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The Chemistry of Quinuclidine

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The review deals with the chemical properties and the biological activity of the derivatives of 1-azabicyclo[2,2,2] octane widely known as quinuclidine. The work of the Soviet School of Chemists, founded by M.V.Rubtsov, in the field of quinuclidine derivatives is reviewed in detail.
In the review an attempt is made in the first place to examine as a whole the chemistry and the biological action of quinuclidine derivatives from the standpoint of the characteristics of the structure of the quinuclidine molecule. The description of the methods of synthesis of various quinuclidine derivatives features prominently in the review. These data are presented with separate discussion of the methods of synthesising the bicyclic quinuclidine system and the methods for the introduction of various substituents into the preformed quinuclidine ring. This system made it possible to give a general account of the abundant factual data which have accumulated so far on the synthesis of quinuclidine derivatives and to emphasise the characteristics of the synthetic studies on this class of substances.
A special section deals with the comparatively new reactions involving the expansion of the quinuclidine ring. The bibliography comprises 227 references.

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I. INTRODUCTION

The heterocyclic quinuclidine 1-azabicyclo[2,2,2]octane system is a structural fragment in a number of natural physiologically active substances and synthetic medicinal preparations†.

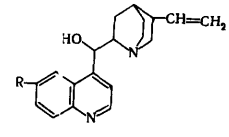
Among natural alkaloids, derivatives of quinoline and indole, containing the quinuclidine ring in the molecule, mention should be made of the cinchonine–cinchonamine (alkaloids of the bark of the cinchona tree)[8–12], sarpagine–ajmaline (Rauwolfia alkaloids)[8,13,14], and macusaine (strychnine alkaloids)[15,16] groups.

In connection with the high chemotherapeutic activity of the cinchona alkaloids, among which quinine occupies a particularly important place as an antimalarial drug, the study of the methods of synthesis of quinine and its analogues has occupied the attention of investigators in many countries for a long time. The ability of natural quinuclidine compounds (quinidine, ajmaline) to reduce the capacity of heart muscle to be stimulated, the comparatively recently discovered high pharmacological activity of certain synthetic quinuclidine derivatives and its wide variety, and the possibility of employing quinuclidine compounds as catalysts for the synthesis of polymers[17] have all stimulated further interest in studies on the quinuclidine series.

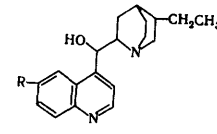
Among important advances in the investigation of natural quinuclidine compounds, mention should be made of the total synthesis of quinine achieved by Woodward and Doering[18] in 1944 and also the synthesis of cinchonamine carried out in 1958 by Ch'ên Ch'ang-Pai et al.[19] The total synthesis of racemic homomeroquinene, an intermediate in the synthesis of quinine, was achieved by Rubtsov from trichlorocollidine[20].

† Previously a number of reviews were published giving a fairly complete description of the development of the chemistry of quinuclidine derivatives[1–7].

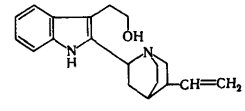
Alkaloids of the cinchonine–cinchonamine group



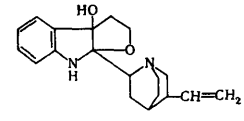
R = H cinchonine, cinchonidine
R = OH cupreine
R = OCH_3 quinine, quinidine, epiquinine, epiquinidine



R = H hydrocinchonine, hydrocinchonidine
R = OCH_3 hydroquinidine, hydroquinine

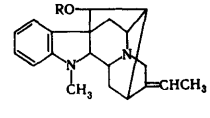


cinchonamine

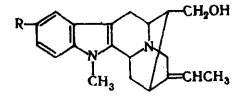


quinamine, conquinamine

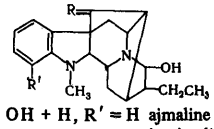
Alkaloids of the sarpagine, ajmaline, and macusaine group



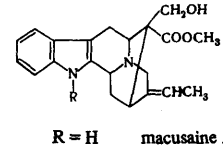
R = H tetraphyllicine
R = $(CH_3O)_3C_6H_2CO$ rauvomitine



R = OH sarpagine
R = OCH_3 lochnerine



R = OH + H, R′ = H ajmaline, isoajmaline, sandwicine
R = O, R′ = H ajmalidine
R = O, R′ = OCH_3 vamalidine



R = H macusaine A
R = CH_3 voachalotine

A number of reviews have been devoted[8-12,21], to problems connected with the chemistry of natural quinuclidine compounds and in particular the history of their discovery and practical applications, the examination of the natural sources, the methods of analysis and isolation, the determination of the structure and reactions of these compounds, and also problems of their stereochemistry. Therefore these data need not be described again and attention may be concentrated in the present review on the general chemical characteristics of quinuclidine derivatives, the methods of synthesising the quinuclidine ring and introducing substituents into the quinuclidine molecule, and also the biological properties of synthetic quinuclidine derivatives.

II. SOME CHARACTERISTICS OF QUINUCLIDINE DERIVATIVES

Quinuclidine (I) is the saturated bicyclic system with a nodal nitrogen atom



(I)

In contrast to aliphatic tertiary amines and *N*-substituted piperidines, quinuclidine has a rigidly fixed structure. The atoms comprising the quinuclidine ring are incapable of altering their relative positions by rotating about their bonds, which are included in a bicyclic system where each ring has the "boat" form. Compared with other 1-azabicycloalkanes, quinuclidine is characterised by high symmetry and only slight strain of the cyclic system. A distinctive feature of the quinuclidine molecule is also almost complete absence of screening of the sp^3-hybridised unshared electron pair at the nitrogen atom. These characteristics of the structure explain many physical and chemical properties of both quinuclidine itself and its various derivatives. For example, quinuclidine is a volatile crystalline substance with a high melting point (158°C). It readily sublimes even on standing in air. Breakdown of the symmetry of the quinuclidine molecule (by its conversion into condensed systems or by introduction of alkyl substituents) leads to a lowering of the melting point[22-26].

Interesting results were obtained in a comparative study of the infrared spectra of quinuclidine and piperidine and piperazine derivatives substituted at the nitrogen atom[27]. The spectra of the monocyclic compounds show in the range 2700–2800 cm^{-1} characteristic absorption bands due to the interaction of the free electron pair of the nitrogen atom with the adjacent axial C–H bonds. Quinuclidine does not absorb in this region, probably because of the absence of such interaction. Characteristic absorption bands at 2430, 2915, and 3405 cm^{-1} have been noted for quinuclidine[28].

The basicity of quinuclidine, which depends on the electron density at the nitrogen atom, is fairly high and close to that of the lower aliphatic amines and *N*-alkylpiperidines. The basicity of the condensed systems of benzo- and dibenzo-quinuclidine is reduced because of the inductive effect of the phenyl groups[26,29]. Comparison of the pK_a of the benzo- and dibenzo-quinuclidines with those of diethylaniline and diphenylamine, which have similar structures, demonstrates clearly the effect of the rigidity of the structure of quinuclidine derivatives (Table)[30].

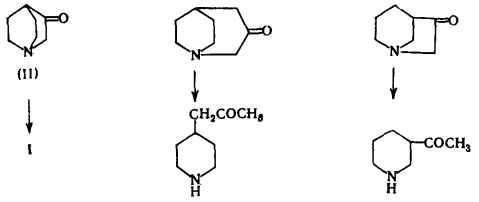
Like other aliphatic tertiary amines, quinuclidine readily forms salts with mineral and organic acids and also quaternary derivatives with alkyl halides. However, kinetic studies have shown[32] that the rate of reaction of alkyl iodides with quinuclidine is much higher than in similar reactions with aliphatic tertiary amines. For example, quinuclidine reacts with methyl iodide 50 times faster and with isopropyl iodide 700 times faster than does triethylamine. The trimethylborane adduct of quinuclidine proved to be more stable than the corresponding adducts of the trialkylamine series. These results can be explained by the virtual absence of steric hindrance at the electron pair of the nitrogen of the bicyclic system.

pK_a values for quinuclidine and related compounds

Compound	pK_a	References
Dimethylamine	10.77	31
Diethylamine	10.93	31
Triethylamine	10.87	31
N-Methylpiperidine	10.08	31
Quinuclidine	10.58	26
Benzoquinuclidine	7.79	26
Diethylaniline	6.56	31
Dibenzoquinuclidine	4.46	26
Diphenylamine	0.79	31.

The considerable chemical stability of the quinuclidine molecule is associated with the characteristics of its structure. Quinuclidine does not change on heating with concentrated mineral acids and on oxidation with potassium permanganate[22].

Leonard et al.[33] showed that, when 3-quinuclidone (II) is subjected to the Clemmensen reduction, the quinuclidine ring is retained, while ring fission occurs in other 1-azabicyclic ketones:

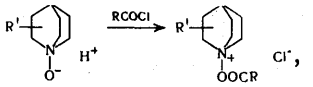


Quinuclidine is not dehydrogenated by mercury acetate, probably because in this case the reaction would have to proceed via a salt of Δ^1-dehydroquinuclidine and the formation of the latter is impossible according to the Bredt rule[2,34]. Quinuclidine can be dehydrogenated only under severe conditions (300°C) using palladium on charcoal or selenium[35]. The C–N bond then breaks and 4-ethylpyridine is formed.

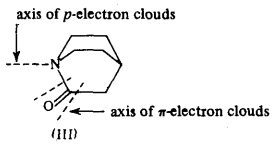
The pyrolysis and hydrogenolysis of quaternary quinuclidine salts leads to high yields of quinuclidine[2,36-38]. The formation of tertiary amines, in this case due to the elimination of aliphatic alcohols, is also a fundamental process accompanying the Hofmann degradation of quaternary quinuclidinium bases[39-41]. For example, in the Hofmann degradation of 1-methylquinuclidinium hydroxide unsubstituted quinuclidine was isolated in 35% yield together with products obtained as a result of the opening of the quinuclidine ring—1-methyl-4-vinylpiperidine and 1-methyl-4-(β-hydroxyethyl)piperidine[39]. All these findings constitute additional confirmation of the thermal and chemical stability of the quinuclidine ring.

