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THE CHEMISTRY OF QUINUCLIDINE DERIVATIVES

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INTRODUCTION

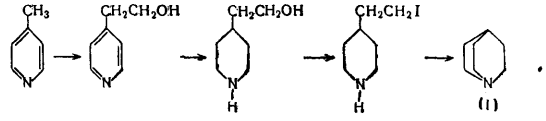
Quinine is one of the oldest and most widely known medicinal substances and its structure and synthesis have been investigated by workers in many countries.

A nitrogen-containing bicyclic system, quinuclidine[1--azabicyclo-(2,2,2)-octane] is a component part of the quinine molecule and of other quinine alkaloids. Up to the last decade little was published on quinuclidines for lack of methods of preparation of these compounds. Recent developments have made it possible to prepare various mono- and disubstituted quinuclidines, some of them with marked pharmacological or chemotherapeutic activity adding further importance to investigations of quinuclidine synthesis.

QUINUCLIDINE

The starting materials for the synthesis of quinuclidine and its derivatives are pyridines, dihalogenoalkylamines, or aliphatic trihalides of suitable structure.

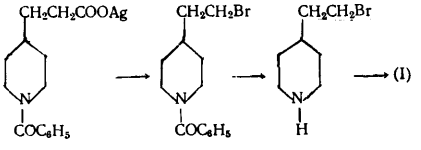
Quinuclidine (I) was first synthesised in 1909 by Löffler and Stiezel[1] according to the scheme



4-Methylpyridine reacts with formaldehyde to form, among other substances, 4-(β-hydroxyethyl)pyridine which, on reduction by the Vyshnegradskii–Ladenburg method and subsequent replacement of the hydroxy group by iodine using hydriodic acid, gives 4-(β-iodoethyl)piperidine; the latter is converted to quinuclidine by dilute alkali. The authors failed to isolate quinuclidine in a pure state. The picrate had m.p. 209°–211°, the base itself being a non-crystallising oily substance.

Later, Meisenheimer[2] followed the same route and obtained quinuclidine in the form of colourless crystals, m.p. 154°, yielding a picrate, m.p. 275°. His physical constants were confirmed by others[3-7] who synthesised quinuclidine by various methods. The method mentioned above had the disadvantage of a low yield of 4-(β-hydroxyethyl)-pyridine (1.5–2%) and consequently a very low yield of quinuclidine (0.4%). However, if 4-methylpyridine is heated with paraformaldehyde at 160°,[8] the yield of the intermediate rises to 48% and considerably higher overall yields of quinuclidine are therefore attainable.

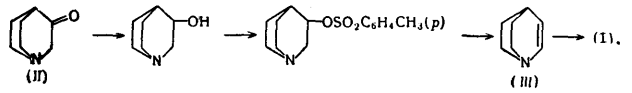
Another method of quinuclidine synthesis was described in 1947:[5]



The silver salt of 1-benzoyl-4-(β-carboxyethyl)piperidine is converted to a bromo-compound (by treatment with bromine in carbon tetrachloride), which gives quinuclidine on hydrolysis of the benzoyl group and subsequent cyclisation with dilute sodium hydroxide.

Clemo and Metcalfe[6] prepared quinuclidine by reducing 3-quinuclidone (II) (for synthesis see p. 42) according to Kishner or Clemmensen. Quinuclidine was isolated as the picrate without mention of the yield.

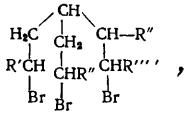
Grob et al.[7] prepared quinuclidine via 1-azabicyclo--(2,2,2)-2-octene (dehydroquinuclidine) (III) starting with 3-quinuclidone:



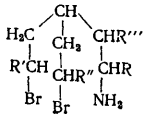
3-Hydroxyquinuclidine, obtained by reduction of (II), was converted to the tosyl ester from which (III) was obtained on heating with sodium ethoxide. Compound (III) is a colourless liquid which solidifies to volatile hygroscopic crystals on cooling; it absorbs hydrogen readily to give quinuclidine. Addition of hydrogen bromide to (III) gives 3-bromoquinuclidine. This substance and the corresponding chloro derivative [isolated with (III) on heating 3-hydroxyquinuclidine with thionyl chloride] are reduced to quinuclidine in the presence of Raney nickel catalyst.

In 1951 Wawžonek[9] reported the preparation of quinuclidine by irradiation of 1-halogeno-4-ethylpiperidines in 85% sulphuric acid with ultra-violet light. This was refuted by Lukeš and Furles[10] who showed that the compound formed was 2-methyl-1-azabicyclo-(2,2,1)-heptane.

Prelog[11] approached the synthesis of quinuclidine from another direction. The methods he developed are based on the action of ammonia under pressure at 100°–120° on aliphatic tribromides of the general formula

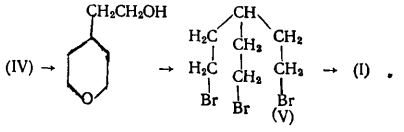


or on "double intramolecular alkylation" brought about by alkali treatment of dibromoalkylamines of the type



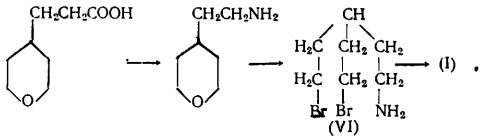
The appropriate dibromoalkylamines and tribromoalkanes were obtained from tetrahydropyrans[12-14], the most widely used compound being tetrahydropyran-4-acetic acid prepared from 4-hydroxymethyltetrahydropyran or from γ-pyrone.

The conversion of the ethyl ester of tetrahydropyran-4--acetic acid (IV) to quinuclidine is represented by the following scheme:



The ester (IV) is reduced by sodium and alcohol to 4-(β--hydroxyethyl)tetrahydropyran which is converted by fuming HBr to the tribromoalkane (V) which yields quinuclidine on heating with a methanolic ammonia. Compound (V) has also been synthesised from acetone dicarboxylic ester via the trimethyl ester of methanetriacetic acid[4].

The dibromoalkylamine (VI) is prepared by converting tetrahydropyran-4-acetic acid to β-(4-tetrahydropyranyl)-propionic acid which undergoes the Schmidt reaction to give 4-(β-aminoethyl)tetrahydropyran. This, treated with hydrobromic acid, yields compound (VI). The latter forms quinuclidine when treated with sodium hydroxide.

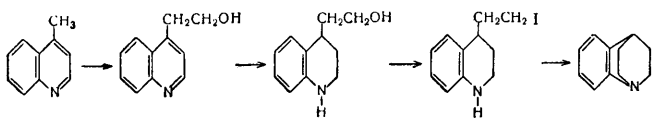


The methods of preparation of quinuclidine from tribromoalkanes and dibromoalkylamines are inferior to synthesis from 4-(β-hydroxyethyl)pyridine and 3-quinuclidone in respect to the number of steps and the yield.

