HETEROCYCLES, Vol. 7, No. 2, 1977

RECENT ADVANCES IN QUINUCLIDINE CHEMISTRY

LEONID YAKHONTOV

S. Ordzhonikidze All-Union Chemical-Pharmaceutical Research Institute, Moscow, USSR

This article aims to review the published and own results in quinuclidine chemistry over recent ten years. The main attention of the paper is concentrated on some peculiarities in reactivity of quinuclidine derivatives and on relationships between the chemical structure and biological activity.

I. INTRODUCTION

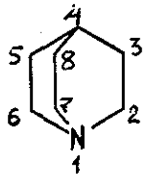
Advances in quinuclidine chemistry before 1967, including the brilliant total synthesis of quinine by R.B.Woodward and W.E.Doering[1], were described in the previous reviews[2-5].

The main investigations in this field for the last ten years (1967-1976) were concerned with peculiarities in the structure and reactivity of quinuclidine derivatives and new structure-activity relationships of such type compounds. New effective drugs have been found and introduced for practical purposes. As to synthetical works[6-15] various types of common methods, which had been discovered before and discussed in the previous review[2], were used for the building of quinuclidine rings.

Progress in quinuclidine chemistry of this period is due to the extensive application for research of the current physico-chemical methods: NMR-, mass-spectroscopy etc.

II. Investigations of Some Features of Quinuclidine Derivatives

As has been stated earlier /2,5/ the quinuclidine [1-azabicyclo (2,2,2) octane] (I), in contrast to tertiary aliphatic amines and N-substituted piperidines, has a rigid structure.



I

The atoms forming the quinuclidine system are limited in changing their relative positions by rotation around bond axes at the bicycle, in which each ring has a "boat"-form.

At the same time the fixed "boat"-configuration leads to the eclipsed conformations by the bridged atoms. The energy of atomic interactions increases and this results in some twisting of molecules with deviations of symmetry from C_{3V}/16/.

The NMR method demonstrated/16-24/ that the experimental spin constants $J^{cis}_{H_2H_3}$ of the unsubstituted and 4-monosubstituted quinuclidines are in good agreement with the constants calculated by Karplus equation, which expresses the relationship between these constants and the relative proton orientation determined by the dihedral angle φ between the plates containing these protons. The experimental values of $J^{trans}_{H_2H_3}$ = 5.3 - 5.6 Hz are in contrast more than 1 HZ different from the calculated for φ=120°. This is an evidence for increase of the H-C-H valent angles of quinuclidine against the common tetrahedral one.

The introduction of substituents at position 3 of the quinuclidine ring changes values $J_{H_2H_3}$. According to the relation $\left.\frac{\partial J}{\partial \varphi}\right|_{\varphi=0} \approx 0$ the decrease of $J^{cis}_{H_2H_3}$ by the introduction at the position 3 carbon-, nitrogen- and oxygen-containing substituents is represented by only the electron-attractive effect of substituents. The increase of value $J^{trans}_{H_2H_3}$ by substituents, in which the first atom is carbon one, cannot be explained only by electronegative effects, but this is an evidence of increase of the dihedral angle between the plates H-C_2-C_3 and H-C_3-C_2, which by $J^{trans}_{H_2H_3}$ = 1 Hz is about 4° in comparison with the angle for unsubstituted quinuclidine. For 3-substituted quinuclidines with oxygen or nitrogen as the first atom at the substituent the value $J^{trans}_{H_2H_3}$ is reduced against for unsubstituted quinuclidine. More strong reduction $J^{trans}_{H_2H_3}$ in comparison with $J^{cis}_{H_2H_3}$ evidently demonstrates a twisting of molecule at the cost of decrease of the dihedral angle between the plates H-C_2-C_3 and H-C_3-C_2. So, the conformations of the bridge with increase (Fig. 1a) or decrease (Fig. 1b) of dihedral angle φ predominante for 3-substituted quinuclidines depending on the character of the first atom of the substituent.

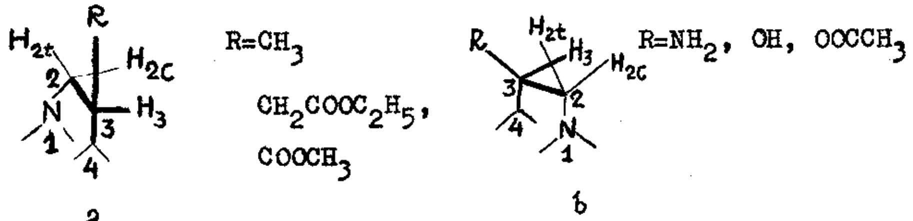


Fig. 1

NMR data do not permit to estimate the character and the value of twisting the molecule while introduction of the second substituent into position 2 cis-orientated to the first one because $\varphi = 0$ and $J^{cis}_{H_2H_3}$ are practically not different for 2,3-di-cis- and 3-mono-substituted quinuclidines. On the contrary, by trans-orientation of the second substituent the values $J^{trans}_{H_2H_3}$ are rather effected. From the difference of the trans constants of 2,3-trans-dicarboxyquinuclidine and unsubstituted quinuclidine $\Delta J^{trans}_{H_2H_3} = 8.2 - 5.3 = 2.9$ Hz, and $\frac{\partial J}{\partial \varphi} \Big/ \varphi = 120^{\circ} \sim 0.24$ Hz/grad., the value of twist of the dihedral angle can be calculated in this case as $10\text{-}12^{\circ}$. The angle between the plates $H\text{-}C_2\text{-}C_3$ and $H\text{-}C_3\text{-}C_2$ for this compound increases, between the plates $R_3\text{-}C_3\text{-}C_2$ and $R_2\text{-}C_2\text{-}C_3$ reduces, in other words, the substituents R_2 and R_3 approach one another (Fig. 2).

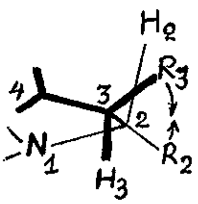
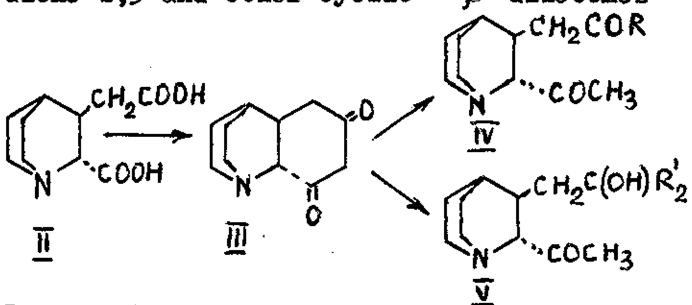


Fig. 2

It is clear, that the above described conformation twists of quinuclidine molecules, especially for compounds without substituents at the bridge carbon atoms, are not significant and the quinuclidine system is usually characterized by a rather rigid structure.

Rigidity of conformation determines specific properties of some 2,3-trans-disubstituted quinuclidines[25]. Thus, for example, tricyclic β-diketone III, which is formed instead of anhydride of dicarboxylic acid II by interaction of trans-diacid II with acetic anhydride has rather specific properties in comparison with cyclohexanedione-1,3 and other cyclic β-diketones[26].

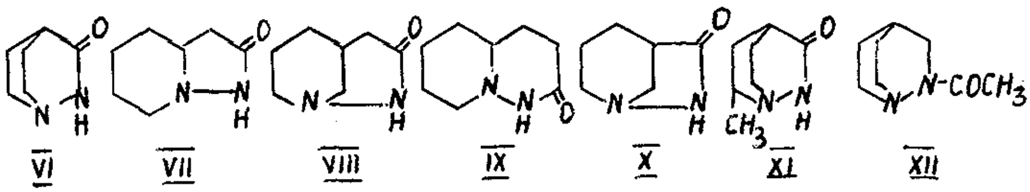


R=OH, OC_2H_5, NC_5H_{10}

R'=CH_3, C_6H_5

Transcondensation of cyclohexanedione and quinuclidine systems inhibits enolization of diketone III and consequently decreases the reactivity of CH_2-group between two carbonyls. Compound III gives neither Knoevenagel reaction with aromatic aldehydes, nor interaction with acrylonitrile. At the same time substances with mobile hydrogen atoms (water, alcohols, amines) split easily diketone III up to 2-acetylquinuclidyl-3-acetic acid or its derivatives (IV). With Grignard reagents compound III transforms into 2-acetyl--3-[β -dimethyl(or diphenyl)- β -hydroxyethyl] quinuclidine (V).

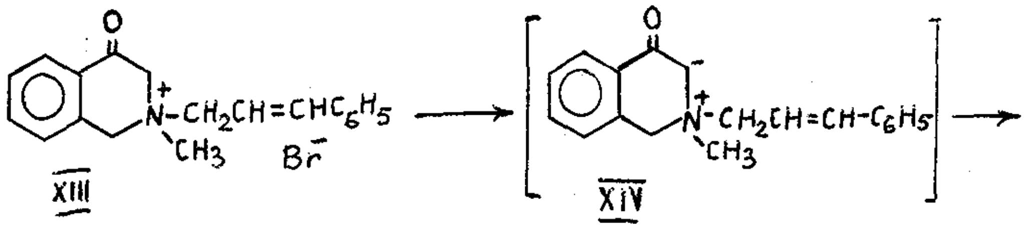
Limits in the change of conformation of quinuclidine systems are responsible for the anomalous basicity of 3-oxo--2-azaquinuclidine (VI). Unlike other 3-oxo-1,2-diazabicycloalkanes: 3-oxo-1,2-diazabicyclo /3,0,4/ nonane (VII), 3-oxo-1,2-diazabicyclo /3,1,3/ nonane (VIII), 3-oxo-1,2-diazabicyclo /4,0,4/ decane (IX) and 3-oxo-1,2-diazabicyclo /2,1,3/ octane (X), having pKa between 2.3 and 2.8, 3-oxo--2-azaquinuclidine (VI) is much less basic compound with pKa 0.81 [27].

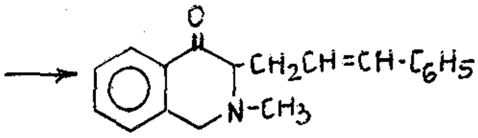


The introduction of carbonyl group into 1,2-diazabycyclic systems, transferring sp^3 hybridization at C_3 atom to sp^2 one, seems to distort the valence angles of the bridgehead nitrogen. The capability of bicycles VII-X to conformational changes permit to avoid this distortion of angles. Only in the case of compound VI, where the conformation of molecule is fasten enough, the distortion of valence angles conserves and exhibits in the decrease of basicity. The same effect can be observed for C-methylated VI (XI), but disappears while removing of the carbonyl group from C_3 or in passing to N-acylated bicycles XII, which have carbonyl function not at the cycle, but at the side chain (for 2-acetyl-,2-trimethoxybenzoyl-, and 2-nitroso-2-azaquinuclidines pK_a are 2.20-2.29)[27].

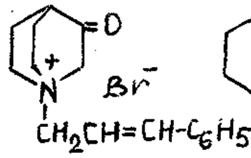
The conformation of quinuclidines determines as well as direction of nucleophilic attacks on the quaternary derivatives of this series. In contrast to N,N-dimethylpiperidinium salts with a "chair" form of the cycle, which, affected by the bases RONa undergo E_2-elimination to form unsaturated amines, the corresponding quinuclidinium salts, where each six member ring has a "boat" form run at the same conditions into S_N2 reaction by α-carbon atom with 1-methyl-4-(β-alkoxyethyl)-piperidines formation[28-29].

As it is shown[30], the quaternary derivative of 1,2,3,4-tetrahydroisoquinolinone-4 (XIII) transforms by reaction with sodium methoxide into allylic ammonium ylid (XIV), which easily undergoes Stevens rearrangement to yield the 3-substituted tetrahydroisoquinolinone XV.

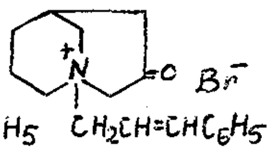




XV



XVI



XVII

The analogical **ylid** obtained from the quinuclidinium salt XVI is rather stable to such rearrangement because of the sterical hindrances by interactions of p-orbitals at the transition state. An intermediate position holds the isomeric quaternary salt of 1-azabicyclo(3,3,1)nonanone (XVII), the **S**tevens rearrangement of whose ylid goes slowly only at the temperature 120°[30].

