REACTIONS OF QUINUCLIDINE COMPOUNDS INVOLVING OPENING OF THE BICYCLIC SYSTEM (REVIEW)

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The reactions of quinuclidine compounds that lead to opening of the 1-azabicyclic system at the N–C and C–C bonds to give piperidine derivatives or, via subsequent rearrangements, derivatives of other heterocyclic systems, are correlated. Processes involving the fragmentation of quinuclidines in chemical reactions and under electron impact and reactions involving expansion of the quinuclidine ring and intermediate cleavage of the bicyclic system are examined.

Quinuclidine (1-azabicyclo[2.2.2]octane) differs from other 1-azabicycloalkanes with respect to its rigidly fixed structure with a high degree of symmetry and only slight strain of the bicyclic system [1]. Investigations by NMR spectroscopy have shown that the eclipsed conformations that arise in the quinuclidine system due to the fixed boat form in both six-membered rings increase the energy of interaction of the unbonded atoms somewhat. This leads to distortion of the geometry of the molecules with deviation of their symmetry from C_{3v}. However, the resulting conformational distortions are slight and are accompanied by a change of no more than 12° in the dihedral angles even for 2,3-disubstituted quinuclidines. The indicated conformational changes in the molecules in series of quinuclidine therefore do not play a substantial role [2]. The specific character of the free electron pair of the nodal nitrogen atom is also associated with the peculiarities of the conformation of quinuclidine compounds. This pair of electrons is deshielded, virtually does not interact with the adjacent axial C–H bonds, and, owing to the rigidly fixed structure of the bicyclic system, is sterically directed along the axis of symmetry of the molecule [1, 3-5].

Quinuclidine structures are characterized by sufficient stabilities. Quinuclidine remains unchanged when it is heated with concentrated acids and is not oxidized by potassium permanganate [6]; the quinuclidine ring is retained in the Clemmensen reduction of 3-oxoquinuclidine, whereas other 1-azabicycloalkanones undergo reductive cleavage to give piperidine derivatives [7]. Only N-deoxidation to give unsubstituted quinuclidine occurs in the pyrolysis of quinuclidine N-oxide, whereas the pyrolysis of N-oxides of monocyclic amines is often accompanied by transformations of the cyclic system [8]. Quinuclidine compounds also display definite stability under electron impact, particularly in low-voltage mass spectroscopy.

Reactions involving Hofmann cleavage of 1-methylquinuclidinium hydroxides differ from the analogous reactions of quaternary bases of unsymmetrical 1-azabicycloalkanes. Whereas in the pyrolysis of the latter the bicyclic system is opened to give a substituted monocyclic system, the Hofmann reaction for the energically more favorable symmetrical quinuclidine and its alkyl-substituted derivatives takes place to a significant degree with retention of the bicyclic system, and the methyl group attached to the nitrogen atom is split out in the form of methanol [9-12].

In addition, a considerable amount of experimental data on various transformations of quinuclidine compounds that are accompanied by opening of the bicyclic system at the C–N and C–C bonds has been accumulated. As a result of these transformations, piperidine derivatives or, via subsequent transformations, derivatives of other heterocyclic systems are formed from quinuclidines under sufficiently mild conditions.

Correlation of the data pertaining to opening of the quinuclidine molecule is the subject of the present review.

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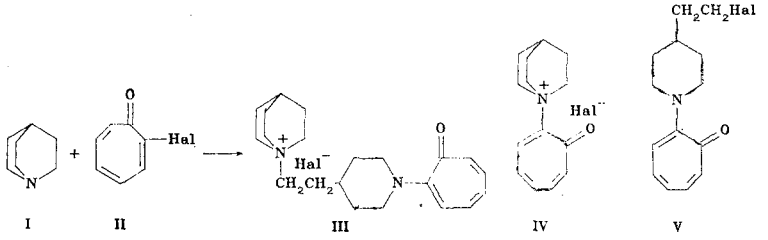
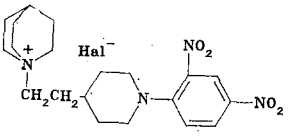
An important factor that facilitates opening of the quinuclidine ring is the introduction of strong electron acceptors at the α-carbon atoms or at the bicyclic nitrogen atom. The reactions of quinuclidine with α-halotropolones may serve as a graphic example. Compound III, which evidently arises as a result of nucleophilic attack by amine I on the saturated α-carbon atom of quinuclidinium salt IV — the primary reaction product — is formed in the reaction of a molar excess of quinuclidine (I) with iodo(chloro)tropolones (II) under mild conditions (in benzene at room temperature). This attack becomes possible owing to delocalization of the electron density from the nitrogen atom to the heptatriene part of the salt IV molecule, which substantially increases the electrophilicity of the α-carbon atoms of the quinuclidine system. Crystallization of salt IV, obtained by mixing equimolar amounts of I and II, also leads to opening of the quinuclidine ring and the formation of N-substituted piperidine V. Halogen ions are the attacking nucleophilic particles on passing from salt IV to 4-haloalkylpiperidines V [13]; in this case 2-chloro- and 2-iodotropolones react with quinuclidine in an inert solvent, whereas 2-fluorotropolone reacts only in dimethyl sulfoxide (DMSO) [14], which constitutes evidence for the substantial significance of the nucleophilicity of the halogen atom that participates in this reaction. A similar pattern (opening of the quinuclidine molecule under the influence of a strong electron-acceptor substituent attached to the nitrogen atom to give VI) is observed in the reaction of quinuclidine with 2,4-dinitrochlorobenzene [14].



