuclidine molecules is also clearly manifested in reactions of 3-oxoquinuclidine (XXXVII) with diazomethane and nitrous acid, of the oxime (XXXVIII) of ketone XXXVII with polyphosphoric acid, and of (3-hydroxy-3-quinuclidyl)dimethyl(diaryl)carbinols (XXXIX) with sulfuric acid. These reactions, which proceed with ring expansion, invariably lead to the formation of one of two possible isomeric 1-azabicyclononanes. Thus 3-oxo-1,4-diazabicyclo[3.2.2]nonane (XL) and 1-cyanomethyl-Δ^3-dehydropiperidine (XLI) are obtained in the reaction of ketone XXXVII with nitrous acid (Schmidt reaction) [45] and of oxime XXXVIII with polyphosphoric acid (Beckmann reaction) [46, 47]:



XXXVII X = O ;
XXXVIII X = NOH
XL XLI XLII XLIII

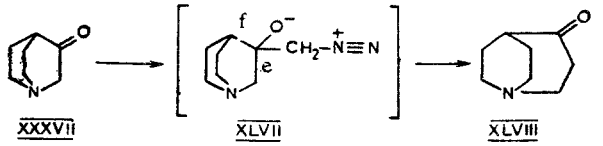
The formation of a second isomeric lactam (XLII) is not observed. The nucleophilicity of σ bond *a* in the intermediate dipolar ion of the XLIII type is apparently reduced owing to the inductive effect of the protonated nitrogen atom of the quinuclidine ring, and migration of the more nucleophilic b bond, which leads to lactam XL, is realized. An analogous pattern is observed in the dehydration of ditertiary alcohols XXXIX with sulfuric acid [48-50]. Of the two possible products of ring expansion (XLIV and XLV), only ketone XLIV is formed.



XXXIX XLVI XLIV XLV

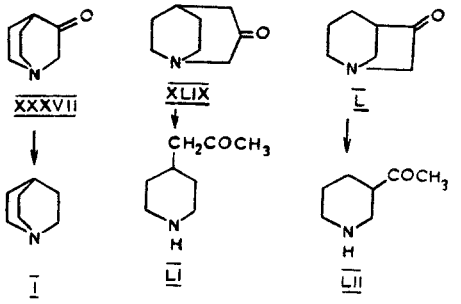
The conversion of glycol XXXIX to ketone XLIV is associated, as in the preceding case, with migration in the intermediate dipolar ion of the XLVI type of σ bond d, which is more remote from the protonated ring nitrogen atom.

In the reaction of 3-oxoquinuclidine (XXXVII) with diazomethane, which proceeds in the presence of an alkaline reagent (barium oxide), the sextet rearrangement is also realized through migration of the more nucleophilic bond. However, in this case, when the ring nitrogen atom is not protonated, the more nucleophilic σ bond proves to be α, β-carbon bond e of the quinuclidine ring, and the final product of the rearrangement is 4-oxo-1-azabicyclo[3.2.2]nonane (XLVIII) [51]:



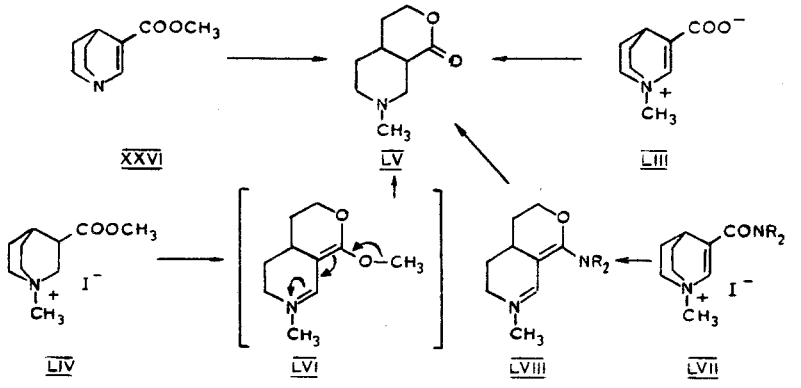
XXXVII XLVII XLVIII

The above-noted peculiarities of the structure of the symmetrical, rigidly fixed quinuclidine structure also determine its considerably greater stability in various reactions as compared with other 1-azabicycloalkanes. Thus, for example, quinuclidine remains unchanged when it is heated with concentrated acids and when it is treated with a strong oxidizing agent such as potassium permanganate [10]. The quinuclidine ring is retained in the Clemmens reduction of 3-oxoquinuclidine (XXXVII), whereas analogous reactions with other 1-azabicycloalkanones (XLIX and L) are accompanied by cleavage of the bicyclic systems [52];



The pyrolysis and hydrogenolysis of quaternary quinuclidinium salts also proceed to a considerable degree with retention of the bicyclic structure [53-55]. In contrast to the quaternary bases of other 1-azabicycloalkanes, in which opening of the bicyclic system proceeds readily during Hofmann degradation, quinuclidinium bases are more inclined to splitting out of aliphatic alcohols with retention of the energetically advantageous bicyclic system [56-58].