The sterical effects seem to be responsible for generation of different products by reactions of tertiary amines with p-nitocumyl chloride and α,p-dinitrocumol. Whereas both of these compounds give with quinuclidine in good yield the normal quaternary salts, the analogical reactions with the less basic noncyclic amines lead to derivatives of α-methylstyrene or cumylic alcohol[31].

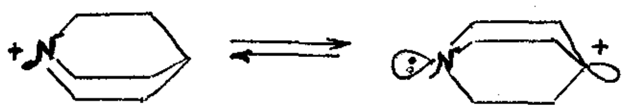
The important peculiarity of quinuclidines structure consists in the specific character of free lone pair electrons on the nitrogen, being in sp_3 and feeling no screen effects from the hydrogen atoms.

The first σ-band is shifted in the photoelectronic spectrum of quinuclidine 0.65 eV higher as compared to bicyclo(2,2,2)octane at the expense of ionization of the free lone pair electrons at the bridgehead nitrogen /32/. UV spectrum of quinuclidine measuring in gas phase is characterized by two intensive absorption bands at 1650-2300 Å, related to Ridberg n→p transition, and several less stronger bands at the region 2300-2500 Å /33/. Some interesting results were obtained by comparison of the IR spectra of quinuclidine with those of N-substituted piperidines and piperazines. For monocyclic compounds there were found characteristic absorption bands at 2700-2800 cm^{-1} resulting from interaction between the free lone pair electrons of the nitrogen and the neighbouring axial C-H bonds. Quinuclidine does not absorb in this region, in all probability because of the absence of such interactions in the quinuclidine ring. There are absorption bands characteristic of quinuclidine at 2430, 2915 and 3405 cm^{-1} /34,35/.

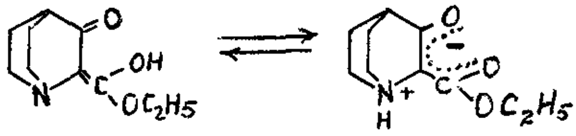
The absence of steric hindrance at the nitrogen lone pair electrons of quinuclidine gives rise to much higher reactivity of this compound in comparison with noncyclic and monocyclic tertiary amines /36-42/, more stronger catalytical activity of quinuclidine at various processes /43-44/.

As it has been shown by kinetic studies /45/, quinuclidine reacts with methyl chloride at room temperature 250 times more readily as triethylamine. The quantitative estimation of the steric hindrance at nitrogen atom and facility of transition state formation by interactions of methyl chloride with quinuclidine and triethylamine have been done by the measuring of chlorine isotope effects at the corresponding Menshutkin reactions: K^{35}/K^{37} is 1.00709 ± 0.00011 for quinuclidine and 1.00640 ± 0.00009 for triethylamine/45/.

Research of protonation and quaternization processes indicated the polar effects of substituents at position 4 of quinuclidine to be transferable through bicyclic system on the bridgehead nitrogen/46-54/. The analogical transmission of substituents effect has been demonstrated by investigations of ^{13}C NMR spectra as well as nitration kinetic of 1-methyl-4-phenyl-quinuclidinium perchlorate in comparison with noncyclic and monocyclic compounds/55/. Isomerism of quinuclidine molecules like



was postulated/56-57/ according to the molecular orbital theory. A high nucleophilicity of the quinuclidine nitrogen due to transition of proton from oxygen to nitrogen by enolization of ethyl 3-oxoquinuclidine-2-carboxylate (XVIII) to form the dipolar ion XIX/58/, whose production is unusual for the common keto-enol systems containing amino group. Predominance of dipolar form XIX in the hydroxyl containing solvents has been found by NMR, IR, UV, potentiometric methods /58,59/



XVIII XIX

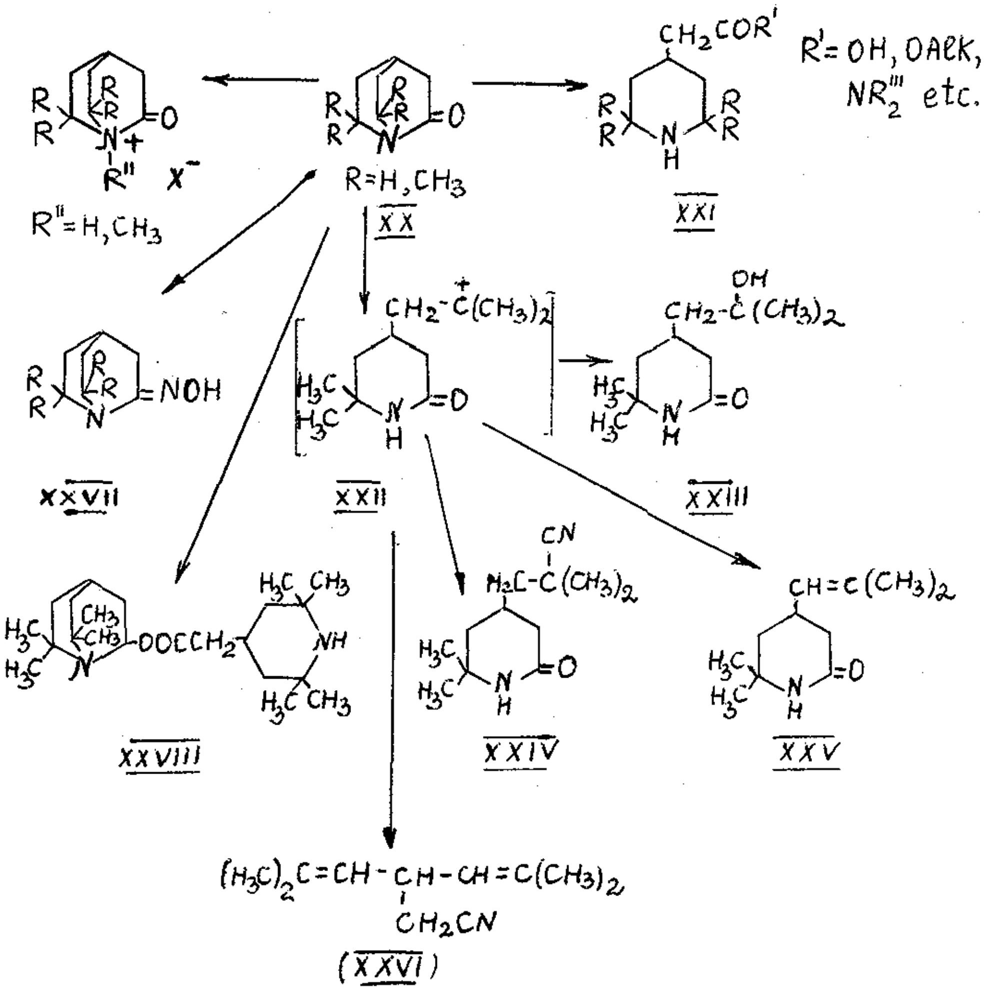
Features of structure and reactivity of ethyl 3-oxo-quinuclidine-2-carboxylate promoted during the last years wide application of this available compound /60/ for syntheses of many condenced quinuclidine systems /61-64/.

Rigid structure of quinuclidine leads not only to unhindrance of the free lone pair electrons of the bridgehead nitrogen, but also to orientation of these electrons along the symmetry axis of molecule. This peculiarity of structure manifests in some features of chemical properties of quinuclidine derivatives having multiple bonds at α,β-positions to the bridgehead nitrogen. In this type of compound the axis of the nitrogen p-electrons is practically orthogonal to the π-electrons of the multiple bond. As a result the necessary condition for conjugation, i.e. parallel axes of π and p electrons with maximum overlap, is not observed and nitrogen atom influences on the neighbouring unsaturated groups not by mesomeric but practically only by inductive effect.

Interesting chemical properties were discovered in such bicyclic amides as quinuclidin-2-ones (XX)/65-69/. The conjugation of type N-C=O, characteristic of common amides, is absent in compounds XX, which are more close to amino-ketones, than cyclic amides. The nitrogen of quinuclidine-2-ones (XX) is easily protonated (common amides and lactams are O-protonated) and can be alkylated. They are very basic (pKa 5.3-5.6) compared with other amides (e.g., N-acetylpiperidine, pKa 0.4).

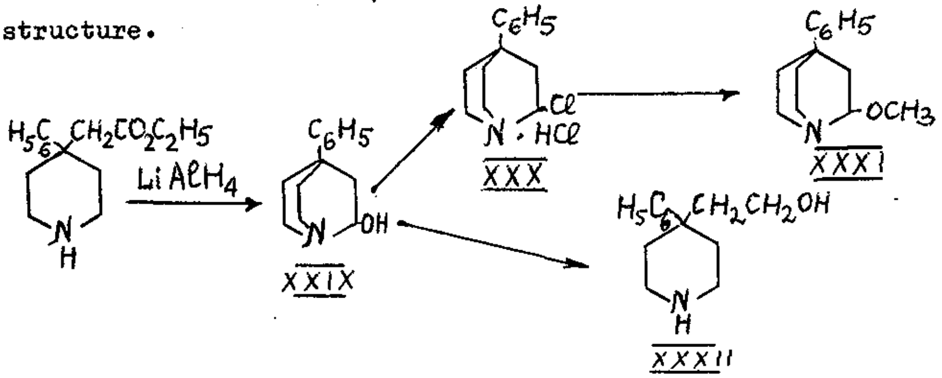
Carbonyl group frequencies for quinuclidin-2-ones in IR spectrum are on the average 80 cm^{-1} higher than for common lactams, and integral intensities of the same absorptions are nearly half those of quinuclidin-2-ones. UV absorption maxima for XX are midway between those for amides and ketones. On account of the lack of amide mesomerism quinuclidin-2-ones gain in reactivity. With the various protonic nucleophilic agents (water, alcohol, amines, etc.) quinuclidin-2-ones interact as effective acylating compounds. The primary forming intermediate adducts are stabilized by breaking quinuclidine $N-C_2$ bond and production piperidyl-4-acetic acid (XXI) or its derivatives: esters, amides, hydrazides etc. Processes of hydrolysis, alcoholysis, aminolysis of quinuclidin-2-ones have rather high rates and the kinetics of these reactions can be measured polarographically (common amides and lactams are polarographically inactive). In the case of 6,6,7,7-tetramethylquinuclidin-2-one (XX, $R=CH_3$)/68-69/ reactions with nucleophilic agents in aprotic solvents (phenyllithium in ether, PCl_5 in benzene, lithium aluminium hydride in ether, acetone cyanhydrine in the exess of this reagent) are also attended by breaking

C-N bond of quinuclidine ring. In contrast to reactions with protic nucleophilic agents, N-C$(CH_3)_2$ rather than N-CO bond is broken in this case and the primary obtained unstable cation XXII is stabilized either by addition of nucleophilic agent to yield XXIII or XXIV, or by elimination of proton to form unsaturated compound XXV; the reaction of XX with PCl_5 results in the opening of piperidine ring and formation of nitrile XXVI.

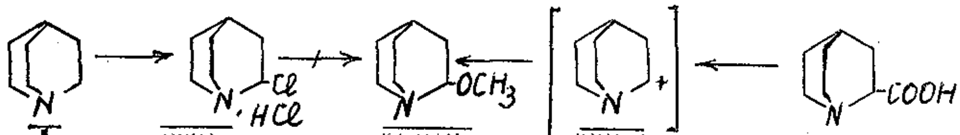


The absence of amide mesomerism at quinuclidin-2--ones (XX) makes their carbonyl groups be able to undergo such reactions as formation of oximes XXVII with hydroxylamine [65], reduction with $LiAlH_4$ N-CO for NCHOH, but not for $N-CH_2$ group (the product of reduction is acylated by the excess of quinuclidin-2-one to XXVIII)[69]. Finally, CH_2 group next to C=O in compounds XX is rather acidic and the hydrogéns can be exchanged by deuterium [67].

Introduction of phenyl group at position 4 of XX increases stability of quinuclidin-2-ones[70], easily breaking in the case of unsubstituted compound[71]. Hydroxy group at *2-hydroxy-4-phenylquinuclidine* (XXIX) have been substituted by chlorine with thionyl chloride. The chloro compound XXX was transformed into methoxy derivative XXXI without breaking of azabicyclic system[70]. Treatment of compound XXIX with $NaBH_4$ leads to opening quinuclidine structure.