The *N*-oxides of quinuclidine derivatives are capable of forming *O*-acylium salts which are stable to hydrolysis in neutral or acid media. On the other hand, their sensitivity

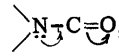
to alkalis is so high that they can be titrated as dibasic acids[42]:

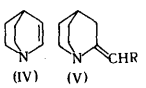


where R = CH_3 or C_6H_5. Interesting chemical properties have been found in bicyclic amides of the type of 2-quinuclidone (III).[43-46] The axes of the free *p*-electron clouds of nitrogen in such compounds prove to be almost perpendicular to the axes of the π-electron clouds of the carbonyl group:

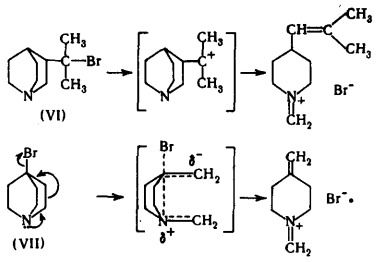


(III)

As a result, conjugation of the type , which is characteristic of amides, is impossible in 2-quinuclidones. A number of properties of 2-quinuclidones, which makes them similar to amino-ketones, are connected with this fact. The nitrogen atom in 2-quinuclidones is readily protonated (ordinary amides and lactams are protonated at the oxygen) and methylated; 2-quinuclidones are highly basic (pK_a = 5.33–5.6)[44] compared with other amides (for example, *N*-acetylpiperidine has pK_a = 0.4). In the infrared spectra of these substances the frequency of the C=O stretching vibrations is on the average higher by 80 cm^{-1} than in ordinary lactams and the integral intensity of the carbonyl band is smaller by a factor of almost 2. The absorption maxima of 2-quinuclidones in the ultraviolet spectra occupy a position intermediate between the maxima of amides and ketones. The absence of amide mesomerism in 2-quinuclidones results in an increase of their reactivity, which is reflected in a higher rate of hydrolysis and alcoholysis of their hydrochlorides. The kinetics of the above reactions can be investigated by polarography, while normal amides and lactams cannot be reduced polarographically. The high reactivity of the C=O group in 2-quinuclidones is reflected also in the acidity of the adjacent CH_2 groups, which shows a tendency to undergo deuterium exchange. Finally, the C=O group in 2-quinuclidone is capable of nucleophilic substitution reactions which are characteristics of ketonic carbonyls—for example the formation of oximes with hydroxylamines[43]. Certain unusual chemical features are shown also by unsaturated quinuclidine derivatives—Δ^2-dehydroquinuclidine (IV),[47,48] its 2-substituted derivatives[49], and quinuclidines (V) with an exocyclic double bond in the 2-position[49]. As was to be expected on the grounds of structural considerations, these compounds differ in their properties from normal tertiary α-vinylamines. For example, dehydroquinuclidines do not exhibit the absorption at 230 nm characteristic of enamines and are not hydrolysed under mild conditions by dilute acids.


(IV) (V)

In contrast to the analogous aliphatic and nitrogen-free bicyclic compounds, the fragmentation of quinuclidine derivatives[50-57] takes place unambiguously. 2-(Quinuclidin-3′-yl)-2-bromopropane (VI) undergoes solvolysis by a stepwise mechanism[50,51] and 4-bromoquinuclidine (VII) is solvolysed by a synchronous mechanism[50,53]:


(VI)

(VII)

Because of the ease of protonation of the nitrogen atom in the quinuclidine ring, the competing reactions involving the isomerisation of the carbonium ion and also substitution and elimination processes do not play a significant role in these cases.

III. METHODS OF SYNTHESIS OF QUINUCLIDINE AND ITS DERIVATIVES

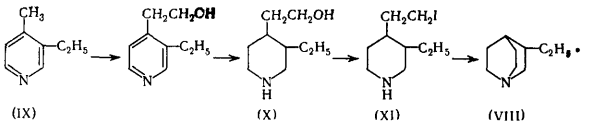
In the course of investigations over a period of many years a large number of a wide variety of quinuclidine derivatives have been synthesised. In order to give a systematic account of the literature data and the methods of preparation of quinuclidine and its substituted derivatives, in this review a distinction is drawn between methods of synthesis associated with the formation of the quinuclidine ring and methods for the introduction of various substituents into the preformed quinuclidine ring. Reactions accompanied by the expansion of the quinuclidine ring with formation of derivatives of other 1-azabicycloalkanes are described in a special section.

1. METHODS FOR QUINUCLIDINE RING CLOSURE

The starting compounds for the formation of the quinuclidine ring may be both piperidine derivatives and aliphatic substances: trihalogenoalkanes and dihalogenoalkylamines. The piperidine derivatives are obtained mainly from pyridine bases. Dihalogenoalkylamines and trihalogenoalkanes are usually synthesised from tetrahydropyran derivatives, dialkoxymalonic esters, or alkanetricarboxylic acid esters.

The quinuclidine ring closure is as a rule achieved by two mechanisms when piperidine derivatives are used: (1) by intramolecular alkylation or acylation or (2) by Dieckmann's intramolecular cyclisation.

Intramolecular alkylation was proposed in 1904 by Koenigs[58,59] for the preparation of the first synthetic representative of the quinuclidine series—3-ethylquinuclidine (VIII):


(IX) (X) (XI) (VIII)

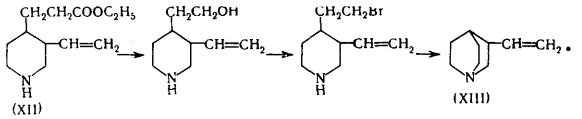
The starting material in Koenigs scheme was 3-ethyl-4-methylpyridine (IX). The product of the condensation of compound (IX) with formaldehyde was reduced with sodium in alcohol. The hydroxy-group in the piperidine derivative (X) obtained was replaced by iodine and 3-ethyl-4-(β-iodoethyl)piperidine (XI) was cyclised under the influence

of sodium carbonate with formation of 3-ethylquinuclidine (VIII).

A similar scheme using 4-methylpyridine as the starting material was employed in 1909 by Löffler and Stitzel[60] to prepare unsubstituted quinuclidine. However, these workers were unable to isolate pure quinuclidine and it was not until 1920 that Meisenheimer[22] obtained it. Meisenheimer[22] also described the conversion of 4-methylquinoline into benzoquinuclidine by Koenigs' method.

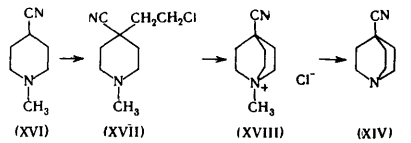
Later intramolecular alkylation of 4-(β-halogenoalkyl)-piperidines in the presence of alkaline reagents (sodium hydroxide, sodium bicarbonate, potassium carbonate, pyridine, etc.) was used frequently to synthesise quinuclidine[61] and its various derivatives. 2-Methylquinuclidine[23,62,63], 4-methylquinuclidine[25], dibenzoquinuclidine[26], 3-hydroxymethyl-3-methylquinuclidine[36,37,64], the lactone of 3-carboxymethyl-3-hydroxymethylquinuclidine[65], etc. were obtained by this procedure.

Lukeš and Galik[66] converted by a similar procedure the ethyl ester of meroquinene (XII), isolated from natural cinchonine, into optically active 3-vinylquinuclidine (XIII):



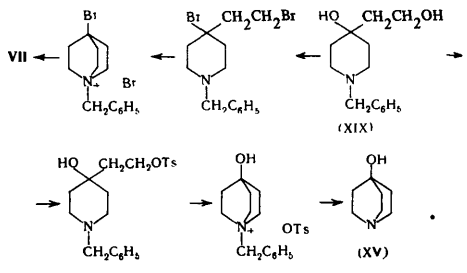
(XII) (XIII)

Grob et al.[67,68] used Koenigs' method to prepare 4-monosubstituted quinuclidines, including 4-cyano- (XIV), 4-bromo- (VII), and 4-hydroxy-quinuclidines (XV). The cyclisation in these syntheses was not based on secondary amines of the piperidine series but was carried out using tertiary *N*-substituted (*N*-methyl- and *N*-benzyl-)piperidines:



(XVI) (XVII) (XVIII) (XIV)

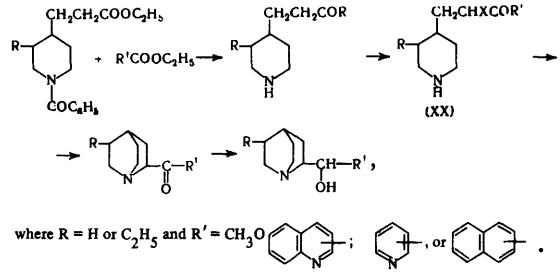
For example, 4-(β-chloroethyl)-4-cyano-1-methylpiperidine (XVII), obtained by the condensation of 4-cyano-1-methylpiperidine (XIV) with dichloroethane, was cyclised to the methochloride of 4-cyanoquinuclidine (XVIII), from which methyl chloride was eliminated on heating in a vacuum to 260–270°C.[67] The analogous conversion of 1-benzyl-4-hydroxy-4-(β-hydroxyethyl)piperidine (XIX) into 4-bromoquinuclidine (VII) and 4-hydroxyquinuclidine (XV)[68] can be represented as follows:



(XIX) (XV)

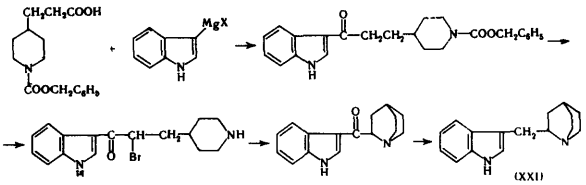
Rabe[69,70] and later other investigators[71–75] employed the above method of formation of the quinuclidine ring in their syntheses of analogues and isomers of cinchona alkaloids.