Quinuclidine is a volatile crystalline substance which forms salts with mineral acids and alkyl halides. It is chemically inert to a number of reagents: it remains unchanged after prolonged heating with concentrated acids (H_2SO_4, HNO_3, HCl) and is not oxidised by potassium permanganate[2]. It is dehydrogenated to 4-ethylpyridine by heating in a sealed vessel at 300°–350° in the presence of catalysts (palladised charcoal or selenium)[15]. The chemical stability and high melting point of quinuclidine (158°) are due to the high symmetry of the molecule which makes the strain in the bicyclic system very slight[2,16].

When 1-methyl quinuclidine quaternary bases undergo the Hofmann reaction[4], 1-methyl-4-vinylpiperidine, 1-methyl-4-(β-hydroxyethyl)piperidine and quinuclidine are formed.

Of the condensed systems containing quinuclidine, benzo- and dibenzoquinuclidine have been described, the former by Meisenheimer[2] who prepared it from 4-methylquinoline by the same method as that used for quinuclidine.

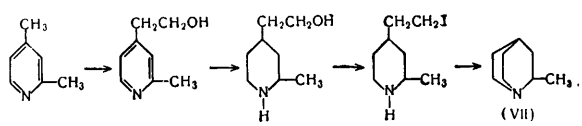


Benzoquinuclidine is a crystalline substance, m.p. 68°–69°, which is stable to acid potassium permanganate and does not undergo diazo-coupling with diazotised *p*-nitroaniline[17]. Dibenzoquinuclidine was prepared by Krogt and Wepster[18] from 9-methylacridine in a similar way.

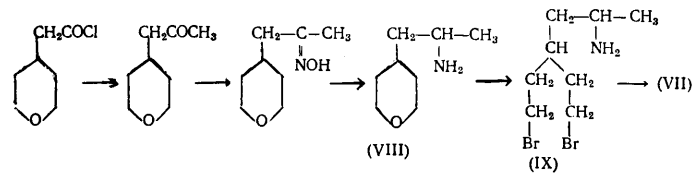
The pharmacological activity of quinuclidine has not been adequately investigated; its hydrochloride is known to have strong hypotensive properties and to relax smooth muscle[19].

2-Substituted Quinuclidines

The simplest member of this group is 2-methylquinuclidine (VII) which was synthesised by Winterfeld in 1930 from 2,4-dimethylpyridine according to a scheme similar to the one described above for the preparation of quinuclidine:



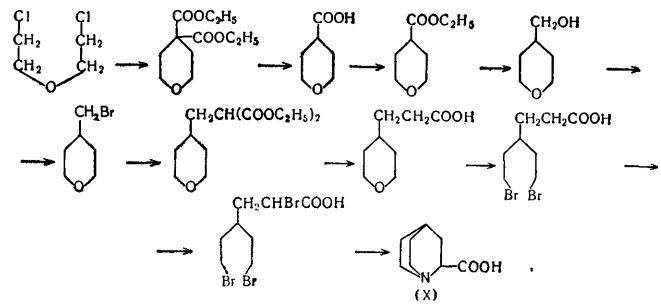
2-Methylquinuclidine was also prepared by Prelog[14] from tetrahydropyran-4-acetic acid. The acid chloride reacts with the methyl Grignard reagent to give 4-acetonyltetrahydropyran. The oxime of the latter is reduced to the amine (VIII) and the pyran ring is then opened by heating with hydrobromic acid. The compound (IX) thus formed is converted to 2-methylquinuclidine by a double intramolecular alkylation:



2-Ethylquinuclidine was prepared similarly from 1-(4-tetrahydropyranyl)-2-butanone[14].

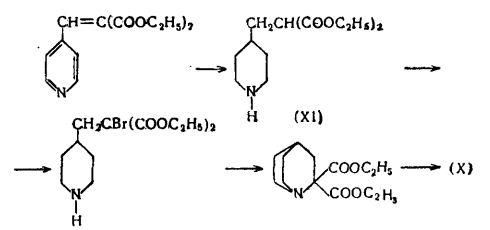
Quinuclidine-2-carboxylic acid (X) is of considerably greater interest. It is a key substance in the preparation of most 2-substituted quinuclidines; a considerable amount of published work deals with its synthesis.

The acid was first synthesised by Prelog and Gerkovnikov[21] in 1937 as follows:



Bis-β-chloroethyl ether reacts with malonic ester to give 4,4-diethoxycarbonyltetrahydropyran which is subject to successive hydrolysis, partial decarboxylation and esterification. The ethyl tetrahydropyran-4-carboxylate obtained is reduced by the Bouveault method; the hydroxyl group is replaced by a bromine atom and the side-chain is lengthened by two carbon atoms using the malonic ester synthesis. Subsequent opening of the pyran ring by heating under pressure with hydrobromic acid, introduction of bromine adjacent to the carboxyl group, and cyclisation of the product, gives (X) as colourless crystals, m.p. 280°. This synthesis consists of ten steps and the overall yield of (X) is only 4%.

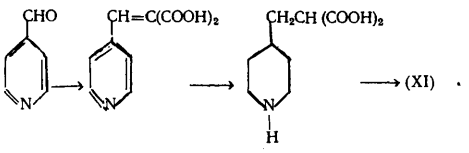
A simpler method for the preparation of (X) was developed in 1953[22]:



When the β-picoline fraction, free from 2,6-dimethylpyridine, is heated with mesoxalic ester and acetic anhydride for 9 h at 90°, 4-(β,β-diethoxycarbonylvinyl)pyridine is formed. This is hydrogenated in anhydrous alcohol over platinum and then treated with bromine in chloroform solution to give 4-(β,β-diethoxycarbonyl-β-bromoethyl)piperidine which, when heated with pyridine, cyclises to 2,2-diethoxycarbonylquinuclidine. The latter is hydrolysed and partially decarboxylated by boiling for 8 h with concentrated hydrochloric acid yielding (X) as the hydrochloride which melts with decomposition at 292°–294°. The synthesis is accomplished in 5 steps and the total yield is 30%.

Various routes to the intermediate product (XI) in the above synthesis of quinuclidine-2-carboxylic acid have

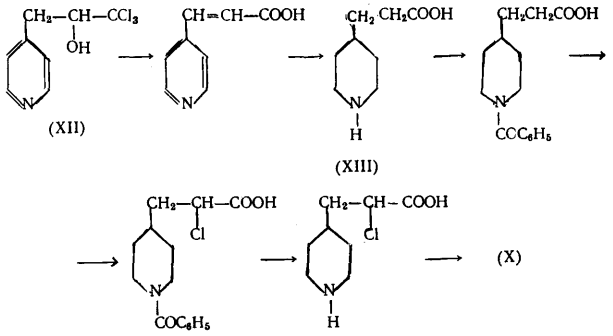
been studied[23]. It was shown that (XI) could be prepared from 4-formylpyridine and malonic ester or malonic acid:



Condensation of 4-formylpyridine with malonic acid in glacial acetic acid gives 4-(β,β-dicarboxylvinyl)pyridine which is very unstable to heat and must first be hydrogenated to the piperidine derivative which is then esterified.