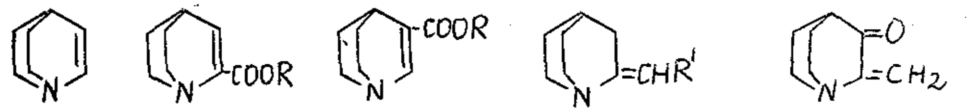


On the contrary, in 2-chloroquinuclidine (XXXIII) unsubstituted at position 4, which was prepared photochemically from quinuclidine (I) in CCl_4 /72/, the chlorine atom was not replaced by methoxy- or phenoxy-group and the corresponding 2-methoxyquinuclidine (XXXIV) was obtained only by electrolysis of quinuclidin-2-carboxylic acid (XXXV) in methanol solution /73/. The process seems to take place through intermediate carbonium cation XXXVI.



I XXXIII XXXIV XXXVI XXXV

The sterically fixed orientation of the nitrogen free lone pair electrons specifies as well some peculiarities of such unsaturated quinuclidines as Δ^2-dehydroquinuclidine (XXXVII)/74/, its 2-(XXXVIII) and 3-(XXXIX) carbalkoxy--derivatives/17/ and quinuclidines XL with double bond at position 2 /75/.



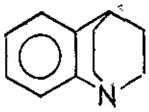
XXXVII XXXVIII XXXIX XL XLI

Formally these compounds are bicyclic enamines. But absence of pπ -conjugation gives rise to their difference from the common tertiary α-vinylamines. For example, Δ^2-dehydroquinuclidines do not have the characteristic absorption for enamines at 230 mμ and are not hydrolyzed under mild conditions by dilute acids.

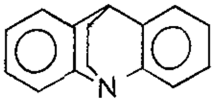
At the same time compounds XXXIX are different from aliphatic vinyloges of amides by reactions with nucleophilic agents, because they have much less deactivated (only at the cost of nitrogen inductive effect) double bonds. Compounds XXXIX are able to add nucleophilic agents such as alcohols, ethylenimine, isopropylmagnesium iodide, etc.[74,76,77], compounds XXXVIII take on as well substances with active methylene group: nitromethane, malonic and cyanoacetic esters, etc. [17,77]. Δ^2-Dehydroquinuclidine (XXXVII), having neither mesomeric effect of the bridgehead nitrogen nor activation of double bond by ester group, can interact with phenyl azide[74,76]. The absence of enamine properties appears distinctly at 2-methylene-3-oxoquinuclidine (XLI)[78-80] and its derivatives[80-86]. According to the Bredt rule, 2-morpholinomethylenequinuclidine (XLII)[87] transforms by hydrolysis into 2-formylquinuclidine (XLIII)[88].

XLII XLIII

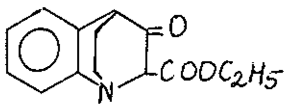
Features of benzo(b) - (LIV) and dibenzo(b,e) - (LV) quinuclidines are also determined by the orientation of free lone pair electrons of the bridgehead nitrogen[89-91]. In contrast to N,N -dialkylanilines, N-alkylated 1,2,3,4-tetrahydroquinolines and indolines compounds LIV and LV have no $p\pi$ -conjugation.



LIV



LV



LVI

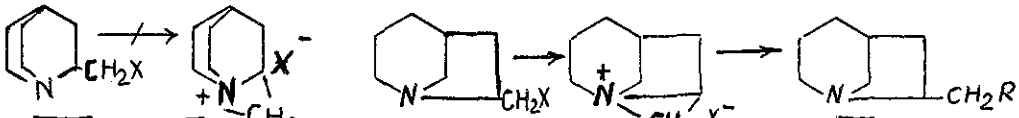
This is reflected in the pka values (pka of N,N--dimethylaniline is 6.56, diphenylamine 0.79, LIV 7.79, OV 4.46) and in decrease of reactivity of the aromatic part of molecules[89,92,93]. For example, benzo(b)quinuclidine (LIV) fails to couple with p-nitrobenzenediazonium chloride [89], bromination of LIV under a variety of conditions yields only a molecular complex or the perbromide, no bromination at the benzene ring occurs[92,93]. However, benzo(b) quinuclidine undergoes electrophilic substitution in the benzene ring with more active agents-mixture of nitric and sulfuric acids or chlorosulphonic acid. But in these cases electrophilic substituents enter, in contrast to analogical reactions with common aromatic amines, not at orto- or para-, but at meta-position to the nitrogen atom. As was established by NMR and dipole moment methods, the products of nitration and chlorosulphonation of LIV are the corresponding 7-substituted benzo(b)quinuclidines[92-93].

The NMR method demonstrated as well that quinuclidine ring in compound LIV is more strain than in the unsubstituted quinuclidine. The reason of that is difference in the bond lengths at the benzo(b)quinuclidine bridges[17-20].

The strain effect gives an explanation of the keto-enol equilibrium shift of ethyl 3-oxobenzo(b)quinuclidine-2-carboxylate (LVI) to the keto-form in comparison with ethyl 3-oxoquinuclidine-2-carboxylate (XVIII). Enol formation in the case of LVI is connected with the energetically unfavourable increase of the strain for all system[17].

Research of the thermodynamic equilibrium and kinetic of deuterium exchange of epimeric ethyl 3-oxobenzo(b)-quinuclidine-2-carboxylates demonstrated[17], that sterical interactions of substituents with hydrogens at the neighbouring (unsubstituted) bridge of quinuclidine are, as could be expected, remarkably greater than with benzene ring. This is in a good agreement with different reactivity of substituents at syn- and anti-positions to benzene ring of various benzo(b)quinuclidine derivatives[17-20]. So, reactions of thionyl chloride with 3-hydroxy-3-cyanobenzo(b)quinuclidine and ethyl 3-hydroxyquinuclidin-3-carboxylate having both anti-position of hydroxyls goes by S_N2 mechanism including attack of C_3 atom from the benzene side and yields 3-syn-chloroderivatives. With syn-hydroxy isomers the same reactions proceed ambiguously and 3-anti-chloro derivatives do not form.

Stericaly fixed orientation of the nitrogen free lone pair electrons determines also the chemical inertness of 2-halogenomethylquinuclidines (LVII)[94].

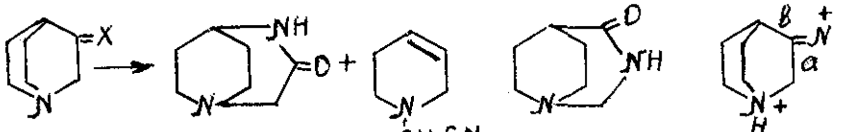


LVII LVIII LIX LX LXI

As is known, reactions of β-aminoalkyl halides with nucleophilic agents are going through intermedium aziridinium derivatives. Such mechanism activates halogen atoms at β-aminoalkyl halides with nitrogen being included into noncyclic, 1-azamonocyclic- and some azabicyclic systems. For example, interactions of nucleophilic agents with halogenomethyl derivatives of 1-azabicyclo (3,2,1) octane seem to be realized according to this mechanism (LIX ⟶ LX ⟶ LXI).

In the case of 2-halogenomethylquinuclidines (LVII) the intermediate aziridinium compounds LVIII cannot be formed because of sterical hindrances. This is why LVII are rather unactive by treatment with various nucleophils (amines, alcohols, cyanides, sodium malonic esters etc.), in all these cases reactions do not go or need vigorous conditions and give products in low yields.

The influence of the bridgehead nitrogen atom is remarkable also by reactions of 3-oxoquinuclidine (LXII) with CH_2N_2 and HN_3, interaction of oxime LXIII with polyphosphoric acid and treatment of (3-hydroxyquinuclidin-3)-dimethyl(diaryl)carbinols (LXIV) by sulfuric acid. These reactions proceeding with expansion of the quinuclidine ring result in formation of a single compound from the two possible isomeric 1-azabicyclononanes. Thus 3-oxo-1,4-diazabicyclo (3,2,2)nonane (LXV) and 1-cyanomethyl- Δ^3-piperidine (LXVI) are obtained by interactions of ketone LXII with HN_3 (Schmidt reaction) or oxime LIII with polyphosphoric acid (Beckmann rearrangement)/96,97/.



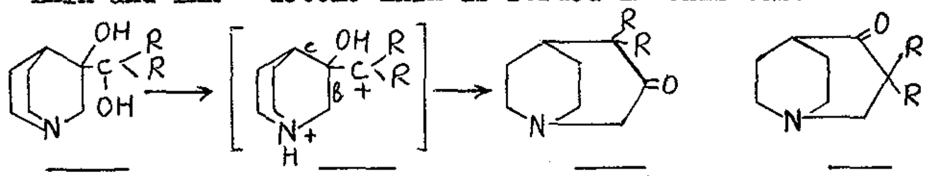
LXII X=O

LXIII X=NOH

LXV LXVI LXVII LXVIII

The second isomeric lactam LXVII does not form. The intermediate dication LXVIII appears to have "a" σ-bond much less nucleophilic as "b" one due to inductive effect of the protonated quinuclidine nitrogen and the migration of the more nucleophilic "b"-bond yields lactam LXV.

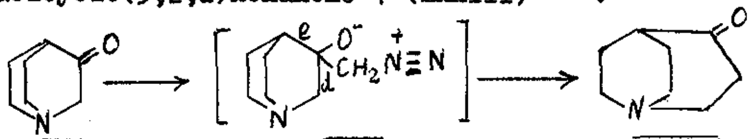
The analogical situation is realized by dehydration of ditertiary alcohols LXIV with sulfuric acid/98/. The single compound from of two possible ring expansion products - LXIX and LXX - ketone LXIX is formed in this case.



LXIV LXXI LXIX LXX

Transformation of glycol LXIV into ketone LXIX is connected as well, as was mentioned above, with migration at the intermediate dication LXXI more nucleophilic "c" σ-bond, being rather far from the protonated quinuclidine nitrogen.

The sextet rearrangement by reaction of 3-oxoquinuclidine (LXII) with diazomethane is realized also by migration of more nucleophilic σ -bond. But in this case the process is going at basic medium, the cyclic nitrogen is not protonated, "d"-bond is more nucleophilic one in comparison with "e"-bond and the final product of reaction is 1-azabicyclo(3,2,2)nonanone-4 (LXXIII)[99].



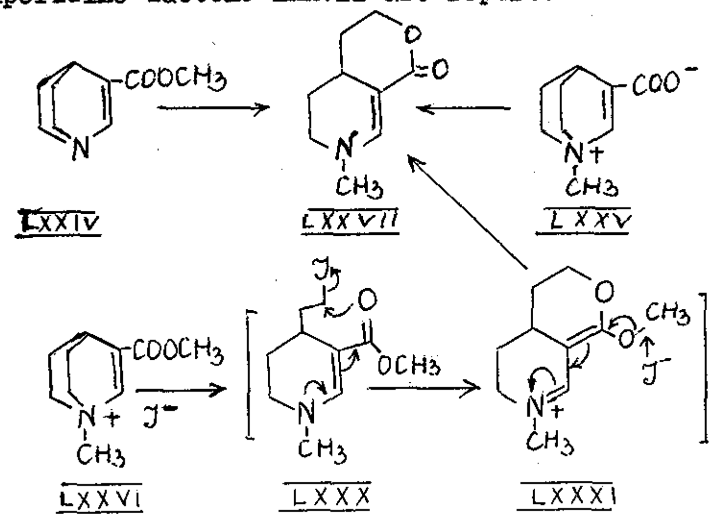
LXII LXXII LXXIII

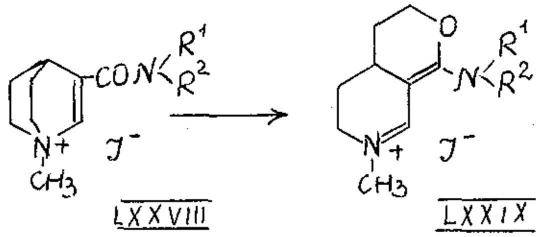
It should be noted that differences in the rates of solvolysis of 2-chloroquinuclidine, alkyl quinuclidine-2-carboxylate and their desaza analoges and isoquinuclidine derivatives made some investigaters[100-103] doubt that the effect of quinuclidine bridgehead nitrogen is only inductive one.

The above-mentioned peculiarities of the symmetrically rigid quinuclidine structure make these compounds significantly more stable to opening of cycle in comparison with other 1-azabicycloalkanes[2]. Quaternary quinuclidinium bases split off aliphatic alcohols more readily than corresponding derivatives of other 1-azabicycloalkanes. The quinuclidine compounds retain the bicyclic system, whereas other 1-azabicycloalkanes usually undergo Hofmann degradation with bicycle opening[104-106].