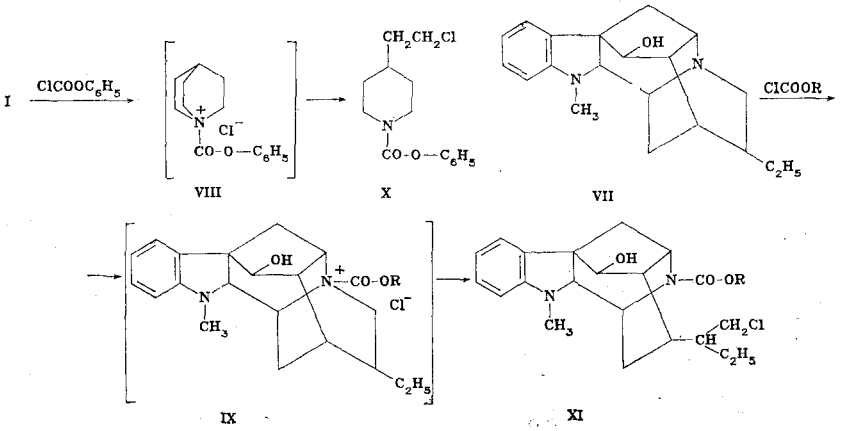
I II III IV V



VI

Chlorocarbonate esters are effective reagents for the cleavage of both unsubstituted quinuclidine (I) and the quinuclidine fragment of 21-deoxyeimaline (VII). The reactions proceed under mild conditions (in dichloroethane at 25°C) through the corresponding quaternary salts VIII and IX, in which the polarized N—C bonds are readily cleaved, and urethanes X and XI are formed in high yields [15].

Chlorocarbonate esters readily cleave 1,2,3,4-tetrahydroisoquinolines with a benzyl group attached to the $C_{(1)}$ atom but do not react with N-methylpyrrolidine and N-methylpiperidine. The ease of opening of quinuclidine compounds that, like N-methylpyrrolidine and N-methylpiperidine, do not contain activating acceptor groupings attached to the α-carbon atoms, by chlorocarbonate esters is probably determined by the great steric accessibility



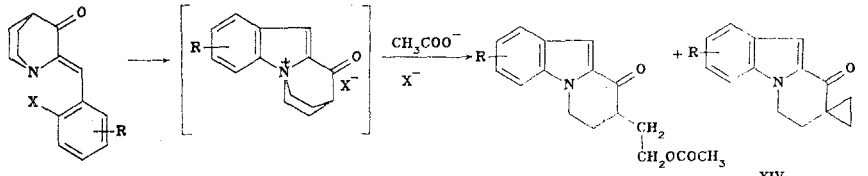
VIII X VII

IX XI

R = C_2H_5, C_6H_5

of the virtually unshielded p electrons of the ring nitrogen atoms to attack by electrophilic reagents — chlorocarbonate esters — to give cleaved quaternary salts VIII and IX.

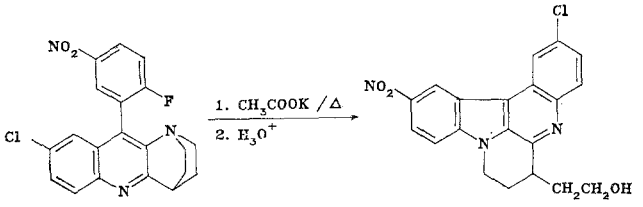
Opening of the quinuclidine ring at the N—C bond, which is accompanied by a skeletal rearrangement, was observed when 2-arylidene-3-oxoquinuclidines with a halogen in the ortho position of the aryl group (XII) were heated in diglyme in the presence of potassium acetate. Tetrahydropyridoindoles XIII and XIV were obtained as a result of rearrangement of the skeleton [16].



XII XV XIII XIV

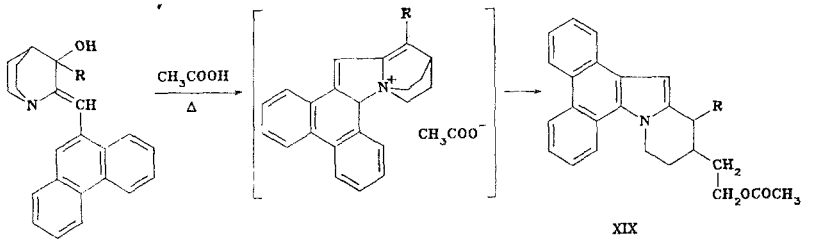
The formation of three-ring systems is evidently associated with intramolecular quaternization of the quinuclidine fragment of XII and subsequent attack by X^- or the acetate anion on the polarized N—C bond of intermediate quaternary salt XV to give acetoxyethyl derivatives XIII or mixtures of them with the corresponding haloethyl derivatives, which then undergo 1,3 elimination to give spiro-cyclopropyl compounds XIV.

Condensed quinuclidine XVI undergoes a similar rearrangement to give polycyclic XVII [17].



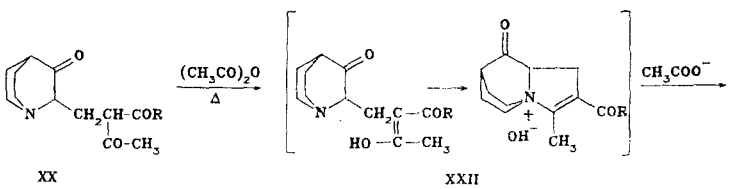
XVI XVII

Substituted 2-phenanthrolinylmethylene-3-oxoquinuclidines XVIII are converted to tetrahydropyridoindole derivatives (XIX) via the same scheme but under milder conditions [18].

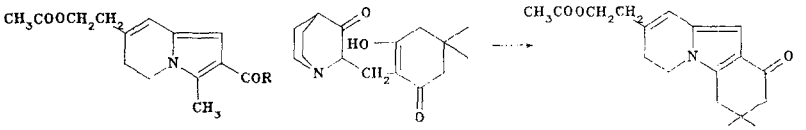


XVIII XIX

The possibility of intramolecular nucleophilic attack on the electrophilic center of the molecule by the quinuclidine nitrogen atom, which promotes quaternization of the nitrogen atom and polarization of the N—C bond, is realized in the case of 3-oxoquinuclidines that contain a β-dicarbonyl substituent in the 2 position (XX, XXII). Heating of these compounds with acetic anhydride is accompanied by the formation of an intermediate quinuclidinium derivative of the XXII type, and the unsubstituted N—C bond of the quinuclidine fragment is cleaved when salt XXII is attacked by the acetate anion to give dihydroindolizine derivatives (XXIII, XXIV) [19].