N-Oxides of the quinuclidine series also display thermal stability [59]. It is well known that the pyrolysis of N-oxides of monocyclic amines is often accompanied by rearrangements with ring expansion, Cope elimination to give hydroxylamine derivatives, and other transformations of the cyclic system. Quinuclidine N-oxide undergoes pyrolysis [59] only above 200°. In this case N-deoxidation to give quinuclidine is observed.



The N-oxides of quinuclidine and its derivatives display a capacity for the formation of O-acylium salts that are resistant to hydrolysis in neutral and acidic media and are titrated by alkalis as dibasic acids [60].

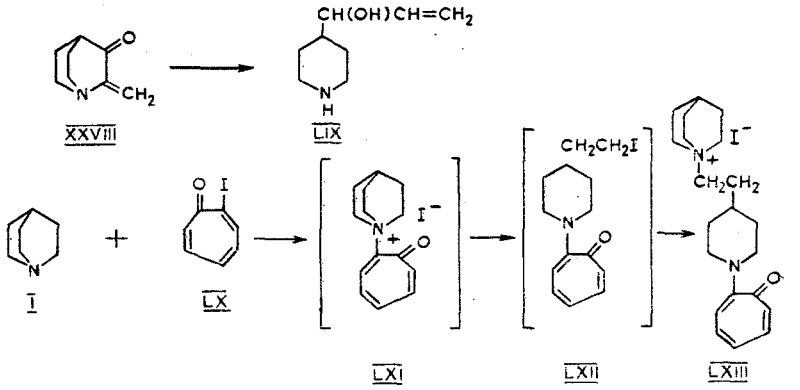
In addition, examples of quite facile opening of the quinuclidine ring are known for some substituted quinuclidines. The thermal conversion of 3-methoxycarbonyl-Δ^2-dehydroquinuclidine (XXVI) and its betaine (LIII) and methiodide (LIV) to lactone LV has been described [61, 62].

Amide methiodides LVII undergo similar rearrangement, and the resulting iminolactones (LVIII) are converted to lactone LV by acid hydrolysis [63]. It has been assumed that the conversion of methiodide LIV to lactone LV is a consequence of two 1,3-sigmatropic rearrangements and that the intermediate is LVI; It has been shown that the alkyl halide liberated in the reaction is formed through the ester function.

The indicated sigmatropic rearrangements of quaternary 3-ethoxycarbonyl-Δ^2-dehydroquinuclidinium salts have also been used as key steps in a new synthesis of indoloquinolizidines [64].

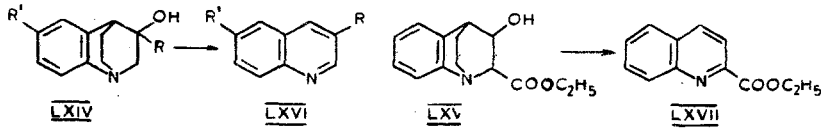
Opening of the quinuclidine ring is observed under mild conditions in the reduction of 2-methylene-3-oxoquinuclidine (XXVIII). The final product of this reaction is 1-(4-piperidyl)-2-propenol (LIX).

The quinuclidine ring in quaternary salt LXI, formed from quinuclidine (I) and 2-iodocyclohepta-2,-4,6-trien-1-one (LX), is cleaved under mild conditions (at room temperature in benzene) [65, 66].



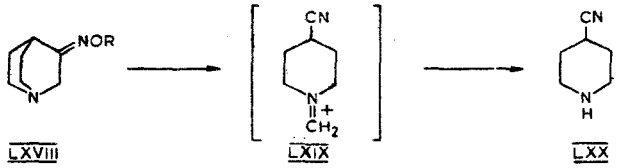
Iodide LXII formed by opening of the quinuclidine ring reacts with excess quinuclidine (I) to give quaternary salt LXIII, which is also the final product of the transformations described above.