Quinuclidine N-oxides are thermally stable/107/. As is known, pyrolysis of monocyclic tertiary amine N-oxides is often accompanied by rearrangements with expansion of ring, Cope elimination and other transformations of cyclic systems. Quinuclidine N-oxide undergoes pyrolysis only at temperatures higher than 200°/107/. N-Desoxidation and sublimation of the obtained quinuclidine (I) takes place in this reaction.

At the same time some substituted quinuclidines open their cycles rather easily. For example, the thermal transformations of methyl Δ^2-quinuclidine-3-carboxylate (LXXIV), its betaine (LXXV) and methiodide (LXXVI) into the piperidine lactone LXXVII are reported/108-115/.





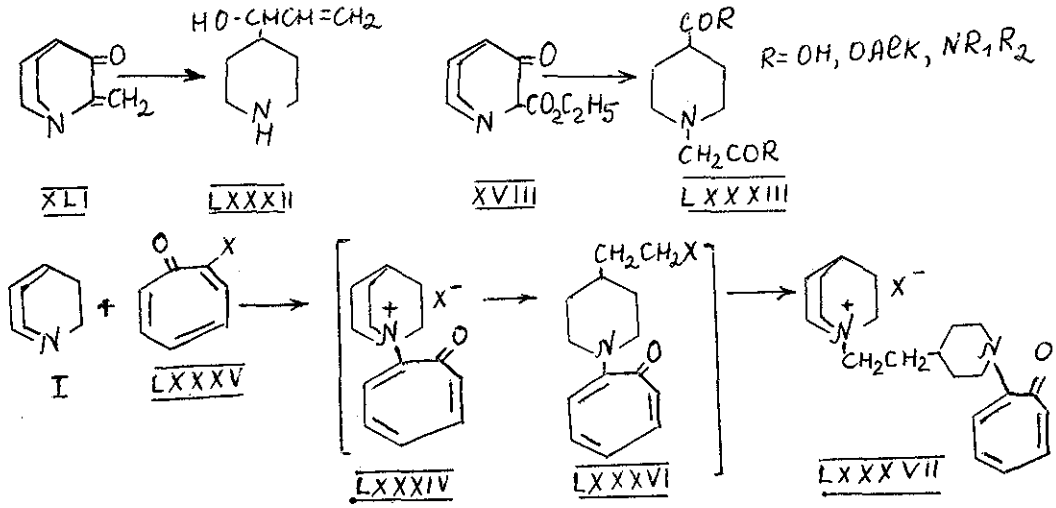
1-Methyl-3-carboxamide-Δ^2-quinuclidinium iodides (LXXVIII) give an analogous rearrangement with conversion of the obtained iminolactones LXXIX by acidic hydrolysis into LXXVII.

It is assumed that the transformation of LXXVI into lactone LXXVII consists in two consecutive rearrangements: the process starts from nucleophilic attack by iodide-ion, which leads to quinuclidine ring opening and then an intermediate LXXX changes into LXXVII through LXXXI. The alkyl halide released is shown to be formed at the expense of the ester group.

Rearrangements of quarternary salts of ethyl quinuclidine-3-carboxylate have been used in a new synthesis of indoloquinazolidines/116/.

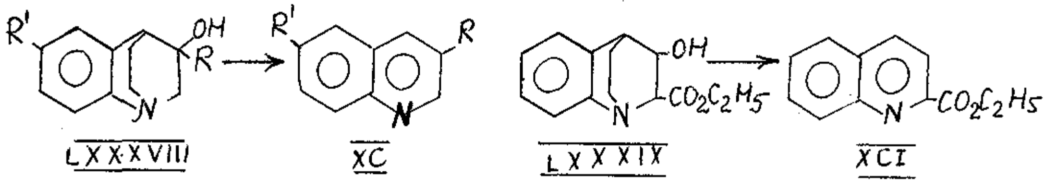
Opening of quinuclidine ring with (piperidyl-4)vinylcarbinol (LXXXII) formation was discovered by hydrogenation of 2-methylene-3-oxoquinuclidine (XLI); C_2-C_3 bond breaking to yield 1-carboxymethylisonipecotinic acid or its derivatives (LXXXIII) took place by interaction of ethyl 3-oxoquinuclidine-2-carboxylate (XVIII) with nucleophilic agents (water, alcohols, amines, etc.) under the mild conditions/77/.

The quinuclidine ring breaks in good yield at room temperature in quaternary salts LXXXIV, formed from quinuclidine (I) and 2-halogenohepta-2,4,6-trien-1-ones (LXXXV) /117-123/.



Delocalization of quinuclidine nitrogen lone pair electrons on the cycloheptatriene system seems to favour the nucleophilic attack of halogenoanions at the α -carbon atom of bicycle and opening of the ring. Halide LXXXVI obtained by quinuclidine ring cleavage gives with the excess of quinuclidine (I) the quaternary salt LXXXVII, which is a final product of the reaction.

The problem of quinuclidine ring opening is connected with application of the Bredt rule to bicyclic systems. So, quinuclidine is not dehydrogenated by treatment with mercuric acetate, apparently because this process should go through a Δ^1-quinuclidinium salt, which violates the Bredt rule. Under vigorous conditions - with palladium on carbon, or selenium at 300° C-N bond fission with aromatization of system and formation of 4-ethylpyridine take place/124/. The quinuclidine ring opens more easily at 3-hydroxybenzo(b)quinuclidines, containing electron withdrawing aryl - or ester groups (LXXXVIII, LXXXIX)/21,22/.

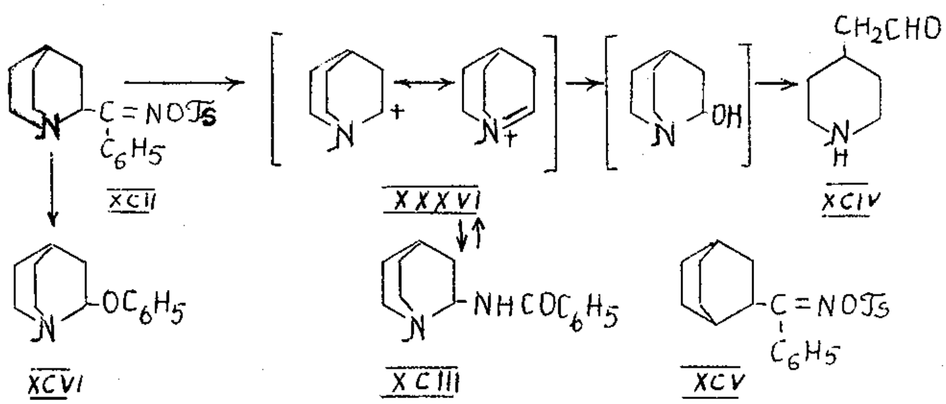


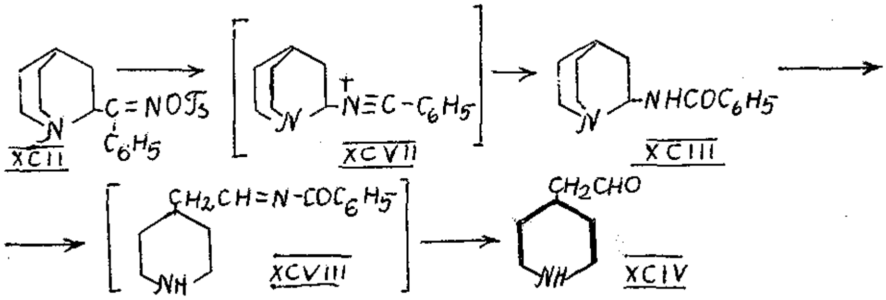
R = C_6H_5, C_6H_4-CH_3-p, R' = H, OCH_3

The ethylene bridge is already thrown out of quinuclidine part of molecules by heating of compounds LXXXVIII and LXXXIX with acetic anhydride and aromatization to quinoline derivatives XC and XCI occurs.

Fragmentation of 4-halogenoquinuclidines, esters of quinuclidin-3-one oxime and 2-benzoylquinuclidine is investigated in detail.

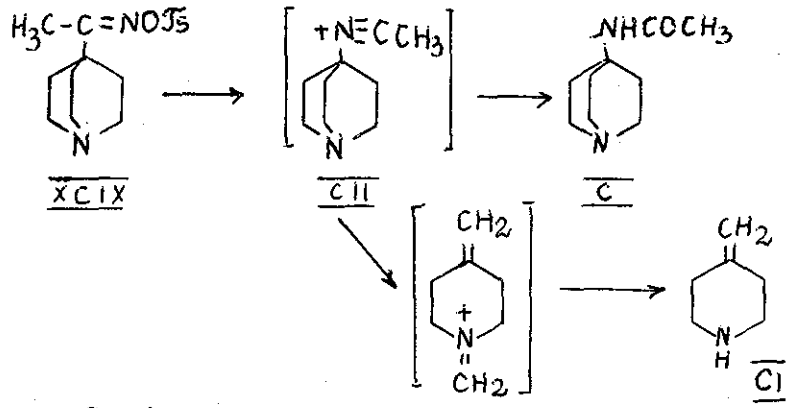
The main product by hydrolysis of 2-benzoylquinuclidine tosyloxime (XCII) is shown to be 2-benzoylaminoquinuclidine (XCIII) obtained along with benzonitrile and (piperidyl-4)acetaldehyde (XCIV), that is an evidence of synchronous fragmentation mechanism through cation XXXVI/100,125/.



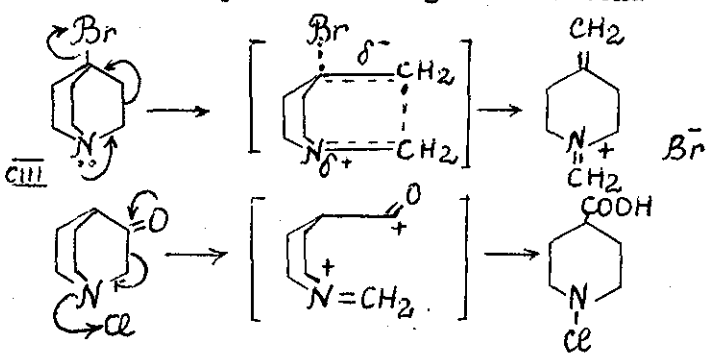


The hydrolysis rate of XCII is 2-4 times less than for its desazaanalogue-2-benzoylbicyclo(2,2,2)octane tosyloxime (XCV)- and much less than for analogous uncyclic compounds. This can be related to steric hindrances in mesomerism of quinuclidyl cation XXXVI. But fragmentation of XCII is not fully suppressed and some authors[100,125] assume that mesomerism of above-mentioned type is realized at XXXVI and the Bredt rule seems not to be applicable for unstable reaction intermediates. Possibility of existence of cation XXXVI is confirmed by formation of 2-phenoxyquinuclidine (XCVI), when compound XCII is heated with phenol. On the other hand, formation of amide XCIII by hydrolysis of XCII may be visualised not only as recombination of cation XXXVI with benzonitrile, but also through intermediate nitrilium-cation XCVII. Aldehyde XCIV formation can be also presented without any participation of carbonium ion XXXVI but through breaking acylimine XCVIII.

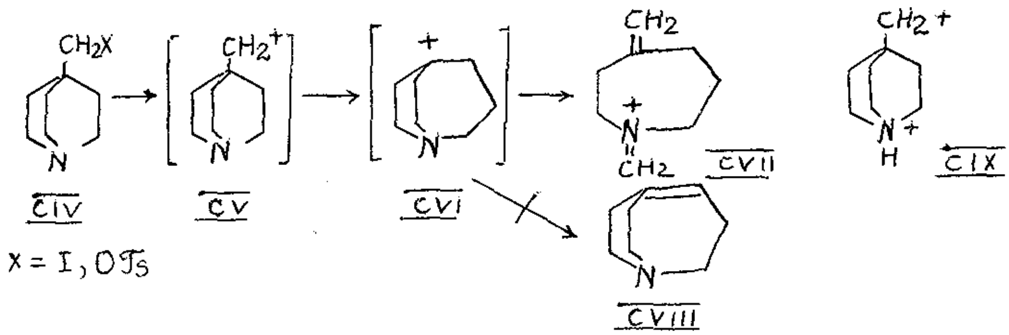
The kinetic study of alkaline hydrolysis of 4-acetylquinuclidine tosyloxime (XCIX) shows that compound XCIX undergoes mainly Beckmann rearrangement to form 4-acetylaminoquinuclidine (C) and fragmentates to 4-methylenepiperidine (CI) only at 3%[126]. Both processes appear to be realized through same intermediate N-(quinuclidyl-4)-acetonitrilium ion (CII).