In this case the starting materials were not 4-halogenoalkyl piperidines or the analogous tosyl esters but halogeno-oxo-derivatives of the piperidine series—4-(β-halogeno-γ-oxoalkyl)piperidines (XX), the syntheses and reactions of which are shown below:



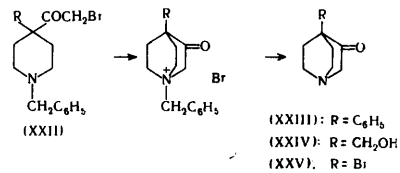
(XX)

A similar scheme was employed also in the synthesis of 2-scatylquinuclidine (XXI):[76]



(XXI)

Starting with the halogeno-oxo-derivatives of piperidine of another type, compounds of the 4-(β-bromo-α-oxoethyl)-piperidine (XXII) series, 3,4-disubstituted quinuclidines were prepared: 3-oxo-4-phenylquinuclidine (XXIII),[38] 4-hydroxymethyl-3-oxoquinuclidine (XXIV),[77] and 4-bromo-3-oxoquinuclidine (XXV):[78]

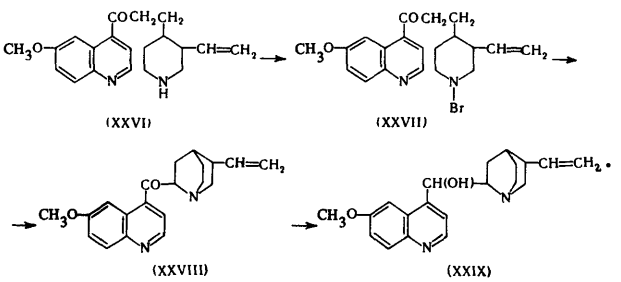


(XXII)

(XXIII): R = C_6H_5
(XXIV): R = CH_2OH
(XXV): R = Br

It was then shown[78] that quinuclidine ring closure is possible only with the axial disposition of both the 4-bromoacetyl residue and of the electron pair at the nitrogen atom. The formation of this conformation in the transition state is facilitated by the introduction of bulky substituents in the 1- and 4-positions of the piperidine ring. The attempts to cyclise compounds without such substituents (for example, 4-bromoacetylpiperidine) were unsuccessful[78].

Rabe[79,80] developed a somewhat different method of quinuclidine ring closure for the synthesis of cinchona alkaloids containing the vinyl group in the molecule. In this case it is difficult to introduce a halogen into the oxoalkyl residue of 4-oxoalkyl-3-vinylpiperidines (XXVI) without affecting the double bond. Therefore *N*-bromo-substituted and not *C*-substituted piperidines were employed for quinuclidine ring closure:

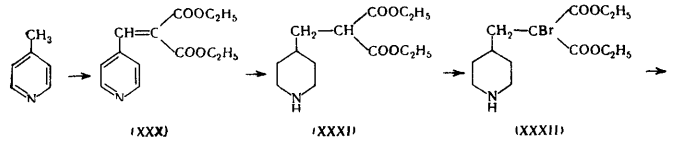


(XXVI) (XXVII) (XXVIII) (XXIX)

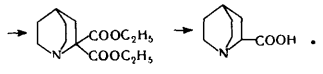
Quinotoxine (XXVI) was converted by treatment with sodium hypobromite into *N*-bromoquinotoxine (XXVII), which was cyclised under the influence of alkoxides to the corresponding quinuclidine derivative—quininone (XXVIII). The scheme developed by Rabe was used in the total synthesis of quinine (XXIX)[18] and also for the preparation of a number of analogues of this alkaloid[81,82].

In contrast to the unambiguous cyclisation of *N*-halogeno-4-oxoalkylpiperidines, considerable difficulties were encountered when 4-alkyl-*N*-halogenopiperidines were used for quinuclidine ring closure. Wawžonek and coworkers[83,84,87] and Lukeš and coworkers[85,86,88] established that the application of the Hofmann–Löffler reaction to 4-alkyl-*N*-chloropiperidines leads to the formation of a mixture of products in which quinuclidine derivatives are present together with the isomeric alkyl-1-azabicyclo[2,2,1]heptanes. The treatment of *N*-(β-chloroethyl)piperidine or its derivatives with a methanol solution of potassium hydroxide[27,89] leads to the formation of Hofmann degradation products, arising in the synthesis of 1,4-bispentamethylenepiperazinium dichloride. The main product is 1,2-bis(*N*-piperidino)ethane[27].

The Koenigs reaction was developed further in the work of Rubtsov, Dorokhova, and Mikhlina[90,91] and also Grob and coworkers[92,93], who employed α-halogeno-acids of the piperidine series and their esters for intramolecular alkylation. Rubtsov and Dorokhova[90] developed in 1953 a simple method for the synthesis of quinuclidine-2-carboxylic acid in five stages:



(XXX) (XXXI) (XXXII)

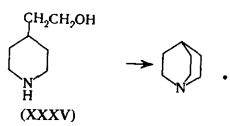


(XXXIII) (XXXIV)

The condensation of γ-picoline with mesoxalic ester gave 4-(ββ-diethoxycarbonylvinyl)pyridine (XXX). The unsaturated ester (XXX) was hydrogenated using platinum to compound (XXXI), which was then treated with bromine. The resulting 4-(β-bromo-ββ-diethoxycarbonylethyl)piperidine (XXXII) was cyclised in the presence of pyridine to 2,2-diethoxycarbonylquinuclidine (XXXIII). The latter was hydrolysed and partially decarboxylated with formation of quinuclidine-2-carboxylic acid (XXXIV).

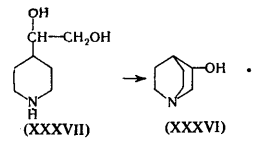
The above principle involving the cyclisation of α-halogeno-esters of the piperidine series was widely employed subsequently for the synthesis of various 2,3- and 2,5-disubstituted quinuclidines: 3-carboxymethylquinuclidine-2-carboxylic acid[94], 3-methylquinuclidine-2-carboxylic acid[95], and 5-[β-hydroxy(methoxy)ethyl]quinuclidine-2-carboxylic acid[96,97].

A variant of the intramolecular alkylation method is the gas-phase cyclodehydration of 4-(β-hydroxyethyl)piperidine (XXXV) proposed by Leonard et al.[98]:



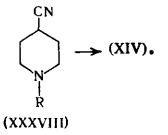
(XXXV)

The same method was used to synthesise 3-hydroxyquinuclidine (XXXVI) from piperid-4'-ylethane-1,2-diol (XXXVII):[99]



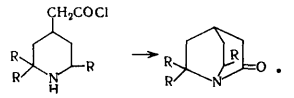
(XXXVII) (XXXVI)

Another variant of the intramolecular alkylation method is the synthesis of 4-cyanoquinuclidine (XIV) by the condensation of 1-alkyl-4-cyanopiperidines (XXXVIII) with ethylene glycol esters in the presence of alkali metals[100]:

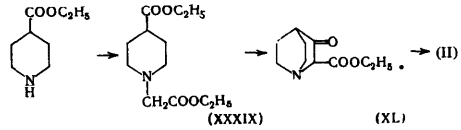


(XXXVIII)

The intramolecular acylation of piperidine derivatives has been used together with intramolecular alkylation for the formation of the quinuclidine ring. Yakhontov and Rubtsov and subsequently Pracejus and coworkers synthesised in this way 2-quinuclidone (III)[43] and its 6,6-dimethyl-[44] and 6,6,6-trimethyl-[45,101] derivatives from the corresponding acid chlorides under the influence of anhydrous potassium carbonate or tertiary amines:



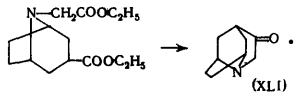
Another method for the closure of the quinuclidine ring is based on Dieckmann's *intramolecular cyclisation*. This procedure was proposed for the first time by Clemo and Metcalfe[102] for the synthesis of 3-quinuclidone (II):[102]



(XXXIX) (XL)

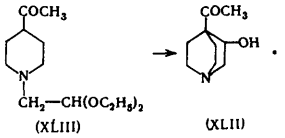
Ethyl isonipecotate was converted by alkylation with chloroacetic ester into ethyl 1-ethoxycarbonylmethylisonipecotate (XXXIX). The latter was cyclised in the presence of metallic potassium in toluene and the resulting β-keto-ester (XL) was hydrolysed and decarboxylated without isolation. Later this method was improved and the yield of the ketone (II) in the cyclisation stage was increased to 84%.[103-107]

The isolation of the intermediate in the synthesis—ethyl 3-oxoquinuclidine-2-carboxylate (XL)[108]—made it possible to develop methods based on it for the preparation of various 2,3-disubstituted quinuclidines[49,108,109]. Subsequently the Clemo reaction was used to synthesise ring-substituted quinuclidines: 5-oxoquinuclidine-2-carboxylic acid[110], 6-methyl-3-quinuclidone[111], 6,7-dimethyl-3-quinuclidone[112], and also compounds of the tropaquinuclidine series (XLI):[113]



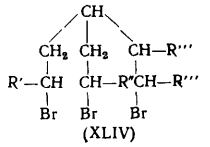
(XLI)

The recently described quinuclidine ring closure by intramolecular aldol condensation in the synthesis of 4-acetylquinuclidin-3-ol (XLII) from 4-acetyl-1-(2′,2′-diethoxyethyl)piperidine (XLIII) [77] is unusual:



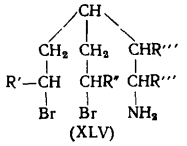
(XLIII) (XLII)

A fundamentally different approach to the synthesis of quinuclidine and its derivatives was developed by Prelog and coworkers [114,115]. The methods which they proposed are based on the action of ammonia under pressure at 100–120°C on tribromoalkanes (XLIV):



(XLIV)

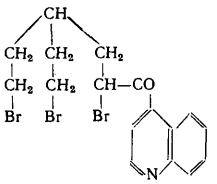
or on double intramolecular alkylation consisting in the treatment with alkali of dibromoalkylamines (XLI):



(XLV)

Quinuclidine [39,114-117], its 2-alkyl- [23,24], 3-alkyl- [24], and 4-alkyl-derivatives [25], and also quinuclidine-2-carboxylic acid [118] were obtained in this way.