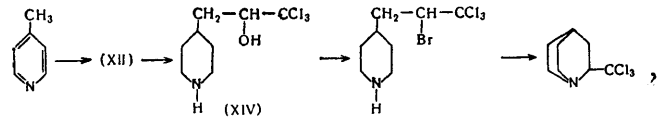
Compound (XI) can also be obtained by the Knoevenagel reaction between 4-formylpyridine and malonic ester and subsequent catalytic reduction of 4-(β,β-diethoxycarbonylvinyl)pyridine. Both variants have the disadvantage that low yields are obtained in the preparation of 4-formylpyridine (12.7% from γ-picoline).

A new synthesis for (X) was proposed by Renk and Grob in 1954[24]:



The starting material is γ-picoline which condenses with chloral in the presence of piperidine to form a chloral derivative (XII). Saponification of (XII) with alcoholic alkali gives 4-(β-carboxyvinyl)pyridine, the potassium salt of which is catalytically (Ni) reduced in aqueous solution to form 4-(β-carboxyethyl)piperidine (XIII). The N-benzoyl derivative of (XIII) is chlorinated with sulphuryl chloride, the N-benzoyl group is saponified by boiling with concentrated HCl, and the product is cyclised by heating with aqueous sodium hydroxide. This synthesis contains 7 steps and the overall yield is 26%.

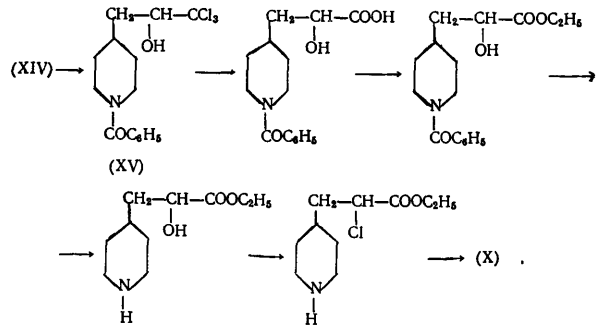
Investigation of other syntheses of (X) from γ-picoline[25] disclosed certain peculiarities in the behaviour of the intermediate compounds. Thus when the following scheme is employed:



the reduction of (XII) with platinum catalyst to (XIV) goes smoothly but substitution of halogen for the hydroxy group in (XIV) runs into difficulties. The reaction does not occur with thionyl chloride or phosphorus halides; however, heating with 68% hydrobromic acid at 120° gives a 40% yield of 4-(γ,γ,γ-trichloro-β-bromopropyl)piperidine. This yields a small amount of 2-trichloromethylquinuclidine on being treated with aqueous sodium carbonate.

During saponification of (XIV), β-(4-piperidyl)lactic acid is formed, esterification of which gives a polymeric ester.

The use of the N-benzoyl derivative (XV) gives monomeric ethyl β-(4-piperidyl)lactate which can be converted to (X) by substituting halogen for the hydroxy group.

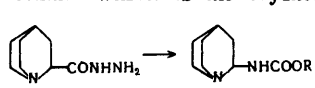


It was found in the course of this synthesis that substitution of chlorine for the hydroxy group in the ethyl β-(4-piperidyl)lactate (using thionyl chloride) only occurred to the extent of 25%; the reaction mixture consisted mainly of the starting material. The overall yield of (X) is therefore considerably lower than in the reaction mentioned above, which so far is the most convenient method of preparing (X).

Quinuclidine-2-carboxylic acid serves as starting material for the preparation of almost all the 2-substituted quinuclidines described.

Bouveault reduction, or treatment with lithium aluminium hydride, of the ethyl ester of (X), gives quinuclidine-2-carbinol. This carbinol is converted by thionyl chloride to 2-chloromethylquinuclidine[14] and by hydrobromic acid (under pressure) to 2-bromomethylquinuclidine[26]. The ethyl ester of (X) with phenyl magnesium bromide gives a good yield of diphenylquinuclidyl-2-carbinol[14]; the amide of (X), treated with thionyl chloride under pressure, yields 2-cyanoquinuclidine[22]. The Borodin reaction on (X) produces 2-bromoquinuclidine in 16% yield[22].

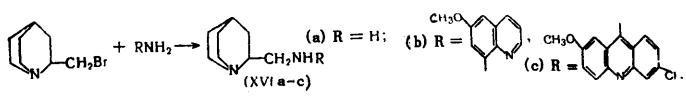
The hydrazide and some of its derivatives can be obtained from the ethyl ester of (X)[27]. The Curtius reaction was applied to the hydrazide and rearrangement of the azide of (X) occurred normally with formation of ethyl N-(2-quinuclidyl)urethane which is an acylated 2-aminoquinuclidine:



(where R = C_2H_5 or iso-C_5H_{11}). However, when attempts are made to isolate 2-aminoquinuclidine (an asymmetrically substituted diaminomethane) a molecule of ammonia is eliminated and the dehydroquinuclidine formed polymerises[28].

Large numbers of substituted 2-aminomethylquinuclidines have been synthesised, in a search for synthetic analogues of quinine alkaloids, and as ganglion blocking agents.

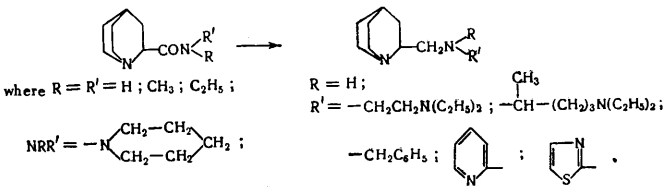
The first members of this series, 2-aminomethylquinuclidine (XVIa), 8-(2-quinuclidylmethylamino)-6-methoxyquinoline (XVIb), and 6-chloro-2-methoxy-9-(2-quinuclidylmethylamino)acridine (XVIc), were prepared by reaction of 2-bromomethylquinuclidine with ammonia, 6-methoxy-8-aminoquinoline, and 6-chloro-2-methoxy-9-aminoacridine[26].



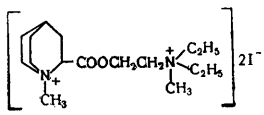
Studies of the chemotherapy of (XVI b and c) showed that these compounds were considerably more active than quinine in trials on canaries infected with *Plasmodium relictum* [29].