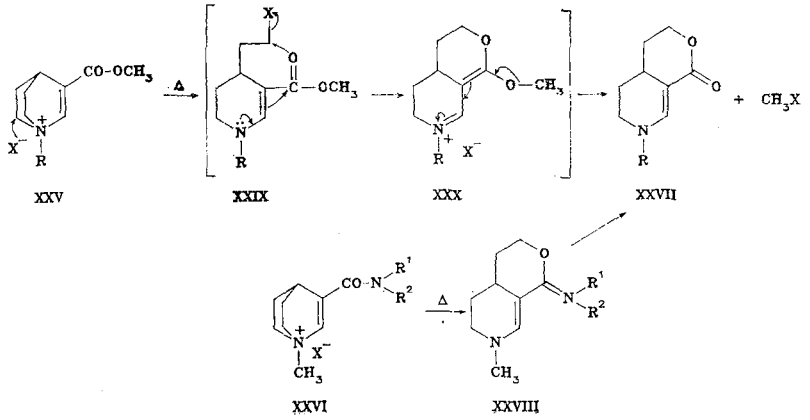


XX XXII



XXIII XXI XXIV

Interesting rearrangements involving cleavage of the quinuclidine ring at the N–C bond and subsequent rearrangement occur when esters and amides of 2,3-dehydroquinuclidine-3-carboxylic acid and their salts and quaternary derivatives (XXV, XXVI) are heated. The products are 4-(β-hydroxyethyl)-2,3-dehydropiperidine-3-carboxylic acid lactones (XXVII) or their imino derivatives (XXVIII); the latter are converted to a lactone (XXVII, R = CH_3) by acidic hydrolysis [20-23].

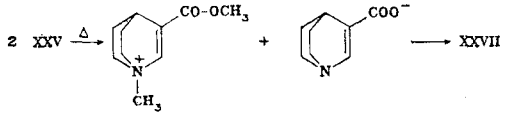


XXV XXIX XXX XXVII

XXVI XXVIII

The ease of rearrangement of XXV is associated mainly with the character of R. Thus the N-allyl and N-propargyl derivatives, in which electron-acceptor substituents, which promote polarization of the N–C bond, are attached to the nitrogen atom, give lactones XXVII at room temperature, whereas the N-methyl derivative requires heating above 100°C, ester hydrochloride XXV (R = H, X = Cl) is converted to a mixture of lactones XXVII (R = CH_3 and R = H) at 185°C, and base XXV (R and X are absent) requires heating at 200°C. Amides XXVI undergo rearrangement when they are heated briefly (30 sec) at their melting points. The mechanism of the examined transformations includes attack by the anion on quaternary salt XXV (R = CH_3) followed by two 1,3-sigmatropic rearrangements through intermediates XXIX and XXX to give lactone XXVII (R = CH_3) and an alkyl halide through the ester function. Since the anion participates in the mechanism of the process, its nucleophilicity is important. It has been shown that esters XXV, in which X = Cl^-, Br^-, and I^-, undergo smooth rearrangement to lactones XXVII. On the other hand, compounds in which X = NO_3^-, ClO_4^-, and 4-$CH_3C_6H_4SO_3^-$ do not undergo rearrangement, evidently because of the insufficient nucleophilicity of these anions.

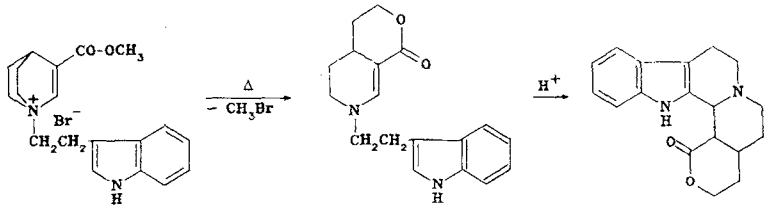
The conversion of ester XXV (R and X are absent) to lactone XXVII (R = CH_3) consists in the formation of cation XXXI and carboxylate ion XXXII from two ester molecules; the cation of this ion pair then undergoes rearrangement to the lactone via the scheme presented above, the nucleophile in which is probably carboxylate ion XXXII.



XXXI XXXII

The described thermal rearrangement was used for the synthesis of indoloquinolizidine alkaloid XXXIII [24].

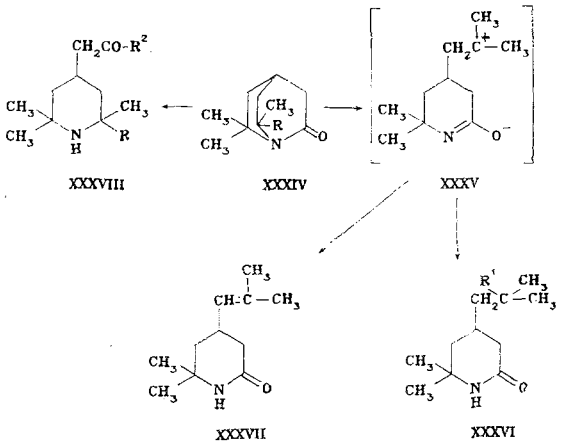
Opening of the quinuclidine ring at the N–C bonds in the examples presented above is associated with an increase in the polarity of this bond under the influence of the –I effect of the substituents, which is intensified in the case of formation of a cationic center on the nitrogen atom. Weakening of the N–C bond in quinuclidine compounds is also observed when bulky substituents are introduced in the α-position relative to the nitrogen atom of the bicyclic system. Thus 2-oxo-6,6,7,7-tetramethylquinuclidine (XXXIV, R = CH_3), which



XXXIII

contains two +I-donor methyl groups attached to the α-carbon atoms of the bicyclic system, is readily cleaved at the N—C$(CH_3)_2$ bond upon reaction in aprotic media with phenyllithium, lithium aluminum hydride, and phosphorus pentachloride or with acetone cyanohydrin in excess reagent. The resulting unstable carbonium ion XXXV is stabilized either by addition of nucleophilic agents to give piperidones XXXVI or by splitting out of a proton, which leads to unsaturated XXXVII [25, 26].