Synchronous mechanism, analogical to that for fragmentation of 4-bromoquinuclidine (CIII)[127] is run also by oxidative fragmentation of quinuclidin-3-one (LXII) under the action of hypochlorites[128]. This process is different from oxidation of other functional substituted amines, where the first step is a cleavage of C-N bond.



Fragmentation of 4-tosyloxymethyl- and 4-iodomethylquinuclidines in alkali medium occurs unambiguously[129-131].



Tertiary carbonium cation CVI, obtained by isomerisation of the primary generated carbonium ion CV, is not sterically possible, according to the Bredt rule, of 1,2-elimination to yield dehydroderivative CVIII. Therefore fragmentation tends to increase and 1,4-dimethylene-1-azacycloheptanium cation (CVII) is formed. Heating of tosylate CIV in acidic medium leads only to substitution of tosyloxy group. The formation of dication CIX is electrostatically impeded because of mutual repulsion of two positive charges.

Features of mass spectra of quinuclidines are also connected with a problem of application of the Bredt rule /103/ to 1-azabicyclic compounds.

It is known, that aliphatic and monocyclic amines undergo α-cleavage with the formation of stable amine fragments by electron impact. Initiation of such type ions, having the plane positive charged bridgehead nitrogen atom is restricted according to the Bredt rule by fragmentation of quinuclidine derivatives which is also characterized by elimination of α-substituents. In consequence the fragmentation of quinuclidine systems is realized through the open form of the molecular ion[132-139]. The specific character of quinuclidine compounds under electron impact is proved by the method of low voltage mass spectrometry. The intensity of fragments responsible for α -cleavage is strongly decreased in this case for quinuclidine derivatives, spending energy on the opening of ring. For other amines whose nitrogen atom is not a bridgehead one no energy is used for the open form of molecular ion formation and the intensity of fragments M-1 is not changed significantly as voltage decreases from 30 to 12eV. Mass spectrometric cleavage of C-N bond in quinuclidine and benzoquinuclidine molecules proceeds mainly at the substituted bridges. Further expulsion of radicals including the substituent brings about formation of the characteristic fragments peaks which have the maximum of intensity.

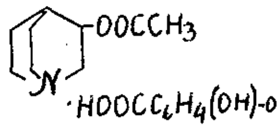
III. Exposure of New Relationships Between the Chemical Structure and Biological Activity in a Series of Quinuclidine Derivatives

As was mentioned in the previous reviews[2-4], research of biological activity of quinuclidine derivatives before 1967 was chiefly connected with two main problems: (1) investigation of natural compounds, their synthetic analogs and products of transformation, the chemotherapeutic and mainly antimalarial properties of substances like quinine alkaloids being predominantly examined. Study of antiarrhythmic activity of quinidine and ajmaline analoges was developed to a less extent. (2) pharmacological investigations of synthetic compounds containing quinuclidine ring.

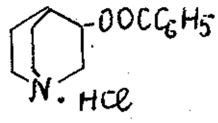
Over last 10 years investigations of the first type had some development. It is necessary to note the progress in discovery of new quinuclidine alkaloids in various species of Gardneria[/140/], Gabinia[/141/] etc.[/142-143/], structural determination of gardneramine[/140/], raukaffricine[/143/], modification of natural alkaloids, including construction or transformation of the quinuclidine ring, and research of the influence of such modifications on biological properties of compounds[/144-153/]. New total syntheses of quinine and its diastereoisomers have been worked out by M.Uskoković and coworkers, who obtained N-benzoylmeroquinene and N-benzoylcincholaipone by several routes from octahydroisoquinolin-5-one and β-collidine[/154-155/]. In the course of these syntheses an interesting way was found for introduction of chlorine atom into ethyl group by photolysis of N-chloropiperidine derivatives. The following synthesis of quinine--quinidine alkaloids was realized either according to some variants of the known Rabe method[/158/] through quininone or through substituted 2-formyl (or 2-alkoxycarbonyl) quinuclidines, which were used for interaction with quinolinemetals /159-161/ by the method first proposed by M.V.Rubtsov and coworkers[/162/]. The substituted alkyl quinuclidine-2-

-carboxylates were also utilized by M.Uskokovič in the total synthesis of cinchonamine[159,163], as it was earlier made in partial synthesis of this alkaloid by Chen Chang bay, R.P.Evstigneeva, N.A.Preobrazhenskii[164].

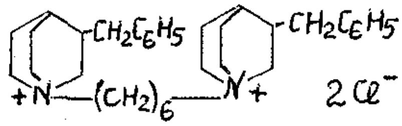
Definite success has been reached in research of new synthetic chemotherapeutically active quinuclidines. Antimalarial properties are found in 2-[(7'-chloroquinolyl-4')-aminomethyl]-quinuclidin-3-ones and the corresponding 3-hydroxyquinuclidine derivatives[165]. Antibacterial activity is elucidated in the substituted 2-aminomethylquinuclidin-3-ones[166], some quinuclidylsulphamides[167] and quaternary quinuclidinium salts[168-169], insecticide and ascaricide properties are recognised in quinuclidin-3-one oximcarbamates[170]. The investigations of pharmacological properties of the synthetic quinuclidine derivatives until 1967 was mainly directed to research of compounds interacting with the cholinergic systems of organism[3]. Utilization of the structural analogy of 3-hydroxyquinuclidine with choline and the higher reactivity of quinuclidine derivatives in comparison with aliphatic substances, including the biochemical processes, provided for creation of the effective drugs-cholinomimetic aceclidine, hypotensive and sedative medicine oxylidine, curarelike compound of competition type-qualidile-which are widely used in the practical medicine in the USSR and some other countries[3].



aceclidine



oxylidine



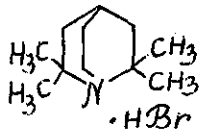
qualidile

During the last 10 years a number of papers and patents have been published dealing with the synthesis of 3-hydroxyquinuclidine/171/, the optical isomerism of this compound, its acetyl derivative (aceclidine) and their quaternary salts /172-178/, with research of the mechanism of biological activity of aceclidine/179-182/ and oxylidine/183-184/. Detailed investigations have been made for the structure and action on cholinergic and central nervous systems of 3-hydroxyquinuclidine benzilate/185-190/, stimulating CNS activity of 3-(3',4',5'-trimethoxybenzoyloxy)quinuclidine/191-192/, depressive action of the corresponding amides /193/, anticholinergic, anaesthetic, antiarrithmic effects of 3-hydroxyquinuclidine carbamates/194-196/, interaction with cholinergic systems of some other 3-acyloxyquinuclidines and their quaternary salts/197-199/, as well as 2-hydroxymethylquinuclidine esters/200/, anticholinergic properties of 3-hydroxyquinuclidine dithienyl and phenylthienylglycolates/201/.

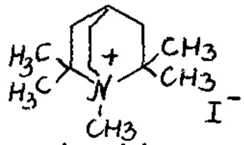
The subsequent investigations demonstrated that in passing from 3-acyloxyquinuclidines to the corresponding benzo(b)-quinuclidine derivatives, changes in polarity, size of molecules, shielding of the functional groups lead to the significant modification of pharmacological activity/204/. The comparative study of 3-hydroxy- , 3-amino-quinuclidine and benzo(b)quinuclidine 3,4,5-trimethoxybenzylates demonstrates the highest neurotropic activity of 3-hydroxybenzo(b)quinuclidine 3,4,5-trimethoxybenzylate/205/, close to activity of trioxazine.

Benzhydrilic ethers of 3-hydroxyquinuclidine demonstrated the selective central anticholinergic activity for parkinsonism treatment/206-210/. Other 3-hydroxyquinuclidine ethers, especially those containing fragments of the tricyclic antidepressants, exhibited some elements of hypotensive and sedative actions /211-215/. As a bicyclic amine quinuclidine was introduced, instead of dialkylaminoalkylic chains, in phenothiazine, thioxantene and other tricyclic systems responsible for the central anticholinergic, neuroleptic, antihystaminic activity of compounds/216-221/. New ganglion-blocking agents were seeked in the series of quaternary quinuclidinium derivatives/222-223/.

The principle of the increase of biological activity at the expense of passing from noncyclic or monocyclic amines to quinuclidine derivatives has been used for creation of the new effective ganglion-blocking drug-temechine/224-225/. In comparison with its piperidine analogue-1,2,2,6,6-pentametylpiperidine- , which is used for practical purposes under the names pempidine, pempiten, normatens, etc. - temechine



temechine



imechine

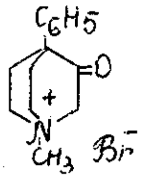
has three times higher selective activity on the N-cholinoreactive system of vegetative ganglions of adrenal glands, carotid tubercles and central nervous system, but does not have nicotine-like effect on the skeletal muscles. Temechine is characterized by a high therapeutical index. It is produced on an industrial scale and used for practical purposes in the USSR as a ganglion-blocking and hypotensive medicine.

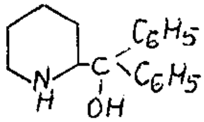
The subsequent investigations of polyalkylquinuclidines allowed to establish[226], that the additional introduction of 8-methyl group into temechine molecule slightly increases toxicity of the preparation with the activity unchanged. Lengthening of 8-alkyl chain causes further increase of toxicity with reduction of ganglion-blocking activity. The analogical effect is also obtained by introduction of some functional groups to 2,2,6,6-tetramethylquinuclidine[227].

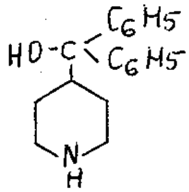
Quaternization of the bridgehead nitrogen leads to other changes in activity. 1,2,2,6,6-Pentamethylquinuclidinium iodide happened to be an effective ganglion-blocking drug of short duration[228]. Under the name imechine it is produced by chemical-pharmaceutical industry of the USSR and used in practical medicine for dirigible hypotonia during operations on the lungs and brain oedemas, stable hypertonia based on the acyte renal insufficiency, for prevention and treatment of hypertonic crisis. In all these cases imechine proved more potent, more dirigible and more convenient for practical purposes than arfonad.

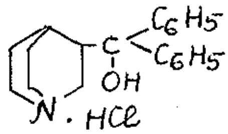
Of significant theoretical and practical interest were also considerations whether the above-mentioned regularities of structure-activity relationships for cholinergic system would be applicable for other type of drugs with the different mechanism of action and whether these quinuclidine derivatives would be also more effective than their noncyclic and monocyclic analog in these cases. To solve this problem the quinuclidine analogs of the antiemetic preparation sulpiride /1-ethyl-2-(2'-methoxy-5'-sulphamidobenzoylaminoethyl)pyrrolidine/ and antitussive preparation-bithiodine /1-methyl-3-bis(thienyl-2)methylenepiperidine/- have been synthesised[229]. Pharmacological investigation of these compounds in comparison with sulpiride and bithiodine shows[229] that the influence of quinuclidine derivatives upon the coughing and vomiting centres is less (for analogs of bithiodine) or even missed (for sulpirid analogs).

The same structure-activity relationship is realized[230] in effects of 3-(quinuclidine-substituted) imidazolines on the adrenergic systems and novocaine quinuclidine analogs in antiarrythmic action. At the same time, according to Polish authors/231-232/, the elements of antiarrithmic activity is exhibited in experiments with quinuclidinoyltetrahydroisoquinolines and quinuclidinoyl-N-aminotetrahydroisoquinolines. Substituted quinuclidinecarboxanilides have weak local anaesthetic action/233-234/, cis-3-amino-2-benzhydrylquinuclidine display diuretic properties /235-236/ whereas antiinflammatory effects are characteristic for 3-hydroxy-2-benzhydrylquinuclidine derivatives/237, 238/ and substituted thiophenoquinuclidines/239/. 3-Hydroxy-2-benzhydrylquinuclidine derivatives/240/, 2-aryl-3-(quinuclidineamino)-propiophenones/241/, substituted quinuclidineacylanilides/242/ were patented as CNS stimulants, substituted 3-hydroxy-2-piperazinomethylquinuclidines/243-244/ and pyrazolonoquinuclidines/245/ were described as depressants of CNS. 3-Substituted 3-hydroxyquinuclidines/246-248/ and derivatives of aminoquinuclidines/249-250/ have been reported in patents and papers as depressants of CNS. Radioprotecting, anticonvulsant, sedative and analgetic properties have been found in some 3-spiroquinuclidine derivatives /251-253/ and condensed quinuclidinocumarines/254/. The high adrenergetic activity was discovered in 1-methyl-3-hydroxy-4-phenylquinuclidinium bromide, which is 3-4 times more active than guanetidine for hypertonia and can be used orally. Under the name MA-540 this preparation is under investigation and patenting as a medicine for hypertonia treatment[255-261].