9-(2-Quinuclidylmethylamino)acridine and 4-(2-quinuclidylmethylamino)-6-methyoxyquinoline were synthesised later by reaction of 2-aminomethylquinuclidine with 9-phenoxyacridine and 6-methoxyquinoline-4-sulphonic acid [30] respectively.

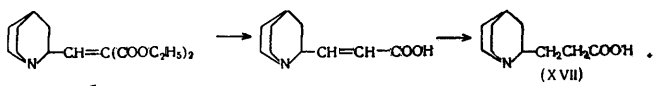
Substituted 2-aminomethylquinuclidines can be easily obtained by reduction of the corresponding quinuclidine-2--carboxamides with lithium aluminium hydride. A number of compounds were thus obtained with yields of 70–80% [31].



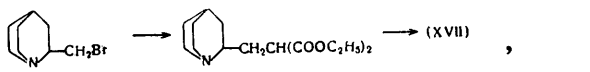
Some members of this series have high ganglion blocking activity, the most marked being that of 2-(β-diethylaminoethyl)aminomethylquinuclidine [32]. Such activity is also present in the dimethiodide of diethylaminoethyl quinuclidine-2-carboxylate which is used under the name of "Dioxin" for the treatment of hypertensive disease [33].



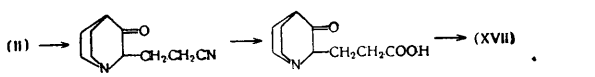
2-Formylquinuclidine is of considerable interest for the synthesis of 2-substituted quinuclidines; it was obtained by reduction of the N-methylanilide of quinuclidine-2--carboxylic acid by lithium aluminium hydride (31% yield) [34]. When 2-formylquinuclidine is condensed with malonic ester by the Knoevenagel method, quinuclidyl-2-methylenemalonic ester is formed. This is converted by boiling concentrated hydrochloric acid into β-(2-quinuclidyl)acrylic acid, which is easily reduced in the presence of Raney nickel to β-(2--quinuclidyl)propionic acid (XVII):



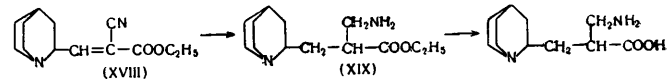
Compound (XVII) has also been prepared by condensing 2-bromomethylquinuclidine with sodium malonic ester and boiling the product with hydrochloric acid [35]:



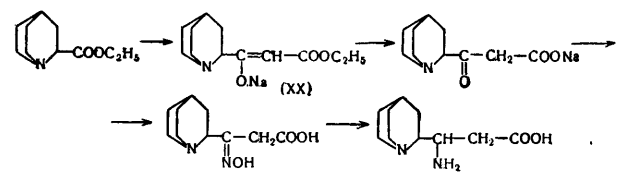
and by cyanethylation of 3-ketoquinuclidine (II), saponification of the nitrile group, and Kishner reduction of the resulting β-(3-keto-2-quinuclidyl)propionic acid [36]:



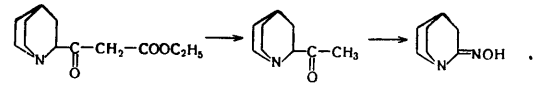
Condensation of 2-formylquinuclidine with cyanacetic ester gives α-cyano-β-(2-quinuclidyl)acrylic ester (XVIII); this is catalytically reduced to the aminoester (XIX) which is hydrolysed in the usual way to α-aminomethyl-β-(2--quinuclidyl)propionic acid [37]:



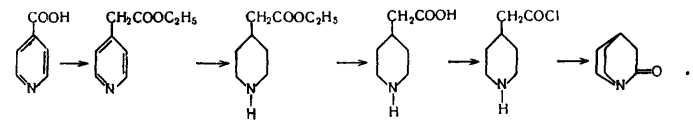
Claisen condensation of the ethyl ester of quinuclidine-2--carboxylic acid with ethyl acetate gives the ethyl ester of β-(2-quinuclidyl)-β-ketopropionic acid, isolated as the sodium derivative of the enolic form, which is but slightly soluble in water (XX). This compound reacts with water (24 h at room temperature) to form the sodium salt of β-(2-quinuclidyl)-β-ketopropionic acid, the oxime of which is readily reduced catalytically to β-(2-quinuclidyl)-β--aminopropionic acid [37]:



Hydrolysis and decarboxylation of the ethyl β-(2-quinuclidyl)-β-ketopropionate is effected by concentrated hydrochloric acid and gives 2-acetylquinuclidine. Treatment of this with isoamyl nitrite in the presence of sodium ethoxide yields 2-quinuclidone oxime:

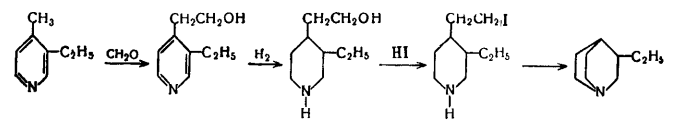


The ketone was also prepared from isonicotinic acid according to the following scheme [38]:



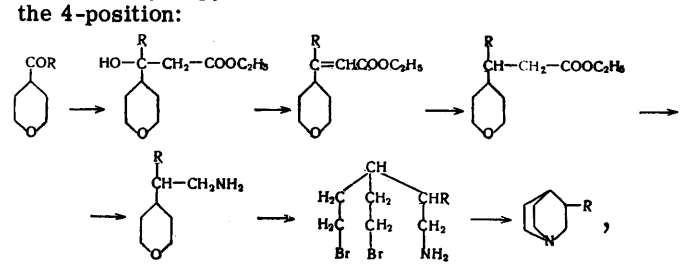
3-Substituted Quinuclidines

Derivatives of pyridine are generally used for the preparation of these compounds. Thus in 1904 Koenigs [39,40] prepared 3-ethylquinuclidine from 3-ethyl-4-methylpyridine as follows:



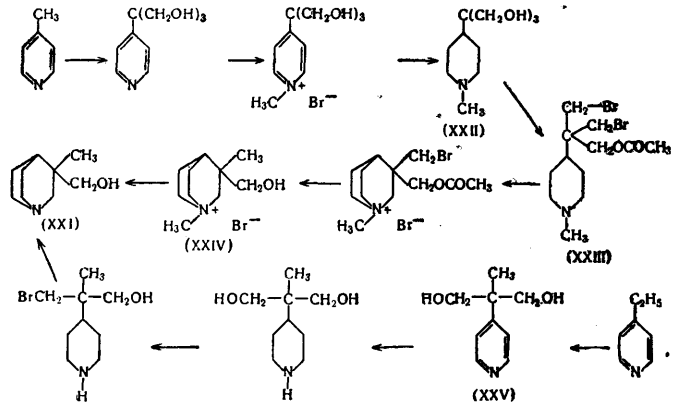
As already mentioned, Meisenheimer [2] used the same scheme for the preparation of quinuclidine and Winterfeld [20] for that of 2-methylquinuclidine.