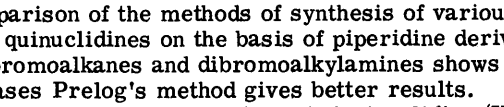
Prelog's attempts to achieve the cyclisation of the tribromoalkyl derivative (XLVI),



(XLVI)

in order to obtain a quinine analogue proved to be unsuccessful [119].

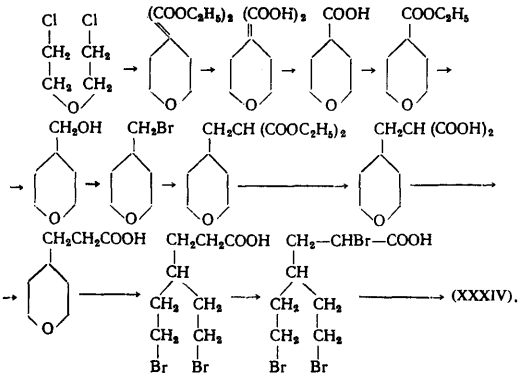
Comparison of the methods of synthesis of various substituted quinuclidines on the basis of piperidine derivatives and tribromoalkanes and dibromoalkylamines shows that in some cases Prelog's method gives better results. For example, in the synthesis of 2-methylquinuclidine (XLVII) by this procedure Lukeš achieved a yield of 37%: [23]



(XLVII) (XLVIII)

The sole example of 3,5-disubstituted quinuclidines described, 3,5-dimethylquinuclidine (XLVIII), [120] was synthesised by Prelog's method.

At the same time the synthesis of quinuclidine derivatives from tribromoalkanes and dibromoalkylamines involves in many cases starting materials which are difficult to obtain and are formed in multistage syntheses with low yields. Prelog's method is also less suitable for the synthesis of quinuclidine derivatives containing functional groups. As an example, one may quote the methods of preparation of quinuclidine-2-carboxylic acid (XXXIV): [118]



In this case the synthesis of compound (XXXIV) is achieved by a multistage procedure (12 stages) and the overall yield is about 4%. In the five-stage synthesis of compound (XXXIV) starting with γ-picoline described above the yield of quinuclidine-2-carboxylic acid is 30%. [90]

2. METHODS FOR THE INTRODUCTION OF SUBSTITUENTS INTO THE QUINUCLIDINE RING

As already mentioned above, the quinuclidine molecule is a saturated bicyclic system. The introduction into this molecule of functional groups by direct substitution presents considerable difficulties and experiments of this kind have not been carried out at all so far. Therefore reactive groups are usually introduced during the closure of the quinuclidine ring and are then used to convert the product into various classes of quinuclidine derivatives. The most readily available compounds containing such functional groups are the carboxy- and carbonyl derivatives: quinuclidine-2-carboxylic acid, 3-quinuclidone, and others. Almost all substituted quinuclidine derivatives of a wide variety of types were obtained from the carboxy- and carbonyl derivatives using the usual methods of organic synthesis.

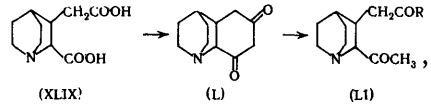
(1) Syntheses of Substituted Quinuclidines from Quinuclidinecarboxylic Acids

At the present time all three monocarboxylic acids of quinuclidine are known: quinuclidine-2-carboxylic [90,118], quinuclidine-3-carboxylic [121,122], and quinuclidine-4-carboxylic [67,100], and also quinuclidine-2-carboxylic acids with various substituents in the 3-position [95,108] and the 5-position [96,110] and quinuclidine-3-carboxylic acids with substituents in the 2-position [123] and the 6-position [111]. Only one compound containing 2-carboxy-groups in the quinuclidine ring has been described: quinuclidine-2,3-dicarboxylic acid [109]. A large number of homologues of quinuclidinecarboxylic acids have been obtained, among which quinuclidine-3-acetic [124-127] and 3-carboxymethylquinuclidine-2-carboxylic acid [94] are of definite interest for further reactions. The syntheses of quinuclidine derivatives from quinuclidinecarboxylic acids may be divided into three large groups: (a) reactions without change in the length of the carbon chain; (b) reactions accompanied by the dissociation of the C–C bond and a decrease in chain length;

(c) reactions associated with an increase in the length of the carbon chain.

a. Reactions without change in the length of the carbon chain. Quinuclidinecarboxylic acids readily form acid chlorides which can be converted without isolation into the corresponding esters [67,96,125,128-130] or amides [125,130,131]. It is noteworthy that other methods have also been used to prepare the esters of quinuclidinecarboxylic acids; esterification in the presence of sulphuric acid and hydrogen chloride and also transesterification with alkali metal alkoxides [96,109,110]. The amides of Δ^2-dehydroquinuclidine-2- and -3-carboxylic acids were obtained from the corresponding esters by the action of alcoholic ammonia [47,49]. Esters of quinuclidinecarboxylic acids have also been used to synthesise many hydrazides and their hydrazones [95,132] and the amides were used to synthesise nitriles [47,49,90].

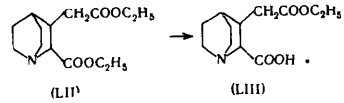
The attempt to obtain the anhydride from 3-carboxymethylquinuclidine-2-carboxylic acid (XLIX) in the presence of acetic anhydride and sodium acetate unexpectedly led to the formation of the tricyclic β-diketone (L). [133] On interaction with substances with a mobile hydrogen atom (water, alcohols, amines), the latter readily underwent ring opening with formation of derivatives of 2-acetylquinuclidine-3-acetic acid (LI): [133]



(XLIX) (L) (LI)

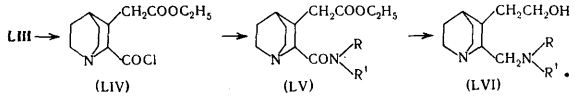
where R = OH, OC_2H_5, or NR'_2.

Esters of acids of the quinuclidine series are readily hydrolysed, the reaction being particularly easy for alkoxycarbonyl groups in the α-position of the quinuclidine ring [134]. On prolonged storage of aqueous solutions of diethyl 3-carboxymethylquinuclidine-2-carboxylate (LII) at room temperature, the acid ester (LIII) is formed [134], and this has been used to synthesise compounds containing various functional groups in the 2- and 3-positions of the quinuclidine ring:



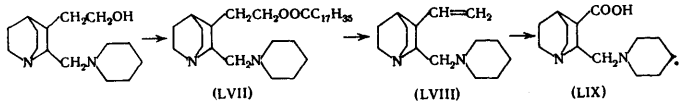
(LII) (LIII)

For example, when compound (LIII) reacts with thionyl chloride, the monochloride (LIV) forms readily and in the presence of primary and secondary amines is converted into the amides of 3-ethoxycarbonylmethylquinuclidine-2-carboxylic acid (LV). [130,134] The reduction of these amidoesters with lithium aluminium hydride leads to 2-alkyl(dialkyl)-3-(β-hydroxyethyl)aminomethylquinuclidines (LVI):



(LIV) (LV) (LVI)

The stearate of 3-(β-hydroxyethyl)-2-*N*-piperidinomethylquinuclidine (LVII) was converted by the Kraft reaction into the unsaturated compound (LVIII) from which 2-*N*-piperidinomethylquinuclidine-3-carboxylic acid (LIX) was obtained by oxidation with potassium permanganate [123]:

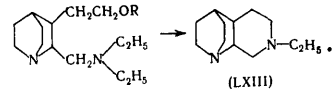


(LVII) (LVIII) (LIX)

The formation as a result of the above reactions of a derivative of quinuclidine-3-carboxylic acid (LIX) is convincing proof that the ethoxycarbonyl group in the 2-position is the first to be hydrolysed in the diethyl ester (LII).

A similar phenomenon obtains also in the diethyl ester of quinuclidine-2,3-dicarboxylic acid [109], which is consistent with the known greater ease of hydrolysis of α-amino-acid esters compared with β-amino-acid esters.

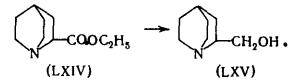
The unusual reaction of 2-diethylaminomethyl-3-(β-hydroxyethyl)quinuclidine is noteworthy [123]. It has been found that, on distillation under atmospheric pressure, compounds (LX) and (LXI) cyclise with elimination of an ester molecule and the formation of a new tricyclic system—*N*-ethylpiperidino[3,4-*b*]quinuclidine (LXIII). The corresponding amino-alcohol (LXII) behaves analogously on heating with phthalic anhydride in the presence of benzenesulphonic acid [123]:



(LXIII)

(LX): R = COC_6H_5
(LXI): R = $COC_{17}H_{35}$
(LXII): R = H

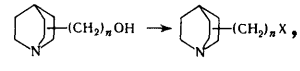
The reduction of ethyl quinuclidine-2-carboxylate (LXIV) by the Bouveault–Blanc method or with lithium aluminium hydride yields quinuclidin-2-yl-methanol (LXV): [24]



(LXIV) (LXV)

The second reduction procedure is easier to handle and gives better yields and therefore lithium aluminium hydride is mainly used in most studies for the preparation of various alcohols [67,95,121,125,134] and glycols [94,109] of the quinuclidine series.