MA 540


pipradrol


azacyclodol


fencarol

The isomeric (quinuclidyl)diphenylcarbinols, previously synthesised to increase the psychotropic activity of the known psychostimulators pipradrol and azacyclodol by introducing the quinuclidine ring instead of piperidine one[262], do exhibit in experiments neither psychostimulating nor CNS depressing activity. (Quinuclidyl-3)diphenylcarbinol has only weak spasmolytic properties[263-265].

The subsequent detailed investigations demonstrated[266] that the various (quinuclidyl-3)-diaryl (or heteryl) carbinols, in contrast to their 2-isomers, are highly effective with respect to histaminergic systems.

(Quinuclidyl-3)diphenylcarbinol hydrochloride is under the name fencarol introduced in the practical medicine as a drug for the treatment of the various type of allergies. It is more effective and less toxic than dimedrol and in contrast to commonly used antihistaminic drugs (dimedrol, pipalfene etc.) has no influence on CNS[266]. Research of quinuclidyldiarylcarbinols, variation of the position of diarylcarbinol group, its distance from quinuclidine, unsaturation of 1-azabicyclic system, character and position of substituents at aryl rings, changing of one or both aryl groups by hydrogen, alkyl, cycloalkyl groups, etc., allowed to find certain regularities in structure-activity relationships and discover new more effective antiallergic compounds being now under detailed investigation /266-269/.

Thus, the investigations over the last ten years have demonstrated high biological activity of quinuclidine derivatives, enriched the practical medicine by new effective drugs and substantiated perspectivity of the further search of new biologically active compounds in this series.

REFERENCES

1. R.B.Woodward, W.E.Doering, J.Amer.Chem.Soc., 1945, 67, 860.

2. L.N.Yakhontov, "Quinuclidine chemistry" in "Advances in Heterocyclic Chemistry" (edit. A.R.Katritzky), Academic Press inc., New York, 1970, vol. 11, p. 473.

3. M.D.Mashkovsky, L.N.Yakhontov, "Relationships Between the Chemical Structure and Pharmacological Activity in a Series of Synthetic Quinuclidine Derivatives" in "Progress in Drug Research" (edit. E.Jucker), Birkhäuser Verlag, Basel-Stuttgart, 1969, vol. 13, p. 293.

4. L.N.Yakhontov, Uspekhi Khimii, 1969, 38, 1038.

5. L.N.Yakhontov, E.E.Mikhlina, Khim Geterotsikl.Sojedin., 1975, 1011.

6. E.E.Mikhlina, V.Ya.Vorobjova, K.F.Turchin, L.N.Yakhontov, Khim.Geterotsikl.Sojedin., 1971, 1413.

7. B.Längström, Chem.Ber., 1974, 5, 170.

8. W.Eckhardt, C.A.Grob, W.D.Treffert, Helv.Chim.Acta, 1972, 55, 2432.

9. J.Paleček, Coll.Czech.Chem.Comm., 1971, 36, 2070.

10. P.M.Altani, J.F.Billmann, J.Moron, Tetrahedron, 1973, 29, 391.

11. D.Berney, T.Jauner, Helv.Chim.Acta, 1974, 57, 1198.

12. A.T.Nielsen, J.Heterocycl.Chem., 1970, 7, 231.

13. Pat. Japan 16312 (1967), Chem.Abst., 1968, 69, 2959.

14. W.Schneider, F.Schumann, G.Modjesh, Pharmazie, 1970, 25, 724.

15. W.Schneider, B.Lang, F.Schumann, Arch.Pharmaz., 1976, 309, 447.

16. L.N.Yakhontov, K.F.Turchin, E.E.Mikhlina, V.Vorobjova, A.D.Yanina, Yu.N.Sheinker, "Voprosy stereokhimii", 1972, v. 1, 117.

17. E.E.Mikhlina, K.F.Turchin, V.Ya.Vorobjova, A.I.Ermakov, R.G.Kostyanovsky, L.N.Yakhontov, Doklady Akad. Nauk SSSR, 1970, 195, 1347.

18. L.I.Mastafanova, K.F.Turchin, L.M.Alekseeva, Yu.N. Sheinker, L.N.Yakhontov, Khim.Geterotsikl.Sojedin., 1971, 1665.

19. K.F.Turchin, E.E.Mikhlina, A.D.Yanina, V.Ya.Vorobjova, L.N.Yakhontov, Yu.N.Sheinker, Khim.Geterotsikl.Sojedin., 1971, 981.

20. A.D.Yanina, K.F.Turchin, E.E.Mikhlina, L.N.Yakhontov, Yu.N.Sheinker, Khim.Geterotsikl.Sojedin., 1972, 222.

21. E.E.Mikhlina, K.F.Turchin, A.D.Yanina, Yu.N.Sheinker, L.N.Yakhontov, Khim.Geterotsikl.Sojedin., 1973, 839.

22. E.E.Mikhlina, V.Ya.Vorobjova, K.F.Turchin, N.A.Komarova, L.N.Yakhontov, Yu.N.Sheinker, Khim.Geterotsikl.Sojedin., 1973, 844.

23. L.N.Yakhontov, L.I.Mastafanova, K.F.Turchin, L.M. Alekseeva, Yu.N.Sheinker, Doklady Akad. Nauk SSSR, 1972, 207, 1150.

24. L.N.Yakhontov, L.I.Mastafanova, K.F.Turchin, T.D. Pervacheva, M.V.Rubtsov, Zh.Organ.Khim., 1968, 4, 1673.

25. K.F.Turchin, E.E.Mikhlina, V.Ya.Vorobjeva, A.D.Yanina, Yu.N.Sheinker, L.N.Yakhontov, Doklady Akad.Nauk SSSR, 1970, 192, 823.

26. E.E.Mikhlina, V.Ya.Vorobjova, M.V.Rubtsov, G.G.Dvorjantseva, Zh.Obshch.Khim., 1965, 35, 110.

27. L.N.Yakhontov, M.A.Portnov, E.E.Mikhlina, M.N.Vaisman, N.A.Komarova, Khim.Geterotsikl.Sojedin., 1972, 220.

28. J.Angel, R.Michelot, B.Tchoubar, Comp.rend., 1970, 271, 557.

29. J.Paleček, Z.Polivka, Coll.Czech.Chem.Comm., 1967, 32, 3909.

30. S.Mageswaran, W.D.Ollis, O.Sutherland, J.Thebtaraneth, Chem.Comm., 1971, 1494.

31. N.Konblum, F.W.Stuchel, J.Amer.Chem.Soc., 1970, 92, 1804.

32. P.Bishof, J.A.Hashmall, E.Heilbronner, V.Hornug, Tetrahedron Letters, 1969, 4025.

33. A.M.Halpern, J.L.Roebber, K.Weise, J.Chem.Phys., 1968, 49, 1348.

34. M.V.Rubtsov, L.N.Yakhontov, E.E.Mikhlina, Zh.Obshch. Khim., 1965, 35, 621.

35. L.G.Johnson, J.Chem.Phys., 1960, 33, 949.

36. W.Gründler, R.Fridemann, H.D.Schädler, Monatsh., 1973, 104, 200.

37. P.Frøyen, R.F.Hudson, Acta Chem.Scand., 1973, 27, 4001.
38. A.M.Halpern, K.Weise, J.Amer.Chem.Soc., 1968, 90, 6297.
39. S.Gran, Ch.Roeming, Acta Chem.Scand., 1968, 22, 1686.
40. H.Böhme, M.Haake, Ann.Chem., 1967, 705, 147.
41. D.L.Coffen, T.E.Mc Entee, J.Org.Chem., 1970, 35, 503.
42. I.Stevens. J.Joke, Inorg.Chem.Acta, 1970, 4, 244.
43. E.J.Parish, B.S.Huang, D.H.Miles, Synth.Comm., 1975, 5, 341.
44. D.H.Miles, B.S.Huang, J.Org.Chem., 1976, 41, 208.
45. S.Gardner, H.Davis, J.Amer.Chem.Soc., 1972, 94, 1901.
46. J.Paleček, J.Hlavatý, Z.Chem., 1969, 9, 428.
47. C.A.Grob, W.Simon, W.D.Treffert, Helv.Chim.Acta, 1972, 55, 2439.
48. J.Paleček, J.Hlavatý, Coll.Czech.Chem.Comm., 1973, 38, 1985.
49. E.Ceppi, W.Eckhardt, C.A.Grob, Tetrahedron Letters, 1973, 3627.
50. C.A.Grob, W.Simon, W.D.Treffert, Angew.Chem., 1973, 85, 310.
51. E.Ceppi, C.A.Grob, Helv.Chim.Acta, 1974, 57, 2332.
52. W.Eckhardt, C.A.Grob, Helv.Chim.Acta, 1974, 57, 2339.
53. C.A.Grob, M.G.Schageter, Helv.Chim.Acta, 1974, 57, 509.
54. C.A.Grob, M.G.Schageter, Helv.Chim.Acta, 1976, 59, 264.
55. A.Ricci, R.Danieli, G.Pirazzini, S.Rossini, Gaz.Chim. Ital., 1975, 105, 751.

56. R.Gleiter, W.D.Stohzer, R.Hoffmann, Helv.Chim.Acta, 1972, 55, 893.

57. M.N.Paddon-Row, L.Radom, A.R.Gregory, Chem.Comm., 1971, 1494.

58. Yu.N.Sheinker, E.M.Peresleni, I.V.Persijanova, E.E. Mikhlina, V.Ya.Vorobjova, A.D.Yanina, L.N.Yakhontov, Khim.Geterotsikl.Sojedin., 1972, 229.

59. K.F.Turchin, Yu.N.Sheinker, E.E.Mikhlina, V.Ya.Vorobjova, A.D.Yanina, L.N.Yakhontov, Khim.Geterotsikl.Sojedin., 1972, 978.

60. L.N.Yakhontov, M.V.Rubtsov, Zh.Obshch.Khim., 1959, 29, 2343.

61. E.E.Mikhlina, V.Ya.Vorobjova, K.F.Turchin, N.P.Kostjuchenko, Yu.N.Sheinker, L.N.Yakhontov, Khim.Geterotsikl. Sojedin., 1970, 651.