The peculiarities of the opening of the bicyclic quinuclidine system are associated with problems involved in the applicability of Bredt's rule. Thus, for example, quinuclidine cannot be dehydrogenated by means of mercuric acetate, inasmuch as the reaction should proceed through the Δ^1-dehydroquinuclidinium salt which is prohibited by Bredt's rule. Quinuclidine is dehydrogenated under severe conditions by palladium on carbon or by selenium at 300°, during which cleavage of the C–N bond and subsequent aromatization of the system are observed to give 4-ethylpyridine [67]. The quinuclidine ring in 3-hydroxy derivatives of benzo[b]quinuclidine derivatives containing electron-acceptor aryl or ethoxycarbonyl groupings (LXIV, LXV) is opened considerably more readily [8, 9].

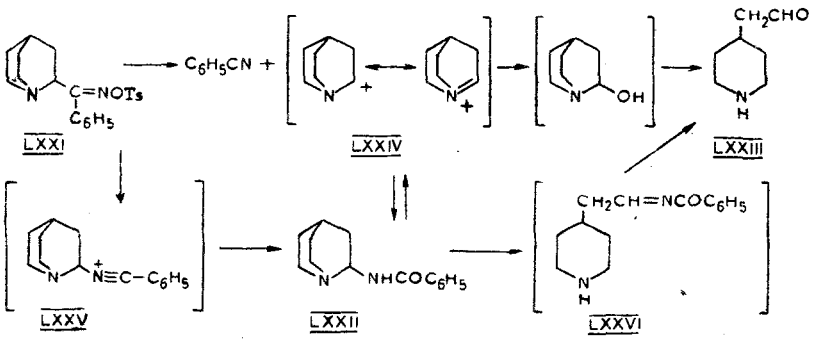


When LXIV and LXV are heated with acetic anhydride, the ethylene bridge is ejected from the quinuclidine portion of the molecule with aromatization of the product to quinoline derivatives LXVI and LXVII.

The fragmentation of 4-haloquinuclidines and ethers of 3-oxoquinuclidine and 2-benzoylquinuclidine oximes has been studied extensively. It has been shown that the acetate, benzoate, and primarily the p-toluenesulfonate of 3-oxoquinuclidine oxime (LXVIII) undergo fragmentation under alkaline saponification conditions with subsequent hydrolysis of the intermediate carbimmonium ion LXIX to secondary amine LXX [48, 68, 69].

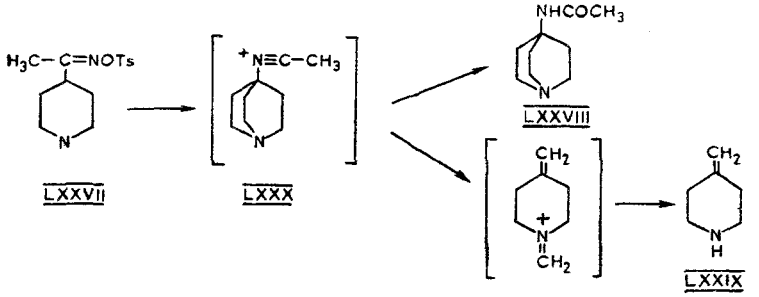


The chief product of the hydrolysis of 2-benzoylquinuclidine oxime tosylate (LXXI) is 2-benzamidoquinuclidine (LXXII), which is formed along with benzonitrile and 4-piperidylacetaldehyde (LXXIII); this constitutes evidence for cleavage of tosylate LXXI via a synchronous fragmentation scheme through quinuclidinium cation LXXIV [70, 71].

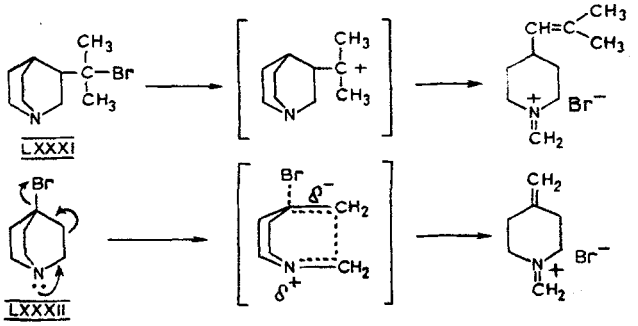


The rate of hydrolysis of LXXI is lower by a factor of two to four than that of its nitrogen-free analog – 2-benzoylbicyclo[2.2.2]octane oxime tosylate – and considerably lower than the rates observed for noncyclic aminotosylates, and this is apparently associated primarily with the steric hindrance to mesomerism in the 1-azabicyclic 2-quinuclidyl cation (LXXIV). However, inasmuch as the fragmentation of LXXI is not suppressed, Grob and Sieber have expressed the assumption that Bredt's rule is not obligatory for the energy-rich intermediates of this reaction. The formation of 2-phenoxyquinuclidine on heating tosylate LXXI with phenol confirms the possibility of the existence of cation LXXIV. Moreover, the development of LXXII during the hydrolysis of ether LXXI can be represented both by recombination of benzonitrile and quinuclidinium cation LXXIV and through intermediate nitrilium cation LXXV. The formation of an aldehyde (LXXIII) is also possible through open acylated imine LXXVI without participation of carbonium ion LXXIV.