Prelog [14] prepared 3-methyl- and 3-ethylquinuclidine from tetrahydropyrans with branched-chain substituents in the 4-position:



where R = CH_3; C_2H_5.

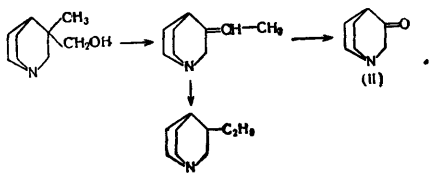
A number of 3-substituted quinuclidines were prepared by Lukeš and Ernest from pyridine derivatives. These authors set out to synthesise 3-vinylquinuclidine from 3-methyl-3-hydroxymethylquinuclidine (XXI). Compound (XXI) had been prepared by two methods: from 4-methyl- and 4-ethylpyridine[41-43] according to the following routes:



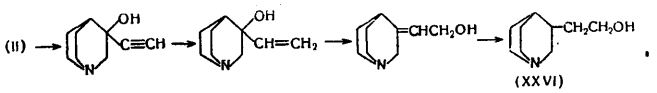
In the first scheme 4-[tri(hydroxymethyl)methyl]pyridine, obtained from 4-methylpyridine and formaldehyde, is converted to the methobromide and then reduced to 1-methyl-4-[tri(hydroxymethyl)methyl]piperidine (XXII). Prolonged heating of (XXII) with hydrobromic acid in acetic acid gives the dibromide (XXIII) which is converted by boiling alcohol into 3-bromomethyl-3-acetoxymethylquinuclidine methobromide. This is reduced to 3-methyl-3-hydroxymethylquinuclidine methobromide (XXIV). Heating (XXIV) under vacuum gives the compound (XXI).

The second and shorter route uses 4-ethylpyridine as the starting material which reacts with formaldehyde to give the glycol (XXV). The hydrobromide of this glycol is hydrogenated to the piperidine stage, one hydroxy group is replaced by bromine, and the product is cyclised to give (XXI) in overall yield of 57%. The conversion of 4-ethylpyridine to (XXI) through 4-(2-methyl-1,3-dihydroxy-2-propyl)pyridine described later[44], has no advantage over the above method.

Compound (XXI) was subjected to dehydration which cannot occur without a retropinacoline rearrangement. It was intended to make use of this in the preparation of 3-vinylquinuclidine, but 3-ethylidenequinuclidine (oxidised to 3-quinuclidone and reduced to 3-ethylquinuclidine), was isolated instead:

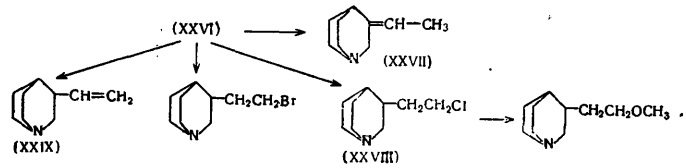


3-Vinylquinuclidine was subsequently prepared from 3-(β-hydroxyethyl)quinuclidine (XXVI)[45] obtained from 3-quinuclidone via 3-hydroxy-3-ethynylquinuclidine as follows:



Reduction of 3-hydroxy-3-ethynylquinuclidine with the calculated amount of hydrogen gives 3-hydroxy-3-vinylquinuclidine which rearranges when heated with hydrogen bromide in glacial acetic acid to 3-(β-hydroxyethylidene)-quinuclidine, isolated as two stereoisomers. When this compound is reduced over a platinum catalyst 3-(β-hydroxyethyl)quinuclidine is formed.

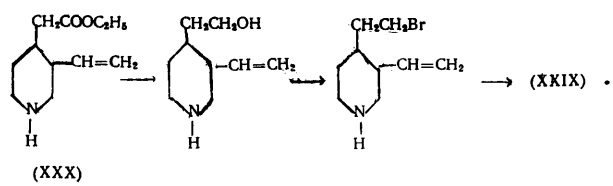
When (XXVI) is dehydrated with phosphorus pentoxide to obtain 3-vinylquinuclidine, the double bond shifts to the semicyclic position and 3-ethylidenequinuclidine (XXVII) is formed. Compound (XXVI) reacts with concentrated hydrochloric acid at 180° to give 3-(β-chloroethyl)quinuclidine (XXVIII) and (XXVII); at lower temperatures (100°–150°) the only product is (XXVIII).



Replacement of the β-hydroxy group in (XXVI) by a bromine atom (HBr) gives 3-(β-bromoethyl)quinuclidine which easily forms the quaternary polymer. When (XXVIII), which has less tendency to polymerise, is treated with potassium hydroxide in methanol the product is 3-(β-methoxyethyl)quinuclidine. Heating (XXVIII) with aqueous potassium hydroxide leads to intramolecular alkylation.

Ernest[47] obtained 3-vinylquinuclidine (XXIX) mixed with 3-ethylidenequinuclidine by dehydrating (XXVI) with phthalic anhydride and benzenesulphonic acid. Racemic (XXIX) was isolated from this mixture by repeated recrystallisation of the styphnates.

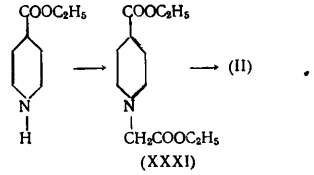
Optically active 3-vinylquinuclidine was prepared by Lukeš and Galik[48] from the ethyl ester of meroquinene (XXX) obtained from naturally-occurring cinchonine[49]:



The ester (XXX) is reduced with lithium aluminium hydride to 3-vinyl-4-(β-hydroxyethyl)piperidine, the hydroxy group is replaced by bromine (HBr), and the bromide is cyclised to 3-vinylquinuclidine.

The synthesis of 3-quinuclidone (II) was a milestone in the preparation of quinuclidine derivatives. This compound served as starting material for the preparation of many 2- and 3-monosubstituted and some 2,3-disubstituted quinuclidines.

Clemo[6] first synthesised 3-quinuclidone as follows:

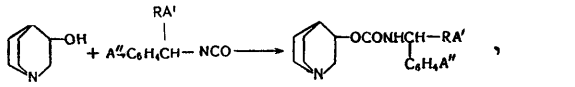


Ethyl isonipecotinate reacts with ethyl chloracetate in the presence of potassium carbonate to give ethyl 1-ethoxycarbonylmethylisonipecotinate (XXXI). Cyclisation of the diester (XXXI) with potassium in toluene, followed by saponification and decarboxylation, leads to 3-quinuclidone.