Halogenoalkylquinuclidines have been synthesised by the reaction of the corresponding alcohols with thionyl chloride or hydrogen halides [24,49,121,135,136]:



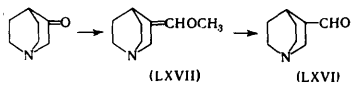
where $n = 1$ or 2.

Examination of the chemical properties of halogenoalkyl-substituted quinuclidines shows that the halogen atoms in the 2-halogenomethyl group are not very labile: for example, 2-chloromethylquinuclidine does not react with ammonia and amines [137] and the corresponding reactions of 2-bromomethylquinuclidine take place with low yields [137].

Although the halogen atoms in 3-halogenoalkylquinuclidines are more reactive, the use of compounds of this type as starting materials in various syntheses is made difficult by the ease of their conversion into quaternary polymeric derivatives [136]. These features of halogeno-derivatives of quinuclidine limit their application only to those cases where powerful nucleophilic agents are employed. Therefore the principal method for the synthesis of aminoalkylquinuclidines is not the interaction of halogeno-derivatives of quinuclidines with amines but the reduction with lithium aluminium hydride of the corresponding quinuclidinecarboxylic acid amides [122,130,131,138].

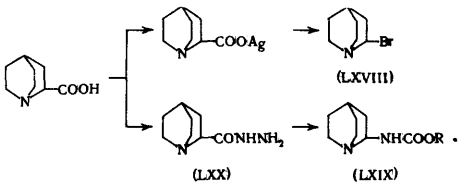
Aldehydes of the quinuclidine series are of considerable interest for the synthesis of various quinuclidine derivatives. At the present time all three monoformylquinuclidines are known. 2-Formylquinuclidine and 3-formylquinuclidine [139,140] have been obtained by the reduction of the

N-methylanilides of the corresponding quinuclidinecarboxylic acid with a calculated amount of lithium aluminium hydride or by the reduction of the ethyl esters of these acids with sodium aluminium hydride; 4-formylquinuclidine[67] has been obtained by the oxidation of quinuclidin-4-ylmethanol with potassium dichromate. 3-Formylquinuclidine (LXVI) has also been synthesised from 3-quinuclidone by its reaction with methoxymethylenetriphenylphosphorane and subsequent hydrolysis of 3-methoxymethylenequinuclidine (LXVII) with hydrochloric acid[141]:



(LXVII) (LXVI)

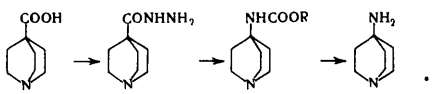
b. Reactions accompanied by the dissociation of a C—C bond and a decrease in the length of the carbon chain. Substances with less carbon atoms have been synthesised from quinuclidine-2-carboxylic acid: 2-bromoquinuclidine (LXVIII)[90] and urethanes of 2-aminoquinuclidine (LXIX).[142] These compounds are of considerable interest, since they contain at the same carbon atom a bromine atom and an amino-group (in 2-bromoquinuclidine) or two amino-residues (in 2-aminoquinuclidine derivatives). Such combination of functional groups leads to the appearance of new chemical properties in these compounds. For example, compound (LXVIII) does not form Grignard reagents and compound (LXIX) is so stable that in the hydrolysis of its urethanes under mild conditions ammonia is eliminated and polymers of dehydroquinuclidine are formed. The synthesis of compound (LXVIII) was achieved using the Borodin reaction[90]; the urethanes of compound (LXIX) were obtained starting with the hydrazide of quinuclidine-2-carboxylic acid (LXX) by the Curtius reaction[142]:



(LXVIII)

(LXX) (LXIX)

Analogous reactions in the quinuclidine-4-carboxylic acid series made it possible to obtain 4-aminoquinuclidine (LXXI):[143]

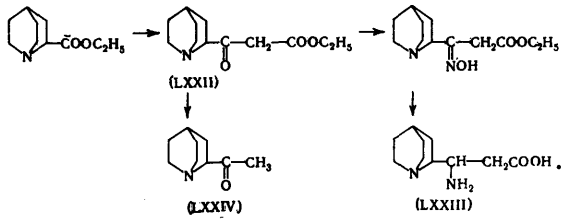


(LXXI)

The same compound was synthesised directly from quinuclidine-4-carboxylic acid by the Schmidt reaction. However, despite the greater number of stages, the first method proved to be more rational.

c. Processes associated with the growth of the carbon chain. Claisen, Grignard, etc. reactions have been used to synthesise quinuclidine derivatives with increase in the length of the carbon chain.

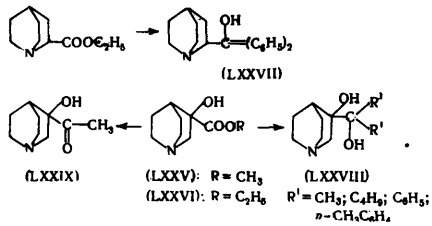
The Claisen condensation of ethyl quinuclidine-2-carboxylate with ethyl acetate led to the formation of ethyl β-oxo-β-(quinuclidin-2-yl)propionate (LXXII), which was then further converted into β-amino-β-(quinuclidin-2-yl)-propionic acid (LXXIII)[108] and 2-acetylquinuclidine (LXXIV):[43]



(LXXII)

(LXXIV) (LXXIII)

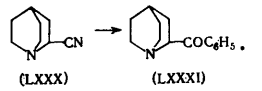
The carbinols (LXXVII)[24] and pinacones (LXXVIII)[144] were obtained by the Grignard reaction from the esters of quinuclidine-2-carboxylic and 3-hydroxyquinuclidine-3-carboxylic acids [compounds (LXXV) and (LXXVI)] respectively:



(LXXVII)

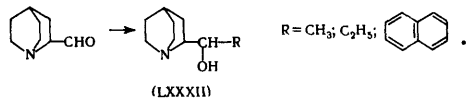
(LXXIX) (LXXV): R = CH_3 (LXXVIII)
(LXXVI): R = C_2H_5 R' = CH_3; C_4H_9; C_6H_5; *n*-$CH_3C_6H_4$

It is noteworthy that in the interaction of the hydroxy-ester (LXXV) with methylmagnesium iodide the process terminates at the stage involving the formation of the ketone (LXXIX). A Grignard reaction has also been described for 2-cyanoquinuclidine (LXXX), which was converted into 2-benzoylquinuclidine (LXXXI):[49]



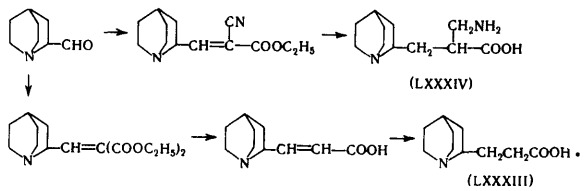
(LXXX) (LXXXI)

The introduction of 2-formylquinuclidine into reactions with organomagnesium compounds led to the development of a new method of synthesis of quinuclidin-2-ylmethanols (LXXXII) which are analogues of cinchona alkaloids[145]:



(LXXXII)

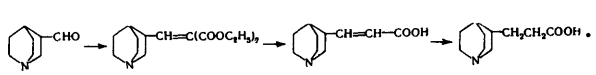
The condensation of 2-formylquinuclidine by the Knoevenagel reaction with cyanoacetic[108] and malonic[129] esters was used to synthesise quinuclidine-2-β-propionic acid (LXXXIII) and its α-aminomethyl derivative (LXXXIV):



(LXXXIV)

(LXXXIII)

Quinuclidine-3-β-acrylic and quinuclidine-3-β-propionic acids were synthesised similarly from 3-formylquinuclidine[140]:

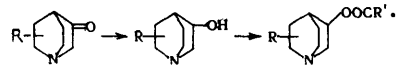


The malonic ester synthesis was used to prepare quinuclidine-2-β-propionic acid from 2-bromomethylquinuclidine[128] and quinuclidine-3-γ-butyric acid from 3-(β-chloroethyl)quinuclidine[125].

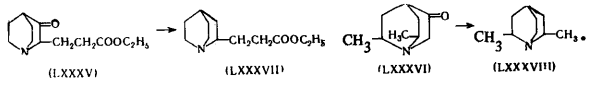
(2) Syntheses of Substituted Quinuclidines from 3-Quinuclidone

Among oxo-derivatives of quinuclidine the most readily available is 3-quinuclidone. The derivatives of 2-quinuclidone have been little investigated and at the present time are hardly used as starting materials in synthetic studies. There is an extremely wide variety of syntheses on the basis of 3-quinuclidone and they can be divided into two groups: (a) reactions with retention of the carbon chain length and (b) reactions involving an increase in the carbon chain length.

a. Reactions with retention of the carbon chain length. The hydrogenation of 3-quinuclidone and its substituted derivatives to the corresponding alcohols with subsequent esterification made it possible to synthesise a large number of esters and urethanes of 3-quinuclidinol, which are of considerable interest from the standpoint of the investigation of their biological activity[33,102,103,111,112,146-151]:

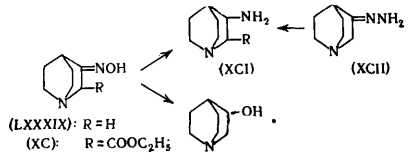


The Clemmensen[33] and Wolff–Kishner[152] reduction of 3-quinuclidone yields quinuclidine. The application of the Wolff–Kishner reaction to 2-substituted derivatives of 3-quinuclidone made it possible to obtain 2-substituted quinuclidine derivatives. Ethyl quinuclidine-2-β-propionate (LXXXVII)[104] and 2,6-dimethylquinuclidine (LXXXVIII)[11] were obtained in this way from the corresponding 3-oxo-derivatives (LXXXV) and (LXXXVI):



(LXXXV) (LXXXVII) (LXXXVI) (LXXXVIII)

The oximes of 3-quinuclidone (LXXXIX)[103,122] and of ethyl 3-oxoquinuclidine-2-carboxylate (XC)[108] were reduced to the amines (XCI):

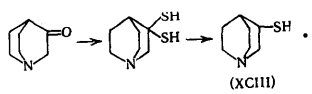


(LXXXIX): R = H
(XC): R = $COOC_2H_5$

(XCI) (XCII)

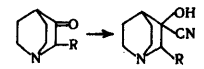
It was found that the reduction of the oxime of 3-quinuclidone (LXXXIX) in acid and neutral media is accompanied by hydrogenolysis and the reaction leads to the formation of 3-quinuclidinol together with 3-aminoquinuclidine (XCI, R = H). The reduction of the hydrazone of 3-quinuclidone (XCII) to 3-aminoquinuclidine takes place more unambiguously[122].