62. E.E.Mikhlina, V.Ya.Vorobjova, L.N.Yakhontov, Khim.Geterotsikl.Sojedin., 1970, 1261.

63. W.A.Remers, G.I.Gibs, M.J.Weiss, J.Heterocycl.Chem., 1967, 4, 344.

64. K.Freter. J.Org.Chem., 1975, 40, 2525.

65. L.N.Yakhontov, M.V.Rubtsov, Zh.Obshch.Khim., 1957, 27, 72.

66. H.Pracejus, Chem.Ber., 1959, 92, 988.

67. H.Pracejus, M.Kehlen, H.Kehlen, H.Matschiner, Tetrahedron, 1965, 21, 2257.

68. E.I.Levkoeva, E.S.Nikitskaya, L.N.Yakhontov, Doklady Akad.Nauk SSSR, 1970, 192, 342.

69. E.I.Levkoeva, E.S.Nikitskaya, L.N.Yakhontov, Khim. Geterotsikl.Sojedin., 1971, 378.

70. H.Bochow, W.Schneider, Chem.Ber., 1975, 108, 3475.

71. W.L.Meyer, R.G.Olsen, Canad.J.Chem., 1967, 45, 1459.

72. B.H.Bakker, W.N.Speckamp, Tetrahedron Letters, 1975, 4065.

73. P.G.Gassman, B.L.Fox. J.Org.Chem., 1967, 32, 480.

74. C.A.Grob, A.Kaiser, E.Renk, Helv.Chim.Acta, 1957, 40, 2170.

75. V.Braschler, C.A.Grob, A.Kaiser, Helv.Chim.Acta, 1963, 46, 2646.

76. W.A.Ramers, G.I.Gibs, M.Weiss, J.Heterocycl.Chem., 1967, 4, 344.

77. E.E.Mikhlina, V.Ya.Vorobjova, G.P.Londareva, L.N. Yakhontov, Khim.Geterotsikl.Soedin., 1974, 1125.

78. A.T.Nielsen, J.Org.Chem., 1966, 31, 1053.

79. A.R.Hansen, H.Bader, J.Heterocycl.Chem., 1966, 3, 109.

80. E.Oppenheimer, E.Bergmann, Synthesis, 1972, 269.

81. E.J.Warawa, J.R.Campbell, J.Org.Chem., 1974, 39, 3511.

82. D.R.Bender, D.L.Coffen, J.Heterocycl.Chem., 1971, 8, 937.

83. G.J.Long, J.R.Ferraro, Chem.Comm., 1973, 719.

84. J.Blum, J.Sasson, S.Iflah, Tetrahedron Letters, 1972, 1015.

85. A.Fisher, E.Oppenheimer, S.Cohen, Tetrahedron, 1975, 31, 317.

86. F.J.Villani, E.A.Wefer, J.Heterocycl.Chem., 1970, 7, 973.

87. L.Duhamel, P.Siret, F.Mulot, Comp.rend., 1974, C, 279, 1159.

88. M.V.Rubtsov, L.N.Yakhontov, Zh.Obshch.Khim., 1955, 25, 2143.

89. B.Wepster, Rec.trav.chim., 1952, 71, 1159.

90. S.Krogt, B.Wepster, Rec.trav.chim., 1955, 74, 161.

91. E.Arnett, C.J.Wu, Chem.Ind., 1959, 1488.

92. R.P.Duke, R.A.Jones, A.R.Katritzky, E.E.Mikhlina, A.D. Yanina, L.M.Alekseeva, K.F.Turchin, Yu.N.Sheinker, L.N.Yakhontov, Tetrahedron Letters, 1970, 1809.

93. E.E.Mikhlina, A.D.Yanina, L.M.Alekseeva, K.F.Turchin, Yu.N.Sheinker, L.N.Yakhontov, R.P.Duke, R.A.Jones, A.R.Katritzky, Khim.Geterotsikl.Soedin., 1971, 385.

94. M.V.Rubtsov, L.N.Yakhontov, "Osnovnye napravleniya rabot VNICHFI", Moscow, 1959, p. 296.

95. E.E.Mikhlina, M.V.Rubtsov, Zh.Obshch.Khim., 1963, 33, 2167.

96. M.V.Rubtsov, E.E.Mikhlina, V.Ya.Vorobjova, A.D.Yanina, Zh.Obshch.Khim., 1964, 34, 2222.

97. E.E.Mikhlina, V.Ya.Vorobjova, V.I.Sheichenko, M.V. Rubtsov, Zh.Organ.Khim., 1965, 1, 1337.

98. E.E.Mikhlina, A.D.Yanina, K.F.Turchin, T.Ya.Filipenko, A.I.Ermakov, Yu.N.Sheinker, L.N.Yakhontov, Zh.Organ.

Khim., 1974, 10, 396.

99. V.Ya.Vorobjova, E.E.Mikhlina, K.F.Turchin, L.N.Yakhontov, Khim.Geterotsikl.Soedin., 1970, 1037.

100. C.A.Grob, A.Sieber, Helv.Chim.Acta, 1967, 50, 2531.

101. R.D.Fisher, T.D.Bogard, P.Kovacic, J.Amer.Chem.Soc., 1972, 94, 7599.

102. P.G.Gassman, R.L.Cryberg, K.Shudo, J.Amer.Chem.Soc., 1972, 94, 7600.

103. G.L.Buchanau, Chem.Soc.Rev., 1974, 3, 41.

104. R.Lukes, O.Stronf, M.Ferler, Coll.Czch.Chem.Comm., 1957, 22, 1173.

105. J.Palecek, Coll.Czech.Chem.Comm., 1966, 31, 1340.

106. J.Palecek, Z.Polivka, Coll.Czech.Chem.Comm., 1967, 32, 3909.

107. E.E.Mikhlina, V.Ya.Vorobjova, S.S.Bobyljeva, L.N. Yakhontov, Khim-Farm.Zh., 1969, N 3, 15.

108. K.H.Hasselgren, J.Dolby, J.L.G.Nilsson, Tetrahedron Letters, 1971, 2917.

109. J.Dolby, K.H.Hasselgren, J.L.G.Nilsson, J.Heterocycl. Chem., 1971, 8, 663.

110. J.Dolby, K.H.Hasselgren, J.L.G.Nilsson, Acta Pharm. Suec., 1971, 8, 97.

111. J.Dolby, Acta Pharm.Suec., 1971, 8, 523.

112. J.Dolby, R.Dahebom, K.H.Hasselgren, J.L.G.Nilsson, Acta Chem.Scand., 1971, 25, 735.

113. K.H.Hasselgren, J.Dolby, G.Hallström, Acta Pharm.Suec., 1974, 11, 533.

114. K.H.Hasselgren, J.Dolby, M.H.Holly, M.Elander, J.L.G. Nilsson, G.Lars, J.Org.Chem., 1974, 39, 1355.

115. J.Dolby, K.H.Hasselgren, S.Castensson, J.L.G.Nilsson, Acta Chem.Scand., 1972, 26, 2469.

116. J.Dolby, K.H.Hasselgren, Acta Pharm.Suec., 1971, 8, 123.

117. F.Pietra, F.Cima, Chem.Comm., 1970, 297.

118. G.Biggi, F.Cima, Chem.Comm., 1971, 1627.

119. F.Pietra, F.Cima, J.Chem.Soc., (B), 1971, 2224.

120. F.Pietra, G.Biggi, F.Cima, J.Chem.Soc. (B), 1971, 3626.

121. G.Biggi, F.Cima, F.Pietra, J.Chem.Soc., Perkin II, 1972, 1424.

122. G.Biggi, F.Cima, F.Pietra, Tetrahedron Letters, 1973, 183.

123. G.Biggi, F.Cima, F.Pietra, Tetrahedron Letters, 1974, 3537.

124. V.Prelog, K.Balenovic, Chem.Ber., 1941, 74, 1508.

125. C.A.Grob, Angew.Chem., 1965, 77, 459.

126. H.P.Fischer, C.A.Grob, Helv.Chim.Acta, 1968, 51, 153.

127. P.Benneisen, C.A.Grob, R.A.Jackson, M.Ohta, Helv.Chim. Acta, 1965, 48, 146.

128. W.H.Dennis, L.A.Hull, D.H.Rosenblatt., J.Org.Chem., 1967, 32, 3783.

129. C.A.Grob, R.M.Hoegerle, M.Ohta, Helv.Chim.Acta, 1962, 45, 1823.

130. C.A.Grob, K.Kostka, F.Kuhnen, Helv.Chim.Acta., 1970, 53, 608.

131. C.A.Grob, K.Kostka, Helv.Chim.Acta., 1970, 53, 613.

132. R.G.Kostyanovsky, E.E.Mikhlina, E.I.Levkoeva, L.N. Yakhontov, Organic Mass Spectrometry, 1970, 3, 1023.

133. A.I.Ermakov, Yu.N.Sheinker, E.E.Mikhlina, L.I.Mastafanova, V.Ya.Vorobjova, A.D.Yanina, L.N.Yakhontov, R.G.Kostyanovsky, Organic Mass Spectrometry, 1971, 5, 1029.

134. A.I.Ermakov, Yu.N.Sheinker, E.E.Mikhlina, L.I.Mastafanova, V.Ya.Vorobjova, A.D.Yanina, L.N.Yakhontov, R.G.Kostyanovsky, Khim.Geterotsikl.Soedin., 1972,1404.

135. A.I.Ermakov, Yu.N.Sheinker, E.E.Mikhlina, A.D.Yanina, V.Ya.Vorobjova, L.N.Yakhontov, R.G.Kostyanovsky, Khim. Geterotsikl.Soedin., 1972, 1411.

136. A.I.Ermakov, Yu.N.Sheinker, E.E.Mikhlina, A.D.Yanina, L.N.Yakhontov, R.G.Kostyanovsky, Khim.Geterotsikl. Soedin., 1972, 825.

137. J.Paleček, J.Mitera, Organic Mass Spectrometry, 1972, 6, 1353.

138. J.Paleček, J.Mitera, Coll.Czech.Chem.Comm., 1974, 39, 2037.

139. A.I.Ermakov, Yu.N.Sheinker, E.E.Mikhlina, A.D.Yanina, V.Ya.Vorobjova, L.T.Mastafanova, L.N.Yakhontov, Khim.

Geterotsikl.Soedin., 1975, 1376.