Under alkaline hydrolysis conditions, 4-acetylquinuclidine oxime tosylate (LXXVII) undergoes 97% Beckmann rearrangement to 4-acetamidoquinuclidine (LXXVIII) and only 3% fragmentation to 4-methylenepiperidine (LXXIX) [72]. Both processes are apparently realized through a single common intermediate N-(4-quinuclidyl)acetonitrilium ion (LXXX).



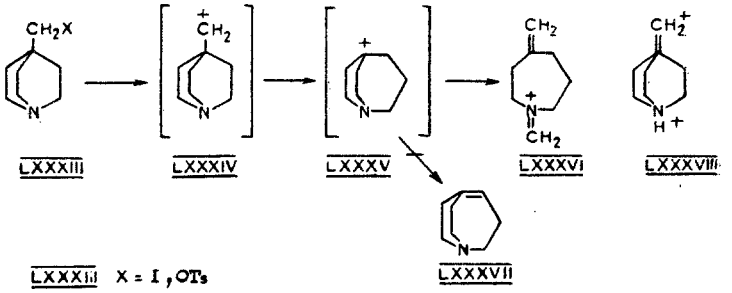
The fragmentation of 2-(3-quinuclidyl)-2-bromopropane (LXXXI) and 4-bromoquinuclidine (LXXXII), in contrast to aliphatic γ-aminoalkyl halides, in which substitution, elimination, and ring closing processes occur simultaneously, processeds unambiguously, via a stepwise mechanism in the first case [73], and via a synchronous mechanism in the second case [74].



This fragmentation mechanism is associated with the rigid bicyclic structure of the quinuclidine ring, in which the stereoelectronic condition – the C_α–Hal bond and the axis of the free electron pair are anticoplanar to the C_β–C_γ bond – is observed.

The fragmentation of 4-tosyloxymethyl- and 4-iodomethylquinuclidines (LXXXIII) in alkaline media also proceeds unambiguously [75].

In this case tertiary carbonium ion LXXXIV, for which 1,2-elimination with the formation of dehydro derivative LXXXVII is sterically impossible (because of Bredt's rule and ring strain), is formed by isomerization of the initially formed carbonium ion (LXXXIV).



LXXXIII LXXXIV LXXXV LXXXVI LXXXVIII

LXXXIII X = I, OTs LXXXVII

The tendency for fragmentation, which leads to the cation of 1,4-dimethylene-1-azacycloheptane (LXXXVI), therefore increases.

When tosylate LXXXIII is heated in acidic media, only the tosyloxy group is substituted; the formation of dication LXXXVIII is electrostatically hindered.

The specific character of the mass spectroscopic behavior of quinuclidine compounds is also associated with the problem of the applicability of Bredt's rule to this class of compounds. It is well known that α cleavage with the formation of stable amine fragments occurs during the disintegration of aliphatic and monocyclic amines under the influence of electron impact. In the course of the fragmentation of quinuclidine compounds for which detachment of a substituent from the α position is also characteristic, the development of ions of this type with a planar positively charged nitrogen atom in the node of the bridge system contradicts Bredt's rule. As a consequence of this, the disintegration of the quinuclidine systems occurs from the open form of the molecular ion [76-79]. The specific character of the behavior of quinuclidine compounds under the influence of electron impact was proved by means of low-voltage mass spectroscopy. The intensity of the fragments corresponding to α cleavage for quinuclidine compounds that consume energy in ring opening decreases sharply in this case. For amines of another type in which the nitrogen atom is not found at the bridgehead and the preliminary formation of an open form of the molecular ion is not necessary, the intensity of the M−1 fragment does not change substantially as the voltage decreases from 30 to 12 eV. The mass spectroscopic cleavage of the C−N bond in quinuclidine and benzoquinuclidine molecules proceeds primarily with participation of the bridge bearing a substituent. The subsequent ejection of fragments including this substituent leads to the formation of characteristic fragments, the peaks of which are of maximum intensity in the spectra.

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