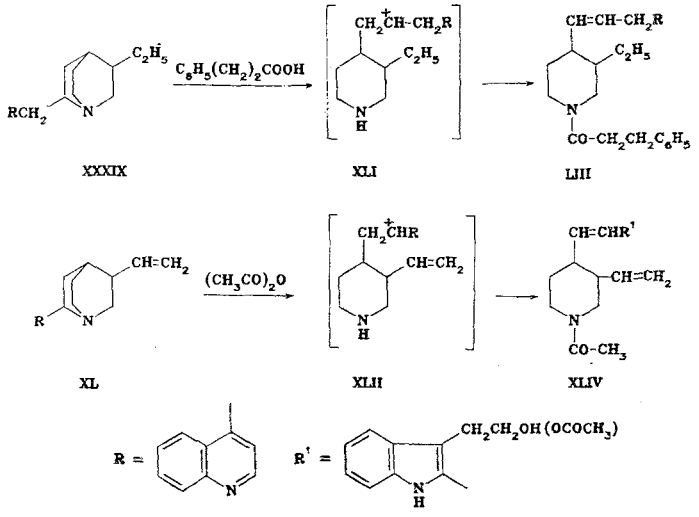
At the same time, protic nucleophilic reagents react with XXXIV at the N—CO bond to give 4-piperidylacetic acid and its derivatives (XXXVIII) [26, 27].



XXXVIII XXXIV XXXV XXXVII XXXVI

R=H, CH_3; R^1=OH, CN; R^2=OH, OAlk, NR_2

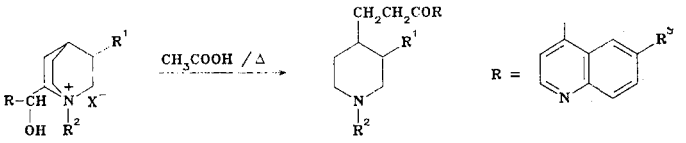
The transformations of the quinuclidine fragments of dihydrodeoxycinchonine (XXXIX) by heating with dihydrocinnamic acid [28] and of cinchonamine (XL) by heating with acetic anhydride [29] proceed via a similar mechanism, evidently through carbonium ions XLI and XLII. Stabilization of the carbonium ions is realized by detachment of a proton and the formation of unsaturated XLIII and XLIV. Although the indicated reagents are not sufficiently effective for opening of the nitrogen-containing rings in other cases [30, 31], their successful use in the examples presented above is determined by the presence in XXXIX and XL in the α position relative to the nitrogen atom of the quinuclidine ring of bulky substituents that participate in the formation of conjugated systems during ring opening.



XXXIX XLI LIII

XL XLII XLIV

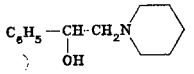
Quinuclidine derivatives that contain (at the α-carbon atom) a hydroxymethyl substituent bonded to an aromatic group are readily cleaved to give amino ketones. This type of cleavage, which is catalyzed by acids, was studied by Rabe, who accomplished the conversion of quinine alkaloids XLV (quinine and cinchonine and their spatial isomers and corresponding methiodides) to toxines XLVI by this method [32, 33]. The reactions of the methiodides, like the reactions of the bases, are carried out in acetic acid but with the addition of sodium acetate. The acid sulfate of cinchonine undergoes a similar transformation to give cinchotoxine XLVI (R = R^2 = H, R^1 = C_2H_5) when it is heated.



XLV XLVI

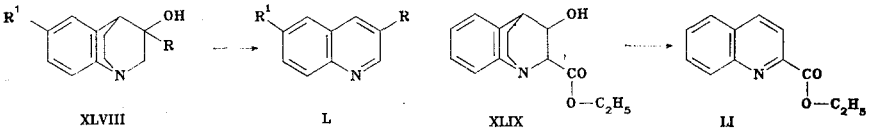
R=4-quinolyl, 6-methoxy-4-quinolyl R^1=C_2H_5, CH=CH_2; R^2=CH_3 or is absent , X=I or is absent

The acidic cleavage of quinine alkaloids XLV is determined by their α-hydroxy amine structure. Other examples of the cleavage of natural compounds that have an α-hydroxy amine fragment (for example, narcotine and hydroxycodeine) to amino ketones are also known [34, 35]; however, the method is not universal. Fragmentation could not be realized by the reaction of 1-(β-hydroxy-β-phenyl)ethylpiperidine (XLVII) with acetic acid and its methiodide under the same conditions in the presence of sodium acetate [36].



XLVII

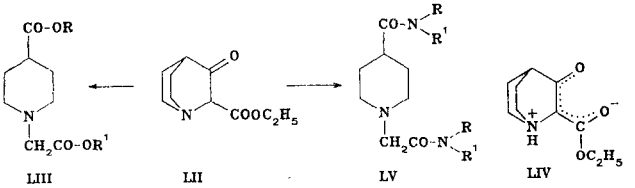
The quinuclidine ring in 3-hydroxy derivatives of benzoquinuclidine with electron-acceptor groupings in the 2 and 3 positions (XLVIII and XLIX) is opened under mild conditions. The N—C bond is cleaved and the ethylene bridge is ejected from the quinuclidine part of the molecule when these compounds are heated with acetic anhydride; the process is accompanied by aromatization and leads to the formation of quinoline derivatives (L and LI) [37, 38].



XLVIII L XLIX LI

R=C_6H_5, 4-$CH_3C_6H_4$; R^1=H, OCH_3

2-Ethoxycarbonyl-3-oxoquinuclidine (LII), which contain a β-keto ester grouping, undergoes ring opening at the $C_{(2)}$—$C_{(3)}$ bond when it is heated with water or alcohol to give, respectively, 1-carboxymethylisonipecotinic acid (LIII, R = R^1 = H) or its diethyl ester (LIII, R = R^1 = C_2H_5). The reaction with alcohol is accelerated by the addition of triethylamine [39].