When 3-quinuclidone is treated with hydrogen sulphide and this is then followed by reduction with sodium tetrahydroborate, a sulphur-containing compound is produced—3-mercaptoquinuclidine (XCIII)[153]:

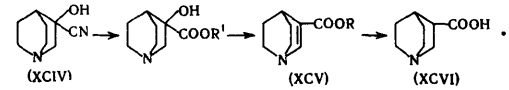


(XCIII)

b. Reactions involving an increase in the length of the carbon chain. The interaction of 3-oxo-derivatives of quinuclidine with potassium cyanide[109,121,154] or acetone cyanohydrin[122] was used to prepare cyanohydrins of the quinuclidine series:

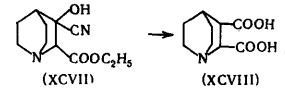


where R = H or $COOC_2H_5$. The hydrolysis of the cyanohydrin of 3-quinuclidone (XCIV) and subsequent dehydration led to the synthesis of 3-alkoxycarbonyl-Δ^2-dehydroquinuclidines (XCV), which were then reduced and hydrolysed to give quinuclidine-3-carboxylic acid (XCVI)[121,122]:



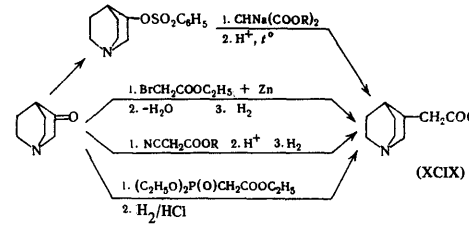
(XCIV) (XCV) (XCVI)

Quinuclidine-2,3-dicarboxylic acid (XCVIII) was obtained similarly from the cyanohydrin of 2-ethoxycarbonyl-3-quinuclidone (XCVII):[109]



(XCVII) (XCVIII)

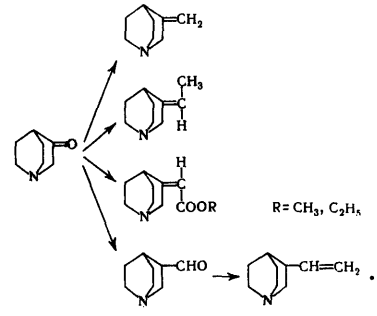
Various methods for incrementing the carbon chain were used to synthesise quinuclidine-3-acetic acid (XCIX):



(XCIX)

Comparison of different syntheses shows that the smallest yield of the acid (XCIX) is observed in sodiomalonic synthesis (13.4%),[125] much better results being obtained in the Reformatsky (40%)[125] and Knoevenagel condensations (65–70%):[126] a nearly quantitative yield can be achieved in the Wittig–Horner reaction[155].

The application of the Wittig–Horner reactions to 3-quinuclidone and other β-oxo-derivatives of quinuclidine[127,140,155-157] made possible the preparation of a wide variety of 3-substituted quinuclidines[128,140,157]:

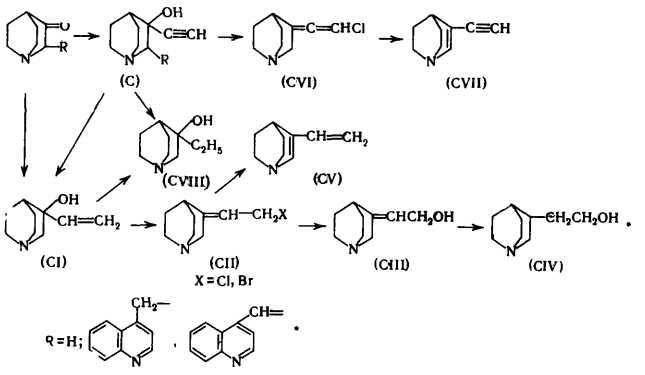


R = CH_3, C_2H_5

For example 3-methylene-, 3-ethylidene-[157], 3-alkoxycarbonylmethylene-[128], and 3-formyl-quinuclidines[140] have been synthesised by means of the above reactions. The reactions were found to be stereospecific[157]. In the synthesis of 3-ethylidenequinuclidine the ylide was found to attack predominantly from the sterically more favourable direction, when the methyl group in the transition complex is furthest removed from the 2 α-protons of the

quinuclidine ring. In the synthesis of 3-alkoxycarbonylmethylenequinuclidines the stereochemistry of the process was determined by the interaction of the nitrogen of the quinuclidine ring with the alkoxycarbonyl groups which led to the formation of only that geometrical isomer in which the above groups are close to one another.

Double application of the Wittig reaction initially with methoxymethylenetriphenylphosphorane and then with methylenetriphenylphosphorane led to the conversion of 3-quinuclidone into 3-vinylquinuclidine in two stages with an overall yield of 50%.[156] The above method for the introduction of the vinyl group into the β-position of the quinuclidine ring is of considerable interest, since various other synthetic procedures[36,37,158,159] either did not result in the formation of unsaturated quinuclidine compounds or involved the migration of the double bond to an exocyclic position. The introduction of an ethyne group into 3-quinuclidone[136,160] and its 2-substituted derivatives leads to 3-ethynyl-3-hydroxyquinuclidines, which are readily hydrogenated to 3-ethyl-3-hydroxyquinuclidines:

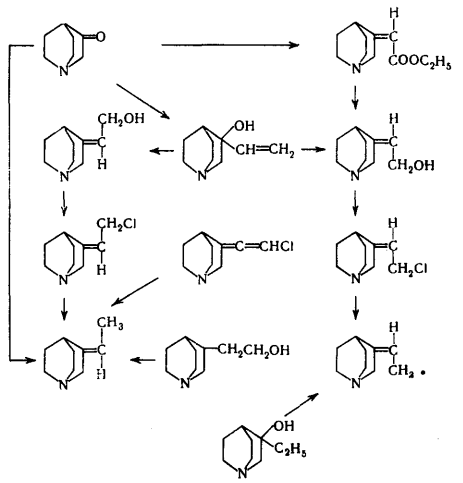


The selective reduction of 3-ethynyl-3-hydroxyquinuclidine, (C, R = H) led to the preparation of 3-hydroxy-3-vinylquinuclidine (CI)[136]. The latter was also synthesised directly from 3-quinuclidone and vinylmagnesium bromide[161].

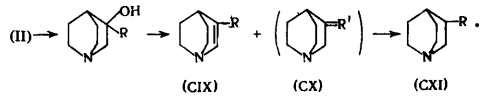
The substitution of the hydroxy-group in compound (CI) by a halogen with thionyl chloride or hydrobromic acid is accompanied by allyl rearrangement with formation of 3-(β-halogenoethylidene)quinuclidines (CII). 3-(β-Bromoethylidene)quinuclidine was converted via the 3-(β-hydroxyethylidene) derivative (CIII) into 3-(β-hydroxyethyl)-quinuclidine (CIV)[136] and then 3-vinyl-Δ²-dehydroquinuclidine (CV) was obtained by the dehydrohalogenation of 3-(β-chloroethylidene)quinuclidine[161].

Similar processes, associated this time with the acetylene–allene rearrangement were observed also when the hydroxy-group in 3-ethynyl-3-hydroxyquinuclidine (C, R = H) was replaced by a halogen. In this case the product was 3-(β-chloroallene)quinuclidine (CVI)[157] which readily eliminates hydrogen halide with formation of 3-ethynyl-Δ²-dehydroquinuclidine (CVII). The study of the allyl and acetylene–allene rearrangements in the series of 3-substituted quinuclidines[161] led to the determination of the effect of these processes on the positions of the multiple bonds in unsaturated quinuclidine compounds. In the course of these investigations it was shown that in the oxidation and ozonolysis of substances containing functional groups in the allyl position relative to the double bond not only the multiple but also the single C–C bonds adjacent to them are dissociated. For example, in the oxidation with potassium permanganate under mild conditions and in the ozonolysis of 3-hydroxy-3-vinylquinuclidine (CI), 3-quinuclidone is formed[161]. Therefore the position of multiple bonds in such allyl systems may be established unambiguously not with the aid of oxidative procedures but by analysing the NMR spectra[161].