140. S.Sakai, M.Aimi, A.Kabo, M.Kitagawa, M.Shiratori, J.Hagihawa, Tetrahedron Letters, 1971, 2057.

141. V.C.Agwada, Y.Morita, U.Renner, M.Hesse, H.Schmid, Helv.Chim.Acta, 1975, 58, 1001.

142. S. Sakai, Heterocycles, 1976, 4, 131.

143. M.A.Khan, A.M.Ahsan, Tetrahedron Letters, 1970, 5137.

144. F.D.Reed, A.Burger. J.Med.Chem., 1971, 14, 554.

145. R.K.Razdan, H.G.Pars, W.R.Thompson, F.E.Granchelli, A.D.Little, Tetrahedron Letters, 1974, 4315.

146. D.L.Coffen, D.A.Katonak, F.Wong, J.Amer.Chem.Soc., 1974, 96, 3966.

147. G.A.Epling, N.K.Ayengar, Tetrahedron Letters, 1976, 3009.

148. H.Zielinski, Acta Pol.Pharm., 1973, 30, 155.

149. M.Gates, B.Sugavanam, W.Z.Schreiber, J.Amer.Chem.Soc., 1970, 92, 205.

150. D.L.Klayman, T.S.Griffin, J.D.Bower, S.W.Page, J.Med.Chem., 1973, 16, 1042.

151. D.L.Coffen, T.E.McEntre, Chem.Comm., 1971, 539.

152. E.C.Taylor, S.F.Martin, J.Amer.Chem.Soc., 1972, 94, 6218.

153. F.I.Carrol, D.Smith, M.E.Wall, Ch.G.Moreland, J.Med.Chem., 1974, 17, 985.

154. M.Uskokovic, J.Gutzwiller, T.Hendersen, J.Amer.Chem.Soc., 1970, 92, 203.

155. G.Grethe, H.L.Lee., T.Mitt, M.Uskokovic, J.Amer.Chem. Soc., 1971, 93, 5902.

156. J.Gutzwiller, M.Uskokovic, J.Amer.Chem.Soc., 1970, 92, 204.

157. J.Gutzwiller, M.Uskokovic, Helv.Chim.Acta, 1973, 56, 1494.

158. P.Rabe, Ber., 1911, 44, 2088.

159. G.Grethe, H.L.Lee, T.Mitt, M.Uskokovic, J.Amer.Chem. Soc., 1971, 93, 5904.

160. G.Grethe, J.Gutzwiller, H.L.Lee, M.Uskokovic, Helv. Chim.Acta, 1972, 55, 1044.

161. G.Grethe, H.L.Lee, T.Mitt, M.Uskokovic, Helv.Chim.Acta, 1973, 56, 1485.

162. L.N.Yakhontov, S.V.Yatsenko, M.V.Rubtsov, Zh.Obshch. Khim., 1958, 28, 1177.

163. G.Guenter, H.L.Lee, M.Uskokovic, Synth.Comm., 1972, 2, 55.

164. Chen Chan-bay, R.P.Evstigneeva, N.A.Preobrazhenskii, Doklady Akad.Nauk SSSR, 1958, 123, 707.

165. T.Singh, R.G.Stein, H.H.Koelling, J.F.Hops, J.H.Biel, J.Med.Chem., 1969, 12, 524.

166. U.S.patent 3726877 (1972), Chem.Abst., 1973, 79, 31939.

167. F.J.Villani, E.A.Wefer, T.A.Mann, C.A.Ellis, J.Med. Chem., 1969, 12, 933.

168. M.Picard, J.Cougue let, J.B.Boyer, R.Gluzel, Ann.Pharm. Franc., 1969, 27, 589.

169. Franc.patent 2035761 (1971), Chem.Abst., 1971, 75, 129688.

170. G.F.R. patent 2019536 (1971), Chem.Abst., 1972, 76, 72423.

171. U.S.patent 3464997 (1969), Chem.Abst., 1970, 72, 43495.

172. J.B.Robinson, B.Belleau, B.Cox., J.Med.Chem., 1969, 12, 848.

173. A.Kalin, E.Sali, E.Shirin, Isr.J.Chem., 1971, 9, 267.

174. R.W.Baker, P.J.Pauling, J.Chem.Soc., Perkin II, 1972, 2340.

175. R.Pyttel, J.B.Robinson, J.Pharm.Sci., 1973, 62, 684.

176. G.Lambrecht, Arch.Pharmaz., 1976, 309, 235.

177. U.S.patent 3919241 (1976), Chem.Abst., 1976, 84, 121670.

178. U.S.patent 3956365 (1976), Chem.Abst., 1976, 84, 108560.

179. T.W.Liberman, J.H.Leopold, Amer.J.Ophthalmol., 1967, 64, 405.

180. P.Bastide, P.Tzonche, F.Rouher, Arzneimittelforsch., 1968, 18, 322.

181. A.K.Cho, D.J.Jenden, S.I.Lamb., J.Med.Chem., 1972, 15, 391.

182. K.B.Schowen, E.E.Smissman, W.F.Stephen, J.Med.Chem., 1975, 18, 292.

183. T.Nogrady, A.A.Algieri, J.Med.Chem., 1968, 11, 212.

184. I.K.Sokolov, Khim.-Farm.Zh., 1977, N 1, 68.

185. P.P.Polak, J.Physiol., 1967, 34.

186. A.Meyerhöffer, J.Med.Chem., 1972, 15, 994.

187. J.J.Guy, T.A.Hamor, J.Chem.Soc., Perkin II, 1973, 942.

188. A.Meyerhöffer, D.Carlström, Acta Cryct., 1969, B.25, 943.

189. J.Fusek, J.Kabes, Z.Fink, Activ.Nerv.Super., 1972, 14, 161, 163.

190. J.Kabes, Activ.Nerv.Super., 1972, 14, 163, 164.

191. G.Grenier, H.Pacheo, Chem.Ther., 1966, 408.

192. U.S. patent 3405134 (1968), Chem.Abst., 1969, 70, 11581.

193. U.S. patent 3702324 (1972), Chem.Abst., 1973, 78, 29490.

194. R.Dahlbom, B.O.Kareen, J.L.G.Nilsson, Acta Pharm.Suec., 1967, 4, 221.

195. J.L.G.Nilsson, J.Wagemark, R.Dahlbom, Acta Pharm.Suec., 1968, 5, 71.

196. Franc. patent 1566045 (1969), Chem.Abst., 1970, 72, 78905.

197. H.Liebermann, S.Elkin, J.Pharm.Sci., 1968, 57, 684.

198. Brit. patent 1219606 (1969), Chem.Abst., 1971, 74, 13022.

199. G.F.R. patent 1935751 (1970), Chem.Abst., 1970, 73, 120520.

200. U.S. patent 3725419 (1973), Chem.Abst., 1973, 79, 5272.

201. K.A.Zaitseva, E.E.Mikhlina, V.Ya.Vorobjova, G.P.Zhikhareva, M.D.Mashkovsky, L.N.Yakhontov, Farmakol.i Toksikol.,

202. 1974, 37, 671.

202. A.D.Yanina, E.E.Mikhlina, K.A.Zaitseva, M.D.Mashkovsky, L.N.Yakhontov, Khim.-Farm.Zh., 1969, N 8, 7.

203. E.E.Mikhlina, V.Ya.Vorobjova, N.A.Komarova, K.A.Zaitseva, M.D.Mashkovsky, L.N.Yakhontov, Khim-Farm.Zh., 1974, N 2, 24.

204. E.W.Mikhlina, K.A.Zaitseva, M.D.Mashkovsky, L.N.Yakhontov, Khim.-Farm.Zh., 1973, N 8, 20.

205. E.E.Mikhlina, A.D.Yanina, L.N.Yakhontov, K.A.Zaitseva, L.F.Roshchina, M.D.Mashkovsky, Khim.-Farm.Zh., 1971, N 10, 10.

206. J.L.G.Nilsson, J.Lars, J.Wagermaak, R.Dohlbom, J.Med. Chem., 1969, 12, 1103.

207. U.S. patent 3560510 (1970), Chem.Abst., 1971, 75, 5735.

208. G.F.R. patent 1800823 (1969), Chem.Abst., 1969, 71, 61246.

209. G.F.R. patent 1938546 (1970), Chem.Abst., 1970, 73, 35238.

210. E.J.Warawa, N.J.Mueller, J.A.Gylys, J.Med.Chem., 1975, 18, 71.

211. L.L.Collins, C.A.Popacostas, S.Elkin, J.Pharm.Sci., 1967, 56, 1668.

212. C.Steel, A.B.Funcke, H.W.Forsteege, W.Th.Nauta, Arzneimittelforsch., 1966, 16, 1342.

213. U.S. patent 3317547 (1967), Chem.Abst., 1967, 67, 64118.

214. Niderland. patent 6701249 (1967), Chem.Abst., 1968, 68, 95696.

215. Franc. patent 2117750 (1972), Chem.Abst., 1973, 78, 97685.

216. G.F.R. patent 2009555 (1970), Chem.Abst., 1970, 73, 131017.

217. G.F.R. patent 2030492 (1971), Chem.Abst., 1971, 74, 141581.

218. G.F.R. patent 2113793 (1971), Chem.Abst., 1972, 76, 34132.

219. Belg. patent 762959 (1971), Chem.Abst., 1972, 76, 153623.

220. F.J.Villani, T.A.Mann, E.A.Wefer., J.Med.Chem., 1975, 18, 666.

221. A.Uzan, G.Lefur, Ann.Pharm.Franc., 1975, 33, 345.

222. J.C.Kellet, W.C.Doggett, J.Pharm.Sci., 1966, 55, 414.

223. R.B.Barlow, N.C.Scott, R.P.Stephenson, Brit.J.Pharmacol.Chemother., 1967, 31, 188.

224. E.S.Nikitskaya, I.M.Sharapov, E.I.Levkoeva, V.S.Usovskaya, A.S.Vlasov, T.E.Kukushkina, L.N.Yakhontov, M.V.Rubtsov, Khim.-Farm.Zh., 1970, N 10, 58.

225. E.S.Nikitskaya, E.I.Levkoeva, V.S.Usovskaya, L.N. Yakhontov, M.V.Rubtsov, Khim.Geterotsikl.Soedin., 1971, 230.

226. E.I.Levkoeva, E.S.Nikitskaya, I.M.Sharapov, L.N.Yakhontov, Khim.-Farm.Zh., 1971, N 9, 16.

227. E.I.Levkoeva, L.N.Yakhontov, Khim.Geterotsikl.Soedin., 1976, 927.

228. E.S.Nikitskaya, I.M.Sharapov, M.D.Mashkovsky, E.I. Levkoeva, A.S.Vlasov, T.E.Kukushkina, L.N.Yakhontov, Khim.-Farm.Zh., 1974, N 8, 59.

229. E.E.Mikhlina, V.Ya.Vorobjova, N.A.Komarova, I.M. Sharapov, A.I.Polezhaeva, M.D.Mashkovsky, L.N.Yakhontov, Khim.-Farm.Zh., 1976, N 11, 56.

230. E.E.Mikhlina, V.Ya.Vorobjova, T.K.Trubizyna, M.D. Mashkovsky, L.N.Yakhontov, Khim.-Farm.Zh., 1973, N 12, 23.

231. S.Biniecki, A.Bulacinski, Acta.Pol.Pharm., 1974, 31, 147.

232. S.Biniecki, A.Bulacinski, Acta.Pol.Pharm., 1975, 32, 517.

233. R.Dahlbom, J.Dolby, Acta Pharm.Suec., 1969, 6, 277.

234. Franc. patent 1566045 (1969), Chem.Abst., 1970, 72, 78905.

235. U.S. patent 3560510 (1971), Chem.Abst., 1971, 75,5735.

236. E.J.Warawa, N.J.Mueller, J.Med.Chem., 1975, 18, 587.

237. G.F.R. patent 1915142 (1969), Chem.Abst., 1970, 72, 31644.

238. E.J.Warawa, N.J.Mueller, R.Jules, J.Med.Chem., 1974, 17, 497.

239. Japan patent 7217797 (1972), Chem.Abst., 1972, 77, 152143.

240. U.S. patent 3506673 (1970), Chem.Abst., 1970, 73, 3814.
241. U.S. patent 3542791 (1970), Chem.Abst., 1971, 74, 125477.
242. U.S. patent 3534053 (1970), Chem.Abst., 1971, 74, 53567.
243. U.S. patent 3462442 (1969), Chem.Abst., 1969, 71, 91343.
244. U.S. patent 3598825 (1971), Chem.Abst., 1971, 75, 110339.
245. U.S. patent 3501471 (1970), Chem.Abst., 1970, 73, 56081.
246. J.L.G.Nilsson, J.Wagermark, R.Dahlbom, W.Benson, Acta Pharm.Suec., 1968, 5, 9.
247. U.S. patent 3792053 (1974), Chem.Abst., 1974, 81, 25574.
248. U.S. patent 3725410 (1973), Chem.Abst., 1973, 79, 5367.
249. G.F.R. patent 2136763 (1972), Chem.Abst., 1972, 76, 140579.
250. R.B.Moffett, J.B.Hester, J.Med.Chem., 1972, 15, 1243.
251. W.Shapiro, M.F.Tansy, S.Elkin, J.Pharm.Sci., 1968, 57, 1725.
252. U.S. patent 3681363 (1972), Chem.Abst., 1972, 77, 140071.
253. A.Fisher, M.Weinstock, S.Girter, S.Cohen, Eur.J.Pharmacol., 1976, 37, 329.

254. U.S. patent 3905969 (1975), Chem.Abst., 1976, 84, 4932

255. M.Torio, H.Machalek, R.Carmine, Chem.Ther., 1971, 6, 391.

256. U.S. patent 3860717 (1975), Chem. Abst., 1975, 82, 149531.

257. E.Hong, Arzneimittelforsch., 1976, 1657.

258. H.Vidrio, E.Hong, Arzneimittelforsch., 1976, 1662.

259. J.Leeling, J.Bare, B.Phillips, P.Medon, Arzneimittelforsch., 1976, 1665.

260. J.Leeling, T.Kowalski, Arzneimittelforsch., 1976, 1668.

261. R.Hartnogel, B.Phillips, E.Fonseca, R.Kowalski, Arzneimittelforsch., 1976, 1671.

262. E.E.Mikhlina, A.D.Yanina, V.Ya.Vorobjova, N.A.Komarova, L.N.Yakhontov, Khim.Geterotsikl. Soedin., 1976, 935.

263. R.Tondeur, M.Urbain, Chem.Therap., 1966, 19, 207.

264. R.B.Moffett, R.E.Stube, L.Skaletzky, J.Med.Chem., 1971, 14, 1087.

265. H.H.Keasling, R.B.Moffett, J.Med.Chem., 1971, 14, 1106.

266. M.E.Kaminka, E.E.Mikhlina, V.Ya.Vorobjova, A.D.Yanina, N.A.Komarova, M.D.Mashkovsky, L.N.Yakhontov, Khim-Farm., Zh., 1976, N 6, 48.

267. M.E.Kaminka, E.E.Mikhlina, V.Ya.Vorobjova, A.D.Yanina, N.A.Komarova, M.D.Mashkovsky, L.N.Yakhontov, Khim.-Farm.Zh., 1976, N 9, 22.

268. L.P.Firsova, A.V.Krasnyansky, S.M.Svetlikin, E.E. Mikhlina, V.Ya.Vorobjova, A.D.Yanina, L.N.Yakhontov,

Zh.Organ.Khim., 1976, 12, 2249.

269. M.E.Kaminka, E.E.Mikhlina, V.Ya.Vorobjova, D.D.Yanina, N.A.Komarova, M.D.Mashkovsky, L.N.Yakhontov, Khim-Farm. Zh., 1977, N 2, 24.

Received, 6th May, 1977