LIII LII LV LIV

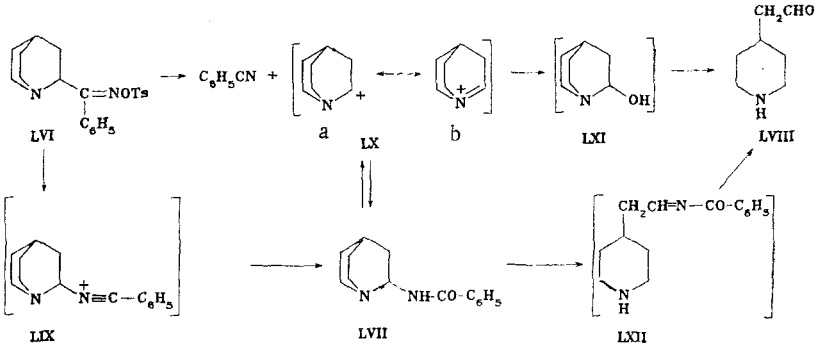
Acetoacetic ester, which is similar to an aliphatic β-keto ester, is resistant to heating with water to 100°C and with alcohol to 180°C. The substantial difference in the reactivities of acetoacetic ester and heterocyclic β-keto ester LII that is observed in their reaction with weak nucleophiles (water and alcohol) is probably associated with the peculiarities of the structure of LII. It has been demonstrated by PMR, IR, and UV spectroscopy that keto ester LII, owing to the high basicity of the quinuclidine nitrogen atom, exists primarily in the form of dipolar ion LIV in hydroxy-containing solvents. Polarization of the $C_{(2)}$—$C_{(3)}$ bond promotes nucleophilic attack on the hydroxy or alkoxy group and subsequent opening of this bond. It should be noted that when keto ester LII is heated with

an aqueous solution of sodium hydroxide, the quinuclidine ring also undergoes partial opening to give sodium 1-ethoxycarbonylmethylisonipecotinate; however, conversion of ester LII to 3-oxoquinuclidine with the simultaneous liberation of alcohol and sodium carbonate predominates here.

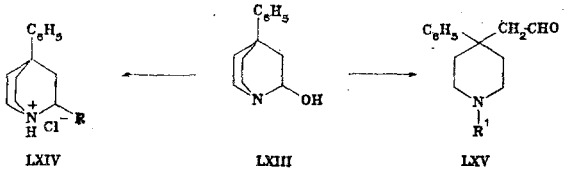
The reaction of keto ester LII with cyclic secondary and aromatic amines proceeds ambiguously: In addition to 3-oxoquinuclidine-2-carboxamides (and their 3-arylimino derivatives in the case of aromatic amines), products of opening of the quinuclidine ring, viz., diamides LV, are formed. This process is catalyzed by water [39].

Processes involving the hydrolytic fragmentation of arylsulfonic esters of oximes of carbonyl derivatives of quinuclidine and quinuclidine compounds with a halogen atom in the γ position, which were studied by Grob and co-workers, occupy an important position among reactions that take place with opening of the quinuclidine ring.

In addition to the principal product of the Beckmann reaction, viz., 2-benzamidoquinuclidine (LVII), benzonitrile and 4-piperidylacetaldehyde (LVIII) are formed in the alkaline hydrolysis of 2-benzoylquinuclidine oxime tosylate (LVI). Two approaches to the indicated reaction products are proposed. The pathway to amide LVII can be represented either through nitrilium cation LIX or by recombination of benzonitrile and quinuclidinium cation LX — products of synchronous fragmentation of tosylate LVI. In the opinion of the authors, the possibility of the existence of cation LX is determined by delocalization of the positive charge on the nodel nitrogen atom and is confirmed by the formation of 2-phenoxyquinuclidine when tosylate LVI is heated with phenol. It has been assumed that resonance form LXb with a double bond at the bridgehead is completely likely for the high energies of the intermediates of this reaction, despite Bredt's rule. The development of aldehyde LVIII is conceived of as being either the result of cleavage of the intermediate unstable 2-hydroxyquinuclidine (LXI) or through the formation of open acylated imine LXII without the participation of carbonium ion LX [40, 41].



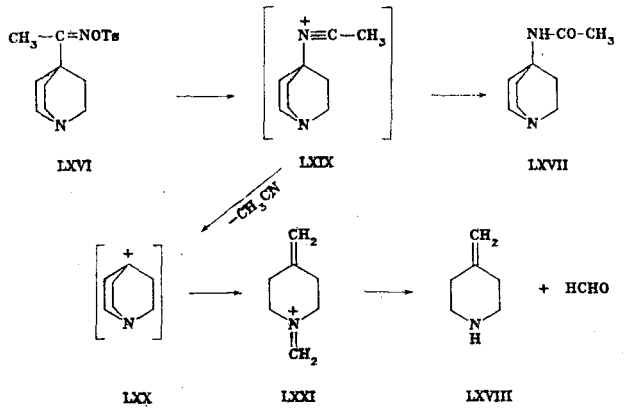
It has been shown that 2-hydroxy-4-phenylquinuclidine (LXIII) is considerably more stable than 2-hydroxyquinuclidine (LXI). Base LXIII remains unchanged when it is refluxed in concentrated acids, and its hydrochloride gives 2-acetoxy-4-phenylquinuclidine hydrochloride LXIV (R = $OCOCH_3$) upon treatment with a mixture of acetic anhydride and acetic acid saturated with hydrogen chloride, whereas it gives 2-chloro derivative LXIV (R = Cl) upon refluxing with thionyl chloride. Although the introduction of a bulky phenyl group hinders cleavage of hemiaminal LXIII, the latter is, nevertheless, converted to sulfonamide LXV (R^1 = $SO_2C_6H_4CH_3$-p) upon reaction with p-toluenesulfonic acid and to amide LXV (R^1 = $COCH_3$) upon reaction with a mixture of acetic acid and acetic anhydride [42].