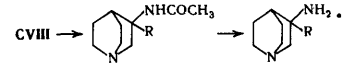
Two series of geometrical isomers of 3-substituted quinuclidines with a semicyclic double bond were synthesised by various reactions of 3-quinuclidone: 3-ethylidene[136,157,162], 3-(β-hydroxyethylidene)-[136,157], and 3-(β-chloroethylidene)-quinuclidines[157]; within each series interconversions were carried out[157] and the steric structure of the compounds was established with the aid of NMR spectra[16,157,163]:



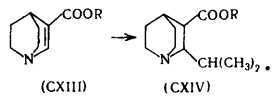
The interaction of 3-quinuclidones with organolithium or organomagnesium compounds is a general method for the synthesis of a large number of tertiary alcohols (CVIII)[47,162,164–168]. Their subsequent dehydration led to the formation together with Δ²-dehydroquinuclidines (CIX) of substances with an exocyclic double bond (CX)[165–168]. The reduction of the unsaturated products made it possible to obtain various 3-substituted quinuclidines (CXI):



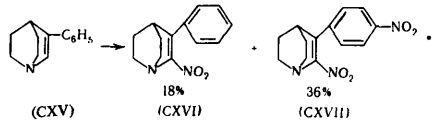
When 3-alkyl(aryl)-3-hydroxyquinuclidines (CVIII) were allowed to react with acetonitrile under the conditions of the Ritter reaction, acetylated 3-alkyl(aryl)-3-aminoquinuclidines (CXII) were obtained:



An interesting method for the introduction of substituents into the 2-position of the quinuclidine ring on the basis of 3-substituted Δ²-dehydroquinuclidines (CIX) has been described[47]. When methyl Δ²-dehydroquinuclidine-3-carboxylate (CXIII) reacts with isopropylmagnesium bromide, 1,4-addition takes place with subsequent formation, in the course of further treatment, of 2-isopropyl-3-methoxycarbonylquinuclidine (CXIV):

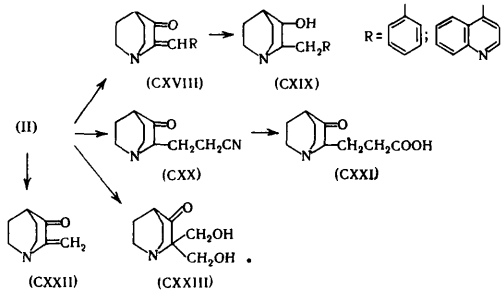


Unusual 2-substituted quinuclidines were obtained also on nitrating 3-phenyl-Δ^2-dehydroquinuclidine (CXV). The reaction products in this case proved to be 2-nitro-3-phenyl-Δ^2-dehydroquinuclidine (CXVI) and 2-nitro-3-(*p*-nitrophenyl)-Δ^2-dehydroquinuclidine (CXVII)[47]:



(CXV) (CXVI) (CXVII)

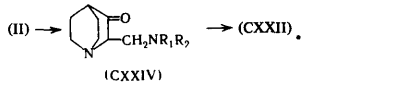
A number of 2-substituted quinuclidines were obtained by the condensation of 3-quinuclidone with aldehydes[77,103,109] and acrylonitrile[104]:



(CXVIII) (CXIX) (II) (CXX) (CXXI) (CXXII) (CXXIII)

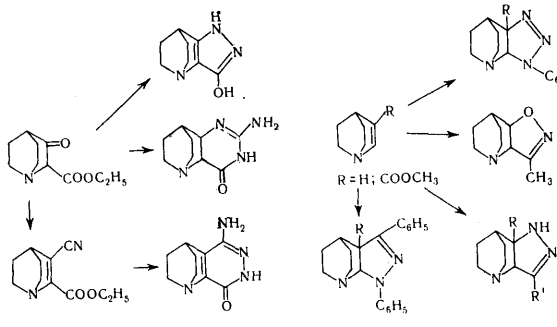
These reactions made it possible to convert 3-substituted quinuclidines into 2,3-disubstituted derivatives. For example 3-quinuclidone was converted via 2-[phenyl(quinolin-4′-yl)methylene]-3-quinuclidone (CXVIII) into 2-[phenyl-(quinolin-4′-yl)methyl]quinuclidin-3-ol (CXIX) and also into 2-(β-cyanoethyl)-3-oxoquinuclidine (CXX) and further into 3-oxoquinuclidine-2-β-propionic acid (CXXI). The formylation of 3-quinuclidone leads to the formation of 2-methylene-3-quinuclidone (CXXII) and, when a large excess of formaldehyde is employed, the product is a β-ketol—2,2-bishydroxymethyl-3-quinuclidone (CXXIII)[77].

2-Methylene-3-quinuclidone (CXXII) was also obtained by the Mannich reaction[170]. The 2-dialkylaminomethyl-3-quinuclidones (CXXIV) formed as intermediates in this case are converted into compound (CXXII) on distillation:



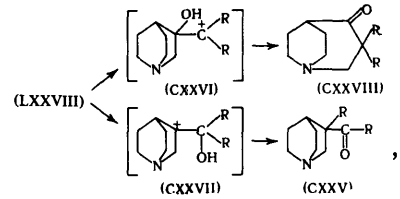
(II) (CXXIV) (CXXII)

Condensed heterocyclic systems containing the quinuclidine ring (pyrazolo-, oxazolo-, triazolo-, pyrimidino-, and pyridazino-quinuclidines[171]) were synthesised from ethyl 3-oxoquinuclidine-2-carboxylate (CXXXV) and also from Δ^2-dehydroquinuclidine and methyl Δ^2-dehydroquinuclidine-3-carboxylate obtained from 3-quinuclidone:



3. REACTIONS INVOLVING THE EXPANSION OF THE QUINUCLIDINE RING

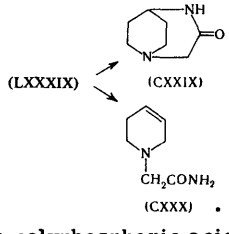
The study of the pinacol rearrangement of ditertiary quinuclidine alcohols of the type of compound (LXXVIII)[144,172] showed that, depending on the nature of the substituents R and the reactants employed, the process takes place either with ring expansion or with the formation of ketones of the quinuclidine series [compounds (CXXV)]:



(LXXVIII) (CXXVI) (CXXVIII) (CXXVII) (CXXV′)

where R = CH_3, C_4H_9, C_6H_5, or *p*-$CH_3C_6H_4$. This is associated with the possible reaction via two types of carbonium ions [(CXXVI) and (CXXVII)] with electrophilic centres at the C_3 atom of the quinuclidine ring or at the carbon atom of the side chain respectively. The subsequent migration of the aryl or alkyl group leads in the first case to ketones of the quinuclidine series (CXXV) and the migration of the methylene group in the second case leads to the formation of 4-oxo-derivatives of 1-azabicyclo[3,2,2]nonane (CXXVIII). For aryl substituents, stabilisation is achieved as a result of the conjugation of carbonium ions of type (CXXVI). Therefore, on treatment with sulphuric acid, 3-($\alpha\alpha$-diaryl-α-hydroxymethyl)-3-hydroxyquinuclidines (LXXVIII, R = Ar) are more readily converted into compounds (CXXVIII) than the analogous 3-($\alpha\alpha$-dialkyl-α-hydroxymethyl)-3-hydroxyquinuclidines (LXXIII, R = Alk). The use of an aprotic reagent, zinc chloride in acetic anhydride, yields carbonium ions (CXXVII) as a result of the elimination of an acetate ion from the initially formed monoacetyl derivatives of the glycols (LXXVIII). Therefore in aprotic media expansion of the quinuclidine ring does not take place and the reaction leads to ketones of the quinuclidine series (CXXV) or dehydration and acylation products of the initial glycols.

The Beckmann rearrangement of the oxime of 3-quinuclidone (LXXXIX) in the presence of polyphosphoric acid or oleum takes place with expansion of the quinuclidine ring and the formation of 3-oxo-1,4-diazabicyclo[3,3,2]nonane (CXXIX)[173,174]:



(LXXXIX) (CXXIX) (CXXX)

In the reaction with polyphosphoric acid the intermediate cation is stabilised after the dissociation of the C_3–C_4 bond not only by the formation of a new C–N bond but also by the elimination of the proton from C_5. In the latter case a product resulting from the opening of the quinuclidine ring is formed: the amide of Δ^3-dehydropiperidine-*N*-acetic acid (CXXX).

The same products of quinuclidine ring expansion or opening arise also on treatment of 3-quinuclidone with hydrazoic acid under the conditions of the Schmidt reaction[175]. However, in the latter case the process is largely displaced towards the monocyclic amide (CXXX).

When the oxime of 3-quinuclidone reacts with arenesulphonyl chlorides in an alkaline medium, *N*-substituted 4-cyanopiperidines are formed[176,177].

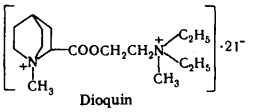
IV. BIOLOGICAL PROPERTIES OF QUINUCLIDINE DERIVATIVES

There have been mainly two aspects to the study of the biological properties of quinuclidine derivatives: on the one hand natural alkaloids, their synthetic analogues, and reaction products were investigated and on the other the characteristics of the pharmacological activity of compounds associated with the presence of the quinuclidine ring were elucidated. In the present review it is probably useful to consider only the investigations of the second type, since, as mentioned above, a number of reviews are available on the biological activity of the quinuclidine alkaloids.

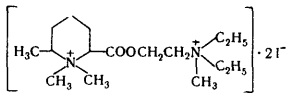
The first study on the pharmacological activity of unsubstituted quinuclidine was carried out by Stern in 1941.[178] In experiments on animals, it was shown that the hydrochloride of unsubstituted quinuclidine exhibits appreciable hypotensive activity and relaxes the smooth musculature, while the corresponding quaternary ammonium salts show a curare-like activity. In the course of subsequent systematic studies of quinuclidine and other 1-azabicycloalkane derivatives in the USSR under the direction of M. V. Rubtsov, synthetic methods were developed and a large number of compounds of this series were obtained and subjected to biological tests. The study of the pharmacological properties of quinuclidine and other 1-azabicycloalkane derivatives carried out under the direction of M. D. Mashkovskii revealed the high activity of compounds of this kind and led to the discovery of effective medicinal preparations, which have found application in medical practice[130,179-182].