Sternbach and Kaiser[50], who synthesised (II) in 1952, modified Clemo's scheme only as regards the preparation of the diester. Instead of alkylating ethyl isonipecotinate they reduced the ethoxycarbonylmethobromide of methyl isonicotinic acid to methyl 1-ethoxycarbonylmethylisonipecotinate. The latter, as in Clemo's scheme, was converted to (II) in 37–43% yield. The yield was increased to 82% by using a potassium alkoxide instead of metallic potassium[36].

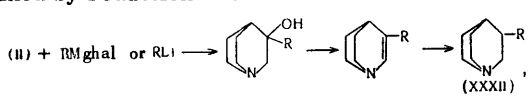
The presence of a reactive keto group in compound (II) made it possible to synthesise various 3-substituted quinuclidines, e.g. the oxime reduced over platinum gives 3-aminoquinuclidine, and reduction of (II) itself gives 3-hydroxyquinuclidine which can be converted by hydrobromic acid to 3-bromoquinuclidine[50]. Esterification of 3-hydroxyquinuclidine with tropic, diphenylacetic, benzilic, fluorenecarboxylic and *o*-acetylmandelic acids gives esters with atropine-like and antispasmodic properties. The most active of these, 3-diphenylacetoxyquinuclidine, is 20 times as active as atropine[51–54]. The esters formed by the above acids with 3-methyl-3-hydroxyquinuclidine have no antispasmodic activity[52].

Urethanes (3-carbamoxyquinuclidines) were also synthesised from 3-hydroxyquinuclidine and isocyanates in order to investigate their biological properties[55]:



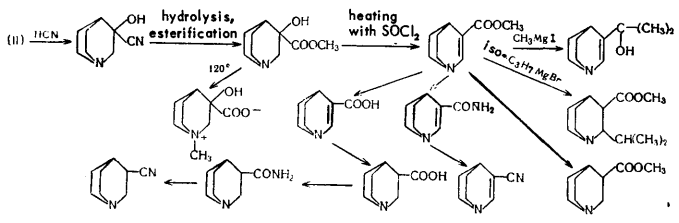
where A' and A" = H, halogen, NO_2, alkoxyl, or alkyl, and R = C_6H_5 or C_6H_{11}.

3-Quinuclidone has been used for the synthesis of 3-aryl- and 3-alkylquinuclidines (XXXII). Organo magnesium or lithium compounds form the 3-hydroxy-3-aryl- and -alkylquinuclidines which are converted to 3-aryl- and 3-alkyl-1-azabicyclo-(2,2,2)-2-octenes by thionyl chloride, sulphuric acid, or acid chlorides. The compounds (XXXII) are then obtained by reduction[7,56].

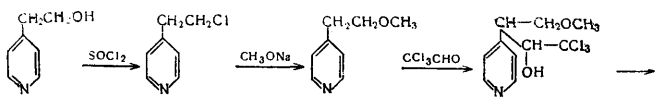


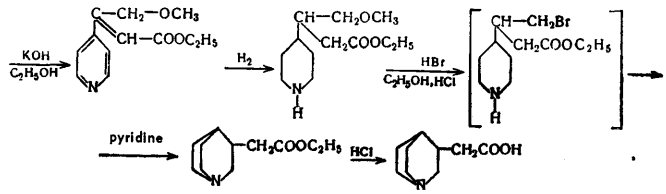
where R = C_6H_5, *p*-$C_6H_4N(CH_3)_2$, *p*-$C_6H_4OCH_3$, *p*-C_6H_4OH, or CH_3.

Grob and Renk[57] used the reactive 3-quinuclidone for the synthesis of quinuclidine-3-carboxylic acid and a number of its derivatives; the following route was adopted:

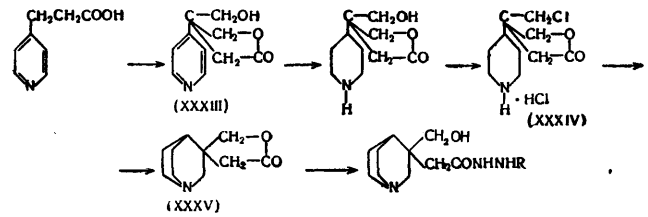


The next homologue, quinuclidine-3-acetic acid[58] was prepared from 4-(β-hydroxyethyl)pyridine, itself obtained by reaction of 4-methylpyridine with formaldehyde:





The synthesis of 3-hydroxymethyl-3-carboxymethylquinuclidine lactone, a derivative of quinuclidine-3-acetic acid, has been described[59]:

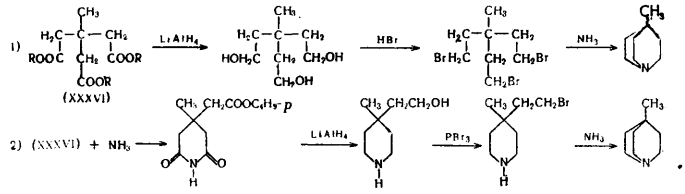


When β-(4-pyridyl)propionic acid or its esters are heated with formalin, the lactone of β,β-di(hydroxymethyl)-β-4-pyridylpropionic acid (XXXIII) is formed. This compound is reduced in alcohol or hydrochloric acid over platinum to the corresponding piperidine which is converted by thionyl chloride to β-chloromethyl-β-(4-piperidyl)-γ-butyrolactone hydrochloride (XXXIV). The base isolated on treating (XXXIV) with one equivalent of alcoholic potassium hydroxide is converted by pyridine to the lactone of 3-hydroxymethyl-3-carboxymethylquinuclidine (XXXV). This lactone forms a hydrazide and a phenylhydrazide with hydrazine hydrate and phenylhydrazine respectively. Benzylamine, piperidine, and decylamine do not open the lactone ring.

4-Substituted Quinuclidines

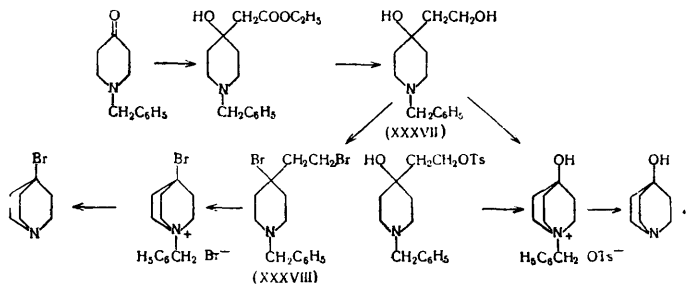
These compounds are the least well investigated of the monosubstituted derivatives of quinuclidine. The synthesis of 4-methyl-, 4-hydroxy-, and 4-bromoquinuclidines and of quinuclidine-4-carboxylic acid and some of its derivatives has been described.