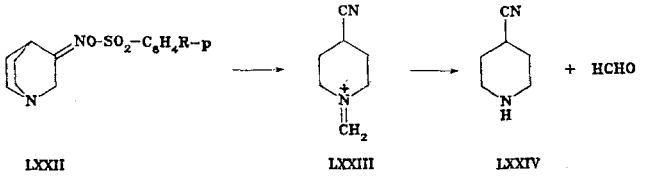
R=$OCOCH_3$, Cl; R^1=$SO_2C_6H_4CH_3$-p, $COCH_3$

As in the case of tosylate LVI, the alkaline hydrolysis of 4-acetylquinuclidine oxime tosylate (LXVI) is accompanied chiefly by Beckmann rearrangement of the first sort, and the principal reaction product is 4-acetamidoquinuclidine (LXVII); a small amount of 4-methylenepiperidine (LXVIII) is also formed. Both processes evidently take place through a common

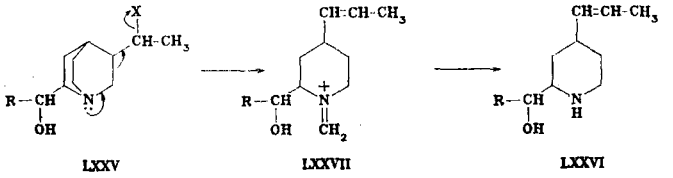
intermediate N-(4-quinuclidyl)acetonitrilium ion (LXIX), which either adds a hydroxy anion to give amide LXVII or splits out acetonitrile to give unstable carbonium ion LXX, which undergoes fragmentation to carbimmonium ion LXXI. Hydrolysis of the LXXI ion leads to 4-methylenepiperidine [43].



Opening of the quinuclidine molecule at the $C_{(2)}$—$C_{(3)}$ bond is also observed in the hydrolysis of 3-oxoquinuclidine oxime sulfonates (LXXII). Carbimmonium ion LXXIII, which arises as a result of fragmentation of ester LXXII, is subsequently saponified to 4-cyanopiperidine (LXXIV) [44-47].

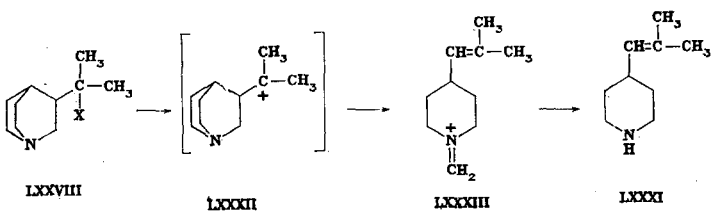


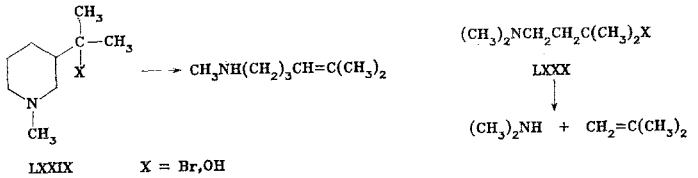
The fragmentation of γ-halo derivatives of quinuclidine was observed in the alkaline hydrolysis of halodihydroquinines and halodihydrocinchonines and their spatial isomers LXXV [48, 49]. This process leads to disubstituted piperidines LXXVI, which are evidently formed through immonium salts LXXVII [50]



R = 4-quinolyl 6-methoxy-4-quinolyl X = Br, I

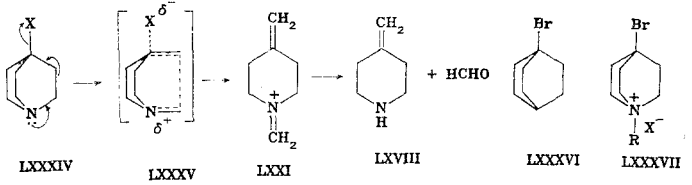
A comparative study of the hydrolysis of γ-haloquinuclidines LXXVIII, γ-halopiperidines LXXIX, and aliphatic γ-halo amines LXXX showed that replacement of the halogen atom by a hydroxy group and dehydrohalogenation occur in addition to fragmentation of these compounds [51]. However, in contrast to LXXIX and LXXX, for which the former two reactions are important, fragmentation to give 4-(2,2-dimethylvinyl)piperidine (LXXXI) prevails for quinuclidine derivatives LXXVIII. On the basis of the ease of hydrolysis of LXXVIII and the character of the side products, a stepwise mechanism of fragmentation through carbonium ion LXXXII and carbimmonium ion LXXXIII is proposed [51].





LXXIX X = Br,OH

Heterolytic fragmentation of 4-haloquinuclidines LXXXIV proceeds extremely readily. These compounds are cleaved by heating in aqueous solution or in 80% alcohol. The reaction is accelerated by the addition of silver ions, which tie up the halogen. It is assumed that the transformations proceed via a synchronous mechanism with simultaneous cleavage of the $C_{(2)}$—$C_{(3)}$ bond, ionization of the $C_{(4)}$—X bond, and the formation of a cationic center at the nitrogen atom through transition state LXXXV. The subsequent course of the process is similar to the process described above. The rigidly fixed structure of the quinuclidine molecule, in which the stereoelectronic condition is observed — the $C_{(4)}$—Hal bond and the axis of the free electron pair of the nitrogen atom are anticoplanar relative to the $C_{(2)}$—$C_{(3)}$ bond — favors the conversion of LXXXIV to 4-methylenequinuclidine (LXVIII). The fact that LXXXVI and LXXXVII do not undergo fragmentation even after refluxing with an aqueous solution of silver nitrate for 4 weeks also constituted evidence for participation of the p electrons of the nitrogen atom in the ionization of LXXXIV molecules; only replacement of the halogen atom by a hydroxy group occurs in the case of bromide LXXXVI, and LXXXVII remains unchanged [52-54].