The experimental investigation of aminoalkyl esters of quinuclidinecarboxylic acids and their halogenoalkylate derivatives and also tertiary amines of the 2- and 3-monosubstituted and 2,3-disubstituted quinuclidine series led to the discovery of preparations which interfere with the transmission of nervous excitation in ganglia[130,183]. Thus ethyl quinuclidine-3-carboxylate shows a nicotine-like activity and 2-diethylaminoethylaminomethylquinuclidine and other similar tertiary amines suppress the excitation in ganglia. The most active ganglion-blocking agents proved to be the quaternary derivatives of dialkylaminoethyl esters of quinuclidine-2- and quinuclidine-3-carboxylic acids. The di-iodomethylate of the diethylaminoethyl ester of quinuclidine-2-carboxylic acid (CXXXI), which was called Dioquin, is one of the most powerful modern ganglion-blocking agents[184-188]. Substances with similar activity, namely the di-iodomethylate of the dimethylaminoethyl ester of quinuclidine-3-carboxylic acid and the di-iodomethylate of the dimethylaminoethyl ester of quinuclidine-2-carboxylic acid, i.e. the dimethyl analogue of Dioquin, are three times more active than Dioquin itself. In subsequent studies of the relation between chemical structure and biological activity it was established that the ganglion-blocking activity persists on going over from the bicyclic quinuclidine system to the monocyclic piperidine system: the di-iodomethylates of the dimethylaminoethyl (CXXXII) and diethylaminoethyl (CXXXIII) esters of 1,6-dimethylpipecolic acid, called Dimecoline and Dicoline[189-196], have been introduced into the medical practice in the USSR as active ganglion-blocking agents for the treatment of hypertonia, stomach ulcers, bronchial asthma, and many other diseases. The introduction into the molecule of the active compound of various branched dialkylaminoalkyl chains instead of the dialkylaminoethyl substituents lowers the ganglion-blocking activity of these substances[197].

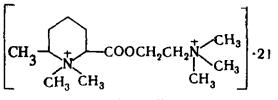
It is interesting to note that the ganglion-blocking activity of secondary-tertiary amines of the type of 2-benzylaminomethyl-3-(β-benzylaminoethyl)quinuclidine (CXXXIV) is closely associated with the presence of the bicyclic quinuclidine system in the molecule in contrast to the analogous activity of the quaternary salts of aminoalkyl esters of quinuclidinecarboxylic acid. In this case, on going over to compounds without the quinuclidine ring, the effect on the ganglia of the vegetative nervous system disappears.



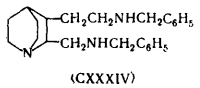
Dioquin
(CXXXI)



Dicoline
(CXXXIII)

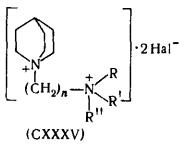


Dimecoline
(CXXXII)

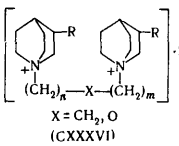


(CXXXIV)

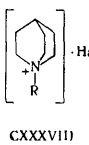
In the search for ganglion-blocking and curare-like preparations diquaternary salts in which one [as in compound (CXXXV)][198,199] or both [as in compound (CXXXVI)][200-202] quaternary nitrogen atoms linked by the alkylidene chain are constituents of the quinuclidine ring were synthesised and tested together with 1-alkylquinuclidinium halides[203] (CXXXVII, R = Alk) and *N*-aminoquinuclidinium salts (CXXXVII, R = NH_2)[204]:



(CXXXV)

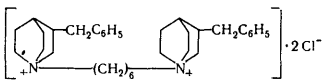


(CXXXVI)



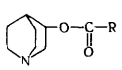
CXXXVII)

The most pronounced curare-like properties were found in the dichloride of 1,6-di-(3′-benzylquinuclidin-1′-yl)hexane (CXXXVIII), which has been introduced in the USSR medical practice under the name of Qualidyl[200,202] as a curare-like preparation with a competitive activity:

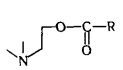


Qualidyl
(CXXXVIII)

The esters of 3-hydroxyquinuclidine (CXXXIX), which are bicyclic analogues of the esters of 2-dialkylaminoethanol (CXL), were found to have interesting pharmacological properties:



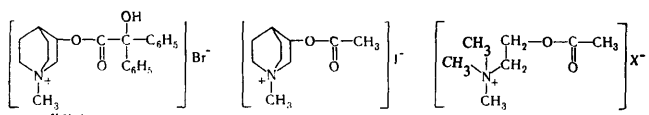
(CXXXIX)



(CXL)

Many esters formed by 2-dialkylaminoethanols with various carboxylic acids are known to have neurotropic properties. The first studies by Sternbach, Kaiser, and coworkers[103,146-148,164] already showed that the esters of 3-hydroxyquinuclidine and aromatic acids (benzilic, tropic, etc.) caused the relaxation of the smooth musculature.

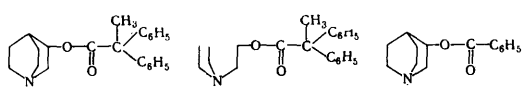
Almost at the same time Duschinsky[149] showed that carbamic esters of 3-hydroxyquinuclidine have a similar effect. The bromomethylate of the benzilate of 3-hydroxyquinuclidine (CXLI), called Clidinium bromide (Quartzan bromide or Marplan) has found application in the medical practice of the USA and of many other countries as a cholinolytic agent[205-211]:



clidinium bromide

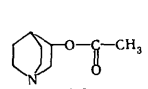
(CXLI) (CXLII) (CXLIII)

A systematic study of the pharmacological properties of the esters of 3-hydroxyquinuclidine and related compounds was carried out by Mashkovskii and coworkers[179,180]. In the first place the iodomethylate of 3-acetoxyquinuclidine (CXLII), which is a bicyclic analogue of acetylcholine (CXLIII), was investigated. The compound exhibited a cholinomimetic activity but its action was weaker than that of acetylcholine. The corresponding tertiary amine, 3-acetoxyquinuclidine, which, in contrast to acetylcholine, shows a more selective effect on muscarine receptors and readily penetrates through the haematoencephalic barrier, is an effective cholinomimetic agent. The salicylate of 3-acetoxyquinuclidine (CXLIV), called Aceclidine[181,212,213] is used in the USSR and a number of other countries in ophthalmology for the treatment of glaucoma and also in surgical and obstetric and gynaecological practice as a means of combating postoperative atonia of the organs in the abdominal cavity, including the postnatal atonia of the mother. Further studies showed that the cholinomimetic activity of Aceclidine is to a considerable degree associated with the presence in the molecule of the quinuclidine ring[151,214,215] and the replacement of 3-hydroxyquinuclidine and other similar bicyclic or monocyclic amino-alcohols results in a reduction or complete loss of activity:



aprolidine (CXLV) aprophene (CXLVI) oxilidine (CXLVII)

The cholinomimetic activity also falls when an alkyl group is introduced in the 6- and 8-positions of the quinuclidine ring. The replacement of the acetyl group in Aceclidine by the residues of homologous aliphatic acids leads initially to a decrease of the cholinomimetic activity (propionic ester) and then to the appearance of cholinolytic properties (butyric and isovaleric esters). The esters of 3-hydroxyquinuclidine and aliphatic–aromatic acids are also powerful cholinolytic agents. For example, the diphenylpropionate of 3-hydroxyquinuclidine (CXLV) (Aprolidin)[216-218] greatly surpasses[219] in its effect on the central and peripheral choline-reactive systems the analogous ester of 2-diethylaminoethanol (CXLVI) [known in the USSR as Aprophen]:



$C_7H_6O_3$

Aceclidine

(CXLIV)

The esters of 3-hydroxyquinuclidine with aromatic acids have a calming effect on the central nervous system. For example, the hydrochloride of 3-benzoyloxyquinuclidine (CXLVII), employed in the USSR under the name of Oxylidine[182,220-226] has a very pronounced sedative activity. Oxylidine is particularly effective in nervous breakdowns associated with the failure of blood circulation in the brain. At the same time Oxylidine also exhibits a hypotensive activity and has found application in the therapy of hypertonia. It is noteworthy that, as in the case of Aceclidine, the high biological activity of other 3-hydroxyquinuclidine esters is also associated with the presence in their molecules of the azabicyclic quinuclidine system. This is confirmed by the weakening of the pharmacological activity in the corresponding esters of 3-hydroxypiperidines and the esters of the completely open-chain type related to 3-hydroxyquinuclidine (*N*-alkyl-*N*-cycloalkylaminoethanols) and also by the lowering of pharmacological activity on going over to analogous esters of other 1-azabicycloalkanols. Possibly the higher activity of 3-hydroxyquinuclidine derivatives, compared with that of the analogous derivatives of other mono- and bi-cyclic amino-alcohols is associated with the characteristics of the quinuclidine molecule, noted above, in which the unshared electron pair of the nitrogen atom is not hindered.

The more ready interaction of the free electron pair of the nitrogen atom in the quinuclidine ring with electrophilic centres of the corresponding receptors in the organism is responsible, according to some workers[227], for the higher psychotropic activity of the benzilic esters of 3-hydroxyquinuclidine compared with the esters of other *N*-substituted amino-alcohols. The low probability of intramolecular bonds and interactions in 3-hydroxyquinuclidine esters, where the acyl component of the molecule and the free electron pair of the nitrogen atom are oriented in different directions, has also been noted. Probably further studies will lead to a more complete elucidation of the effect of the characteristics of the chemical behaviour of the quinuclidine molecule, its conformation, the nature of the free electron pair of the nitrogen atom, etc. on the physiological activity of various quinuclidine derivatives and will lead to the discovery of new active compounds.

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