Lukeš and Ferles[60] prepared 4-methylquinuclidine by two methods:



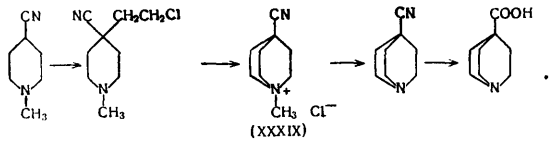
4-Hydroxy- and 4-bromoquinuclidine[61] have been prepared from 1-benzyl-4-piperidone. This was converted by the Reformatsky reaction to 1-benzyl-4-hydroxy-4-ethoxycarbonylmethylpiperidine which was reduced by lithium aluminium hydride to the diol (XXXVII) whose monotosyl (Ts) derivative was cyclised by heating in benzene to a quaternary salt of 4-hydroxyquinuclidine. The latter is reduced over palladised charcoal to 4-hydroxyquinuclidine.

When the diol (XXXVII) is heated with hydrobromic acid it is converted to the dibromide (XXXVIII) which is cyclised to 1-benzyl-4-bromoquinuclidinium bromide. On reduction, this yields 4-bromoquinuclidine[62].



(XXXVIII)

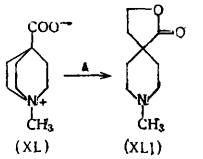
Quinuclidine-4-carboxylic acid was synthesised by Grob and Renk[63] as follows:



(XXXIX)

1-Methyl-4-cyanopiperidine reacts with 1,2-dichloroethane in the presence of sodium phenate to give 1-methyl-4--cyano-4-(β-chloroethyl)piperidine which cyclises to 4-cyanoquinuclidine methochloride (XXXIX). When the latter is heated under vacuum to 260°–270° methyl chloride is eliminated and 4-cyanoquinuclidine is formed. This is hydrolysed to quinuclidine-4-carboxylic acid which does not melt at 370° and presumably exists as a zwitterion.

4-Cyanoquinuclidine methochloride can be hydrolysed to a crystalline betaine (XL):

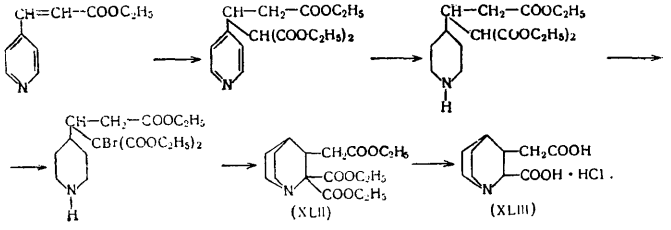


(XL) (XLI)

Heating above 250° transforms (XL) into an isomeric base which is considered to be the lactone (XLI) of 1-methyl-4--(β-hydroxyethyl)piperidine-4-carboxylic acid. The following have been prepared from quinuclidine-4-carboxylic acid: various esters by treating the acid chloride with alcohols, 4-hydroxymethylquinuclidine by reducing these esters with lithium aluminium hydride, 4-formylquinuclidine by oxidation of this alcohol with potassium dichromate, and 4-methylquinuclidine by reduction of 4-formylquinuclidine semicarbazone by the Wolf–Kishner method.

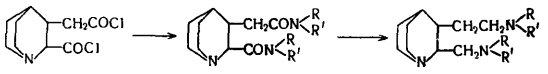
2,3-Disubstituted Quinuclidines

Published data on the preparation of various members of this group are based on 3-carboxymethylquinuclidine-2--carboxylic acid[64] obtained according to the following scheme:



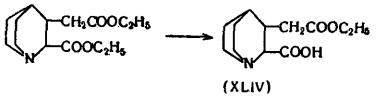
(XLII) (XLIII)

Ethyl of β-(4-pyridyl)acrylate undergoes a Michael condensation with malonic ester to yield ethyl β-diethoxycarbonylmethyl-β-(4-pyridyl)propionate. Reduction of the triester over platinum to the piperidine stage, followed by bromination and cyclisation of the bromoester in boiling pyridine, gave 55% of 3-(ethoxycarbonylmethyl)-2,2-(diethoxycarbonyl)quinuclidine (XLII). When the latter is boiled with hydrochloric acid, 3-carboxymethylquinuclidine-2-carboxylic acid hydrochloride (XLIII) is formed. The ethyl ester of this acid is reduced by lithium aluminium hydride to 3-(β-hydroxyethyl)-2-hydroxymethylquinuclidine which gives 3-(β-chloroethyl)-2-chloromethylquinuclidine with thionyl chloride. The dichloride of 3-carboxymethylquinuclidine-2-carboxylic acid has been converted to several amides which are reduced by lithium aluminium hydride to the amines[31]:



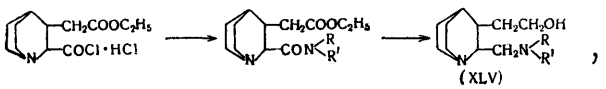
where R = R' = CH_3, C_2H_5; R = H; R' = $C_6H_5CH_2$.

The diethyl ester of 3-carboxymethylquinuclidine-2-carboxylic acid has an interesting property[65]. When its aqueous solutions are kept at room temperature over a long period one of the carbethoxy groups is hydrolysed and an acid ester is formed. Because of the ease of hydrolysis of ethyl quinuclidine-2-carboxylate, this acid ester was considered to be 3-ethoxycarbonylmethylquinuclidine-2-carboxylic acid (XLIV); this structure was confirmed by the conversions mentioned below:



(XLIV)

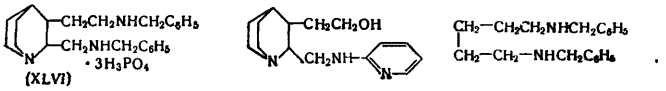
With thionyl chloride the acid ester readily forms an acid chloride which gives amides of 3-ethoxycarbonylmethylquinuclidine-2-carboxylic acid with primary and secondary amines. Reduction of these amides by lithium aluminium hydride yields 3-(β-hydroxyethyl)-2-(alkylaminomethyl)quinuclidines (XLV)[65]:



(XLV)

where R = R' = CH_3, C_2H_5, H; R = H; R' = α-pyridyl; NRR' = 1-piperidyl.

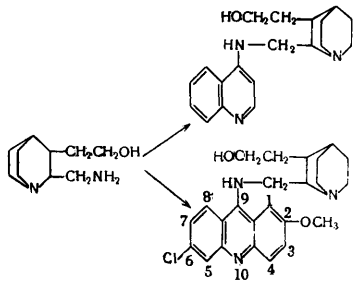
A number of 2,3-disubstituted quinuclidines have ganglion-blocking properties, the highest activity being shown by 2-benzylaminomethyl-3-(β-benzylaminoethyl)quinuclidine triphosphate (XLVI) and 2-(2'-pyridylaminomethyl)-3--(β-hydroxyethyl)quinuclidine[32].