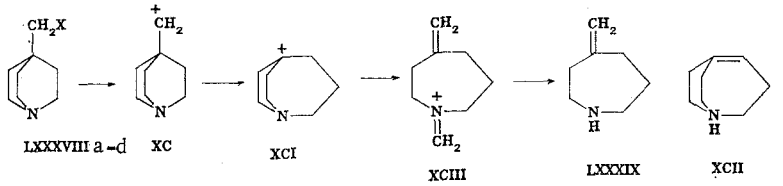


LXXXIV LXXXV LXXI LXVIII LXXXVI LXXXVII

X=Cl, Br, I, OTs; R=H, CH_3

It should be noted that protonation of amines LXXVIII-LXXX also suppresses their solvolytic fragmentation.

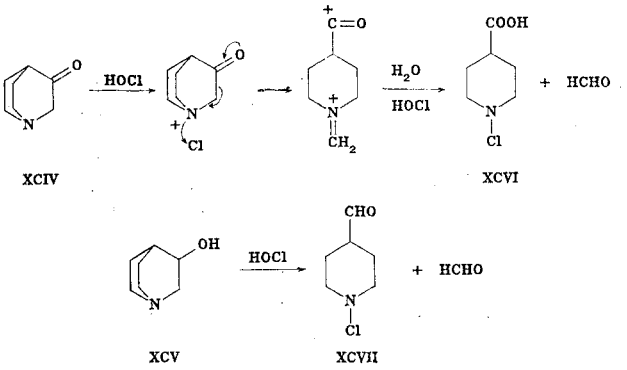
4-(Halomethyl)quinuclidines LXXXVIII behave somewhat differently. 4-(Iodomethyl)-quinuclidine remains unchanged under the conditions of solvolysis of LXXXIV. The more reactive 4-(tosyloxymethyl)quinuclidine (LXXXVIIIa) is converted to 4-methylene-1-azacycloheptane (LXXXIX) upon prolonged heating with aqueous ethanol containing an equivalent of sodium hydroxide. In this case the initially formed carbonium ion XC undergoes rearrangement to the energy-rich carbonium ion XCI, which, because of steric hindrance, cannot be stabilized by splitting out of a proton to give dehydro derivative XCII, and fragmentation of the XCI ion to give carbimmonium ion XCIII becomes preferable. As a consequence of protonation of the nitrogen atom, the solvolysis of ester LXXXVIIIa in acidic solution proceeds extremely slowly and leads to a mixture of products of replacement of the tosyloxy group, viz., 4-(chloromethyl)- and 4-(hydroxymethyl)quinuclidines (LXXXVIIIc, d) [55].



LXXXVIII a-d XC XCI XCIII LXXXIX XCII

a X=OTs; b X=I; c X=Cl; d X=OH

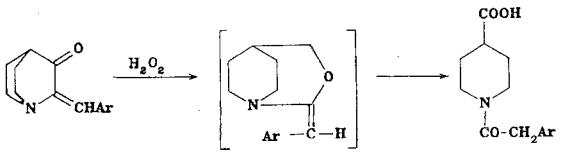
The oxidative fragmentation of 3-oxo- (XCIV) and 3-hydroxyquinuclidine (XCV) proceeds in the same way as the solvolytic cleavage of 4-haloquinuclidines. The quinuclidine ring of these compounds is cleaved at the $C_{(2)}$—$C_{(3)}$ bonds by the action of hypochlorous acid, and 1-chloroisonipecotinic acid (XCVI) and 1-chloro-4-formylpiperidine (XCVII) are formed as a result of the subsequent transformations presented in the scheme [56].



XCIV XCVI

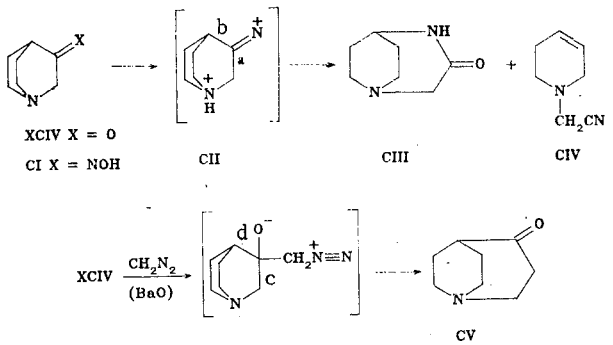
XCV XCVII

The oxidation of 3-oxoquinuclidines XCVIII, which contain an arylmethylene grouping in the 2 position, with hydrogen peroxide also proceeds with opening of the quinuclidine bicyclic system to give 1-substituted isonipecotinic acids (XCIX). Lactones C, the hydrolysis of which gives acids XCIX, are probably intermediates [57].



XCVIII C XCIX

The reactions of quinuclidine derivatives with expansion of one of the rings, which lead to difficult-to-obtain homologous bicyclic systems, viz., 1-aza- and 1,4-diazabicyclo-[3.2.2]nonanes, are of considerable interest. The following are reactions of this sort: a) the reaction of 3-oxoquinuclidine with diazomethane; b) the Beckmann rearrangement of 3-oxoquinuclidine oxime; c) the reaction of 3-oxoquinuclidine with hydrazoic acid (the Schmidt reaction); d) the pinacol rearrangement of ditertiary alcohols of the quinuclidine series.



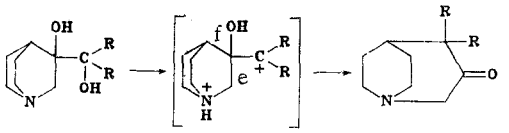
XCIV X = O
CI X = NOH CII CIII CIV

XCIV CV

An intermediate in the Schmidt and Beckmann reactions, which are catalyzed by strong acids (sulfuric and polyphosphoric acids), is dipolar ion CII, in which, owing to the inductive effect of the protonated ring nitrogen atom, the more nucleophilic b bond migrates to form only one of two possible lactams, viz., CIII. Cleavage of the $C_{(3)}$—$C_{(4)}$ bond to give unsaturated nitrile CIV occurs simultaneously [44, 47, 58].

In the reaction of 3-oxoquinuclidine (XCIV) with diazomethane, which proceeds in the presence of an alkaline reagent (barium oxide), the sextet rearrangement is realized via migration of the more nucleophilic δ bond c to give 4-oxo-1-azabicyclo[3.2.2]nonane (CV) [59].

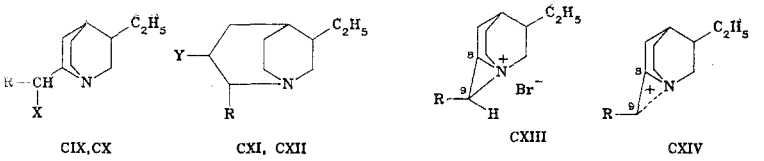
Like the Schmidt and Beckmann reactions, the dehydration of ditertiary alcohols of the quinuclidine series (CVI) by the action of sulfuric acid proceeds with the formation of one of two possible isomers, viz., ketone CVII, which arises as a result of migration of the more remote (from the protonated nodal nitrogen atom) and, consequently, more nucleophilic δ bond f in intermediate dication CVIII [60-62].



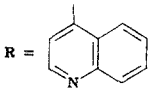
CVI CVIII CVII

It is apparent from the examples presented above that the processes take place unambiguously and other isomeric bicyclic ketones or lactams are not formed in the case of quinuclidine derivatives as a consequence of the substantial effect of the nodal nitrogen atom, which, depending on the reaction conditions, determines a relative increase in the nucleophilicity of one or another bond.

The conversion of 2-substituted quinuclidine to a 1-azabicyclo[3.2.2]nonane derivative was observed when hydrocinchonine (CIX) was treated with phosphorus tribromide. A small amount of isomeric bromide CXI is formed along with the normal bromide. Bromide CX undergoes more nearly complete rearrangement on treatment with silver salts, and 2-(4-quinolyl)-3-methoxy-1-azabicyclo[3.2.2]nonane (CXII) is formed [63, 64].



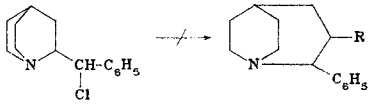
CIX,CX CXI, CXII CXIII CXIV



CIX X=OH; CX X=Br; CXI Y=Br; CXII Y=OCH_3

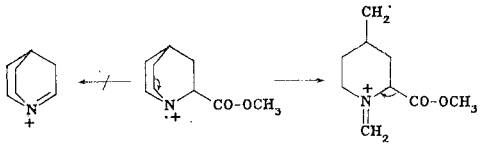
It has been assumed that the intermediate in the rearrangement, which has been called the heterocinchonine rearrangement, is ethyleneimmonium salt CXIII and that subsequent attack on the $C_{(9)}$ or $C_{(8)}$ atom by the nucleophile leads to bromide CX or CXI. An alternative mechanism based on Wagner–Meerwein rearrangement with migration of the $N–C_{(8)}$ bond to the $C_{(9)}$ cationic center in accordance with the CXIV structure has also been advanced with allowance for the great strain of ethyleneimmonium ion CXIII, which is associated with the rigidly fixed structure of the quinuclidine molecule and the certain orientation of the p electrons of the nitrogen atom.

The described rearrangement could not be extended to other α-(halomethyl)quinuclidines: The formation of CXVI was not noted in the solvolysis of 2-(α-chlorobenzyl)quinuclidine (CXV) [63].



CXV CXVI

The behavior of quinuclidine derivatives under electron impact under mass-spectrometric conditions differs substantially from the fragmentation of aliphatic and monocyclic amines. Whereas α cleavage to give stable amine fragments is characteristic for the latter, this type of fragmentation, which leads to the formation of cation CXVIII with a double bond at the bridgehead is hindered for quinuclidine derivatives such as CXVII. As a consequence of this, the fragmentation of quinuclidine compounds proceeds through the open form of molecular ion CXIX with cleavage of primarily the bridge bond, which contains a functional group [cleavage of the $C_{(2)}–C_{(3)}$ bond] [65-69]. 2-(Ethoxycarbonyl)quinuclidine, 3-oxo-, 3-hydroxy-, 3-acyloxyquinuclidines and their benzo analogs, 2-oxo-6,6,7,7-tetramethylquinuclidine, 2-ethoxycarbonyl-3-oxoquinuclidine, and benzoquinuclidine undergo fragmentation via this pathway. In the case of functionally 2-substituted 5-oxoquinuclidines the open form of the molecular ion is formed through cleavage of the bridge bond, which contains an oxo group. Some 3-substituted benzoquinuclidines such as 3-(ethoxycarbonyl)-, 3-amino-, and 3-(hydroxymethyl)benzoquinuclidines under electron impact form two open forms of the molecular ion, which are formed as a consequence of cleavage of the bridge bond that contains a substituent [$C_{(2)}–C_{(3)}$] and the bridge bond without a substituent [$C_{(5)}–C_{(6)}$].



CXVIII CXVII CXIX

Thus the material presented in this review provides evidence that the introduction of strong electron-acceptor substituents in the 1 or 2 position of quinuclidine destabilizes the bicyclic system. Bulky groups in the α position relative to the nodal nitrogen atom have a similar effect, particularly when the subsequent reactions increase the conjugation of the system. Quinuclidine derivatives that contain the following groupings of atoms are also unstable: —COCH(N<)COOR, >N— CH=C(COOR)—, ArCH=C(N<)—CO—, RCO(R¹CO)CH_2CH_2·C(N<)CO, and halogen atoms in the γ position relative to the nodal nitrogen atom. Compounds of this type are cleaved quite readily with opening of the quinuclidine system to give piperidines or with rearrangement of the skeleton of the molecule to give derivatives of other heterocycles.

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