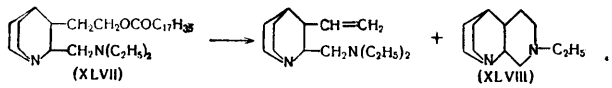
(XLVI)

The latter compound also enhances uterine contractions. It is noteworthy that 1,5-dibenzylaminopentane, which contains an arrangement of atoms incorporated in (XLVI), has no ganglion-blocking properties. This indicates that only a combination of a definite grouping of atoms and the quinuclidine ring gives compounds with a high degree of pharmacological activity.

Compounds (XLV) containing the quinoline or acridine ring system as a substituent on the nitrogen atom were prepared by condensing 2-aminomethyl-3-(β-hydroxyethyl)-quinuclidine with 4-chloroquinoline (in the presence of phenol) and 2-methoxy-6-chloro-9-phenoxyacridine respectively[65].

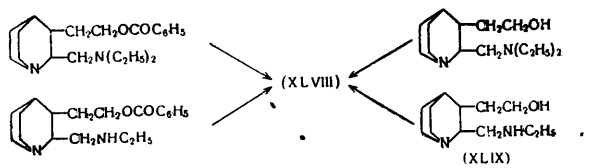


An extensive study has been made of the formation of 2-(N-substituted-aminomethyl)-3-vinylquinuclidines by distilling esters of 2-(N-alkyl- or N,N-dialkyl-aminomethyl)--3-(β-hydroxyethyl)quinuclidines under atmospheric pressure[66]. Two substances are formed from 2-(diethylaminomethyl)-3-(β-stearylhydroxyethyl)quinuclidine (XLVII): 2-diethylaminomethyl-3-vinylquinuclidine and 1'-ethylpiperidino-3',4' : 2,3-quinuclidine (XLVIII), the yield of the former being approximately 10% of the total:

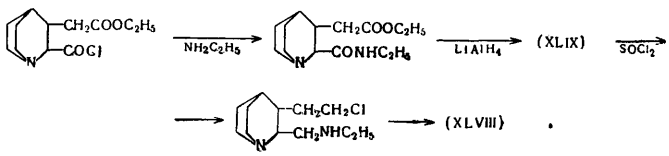


Ethyl stearate was also isolated from the distillation products of (XLVII), thus confirming the formation of the tricyclic compound (XLVIII).

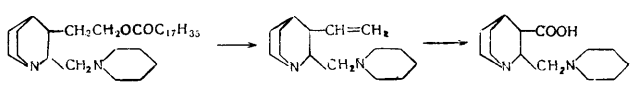
Distillation of 2-diethylaminomethyl- and 2-ethylaminomethyl-3-(β-hydroxyethyl)quinuclidine benzoate, or heating the alcohols with phthalic anhydride in the presence of benzenesulphonic acid, gives only (XLVIII):



The structure of (XLVIII) was confirmed by synthesis as follows:

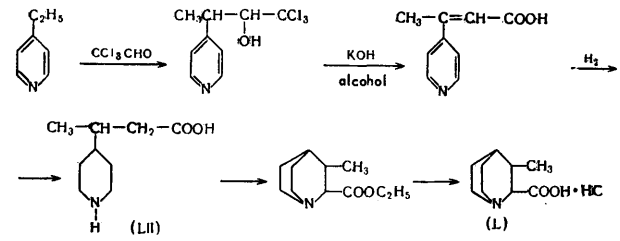


Distillation of 2-(N-piperidinomethyl)-3-(β-stearylhydroxyethyl)quinuclidine at atmospheric pressure yields a single product, namely 2-(N-piperidinomethyl)-3-vinylquinuclidine. The position of the double bond was proved by the oxidation of this compound to 2-(N-piperidinomethyl)-quinuclidine-3-carboxylic acid[66].

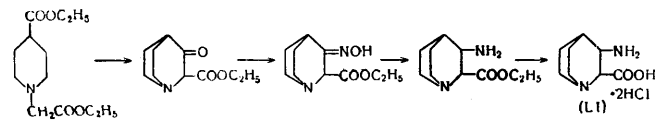


It was shown that distillation of esters of 2-(diethyl- and ethylaminomethyl)-3-(β-hydroxyethyl)quinuclidine gives predominantly the tricyclic compound (XLVIII) formed by simultaneous elimination of a molecule of ester or acid derived from the acyl group esterifying the original alcohol and an alkyl group or hydrogen of the aminomethyl group in the 2-position of the quinuclidine nucleus. Only the vinyl derivative is obtained upon distillation of compounds in which the nitrogen atom in the aminomethyl group forms part of a cyclic system which is stable to fission at high temperature.

3-Methylquinuclidine-2-carboxylic acid (L) and 3-aminoquinuclidine-2-carboxylic acid (LI) are also members of the 2,3-disubstituted series of quinuclidine derivatives. The ethyl ester of the acid (L) was synthesised[67] by successive treatment of β-(4-piperidyl)butyric acid (LII) with phosphorus trichloride, bromine, absolute ethyl alcohol, and pyridine. The procedure may be represented as follows:

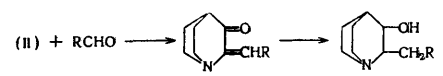


Compound (LI) was prepared as follows[68]:



Dieckmann cyclisation of 1-ethoxycarbonylmethyl-4--ethoxycarbonylpiperidine gives ethyl 3-quinuclidone-2--carboxylate. This forms an oxime which is reduced over platinum to an amino-ester which can be hydrolysed to (LI).

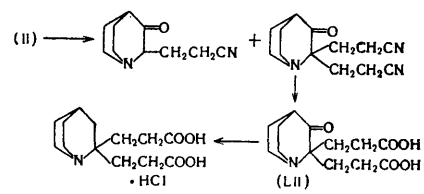
A number of 2,3-disubstituted quinuclidine derivatives have been obtained from 3-quinuclidone. When the ketone is condensed with 4-formylquinoline and benzaldehyde, a substituted ruban[69] and 2-benzal-3-quinuclidone[50] are formed respectively. Reduction of these compounds saturates the double bond and converts the keto-group to hydroxyl.



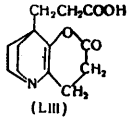
where R = phenyl and 4-quinolyl.

The tropic and diphenylacetic acid esters of 2-benzyl-3--hydroxyquinuclidine were synthesised and found to be pharmacologically inactive[50].

Since 3-quinuclidone contains an active methylene group, it can be condensed with acrylonitrile[36], giving a mixture of 2-(β-cyanoethyl)-3-quinuclidone and 2,2-di(β-cyanoethyl)--3-quinuclidone:



The structure of the former was proved by converting it to β-(2-quinuclidyl)propionic acid (see above), that of the latter by hydrolysis to the keto-diacid (LII). When (LII) was treated with acetic anhydride compound (LIII),



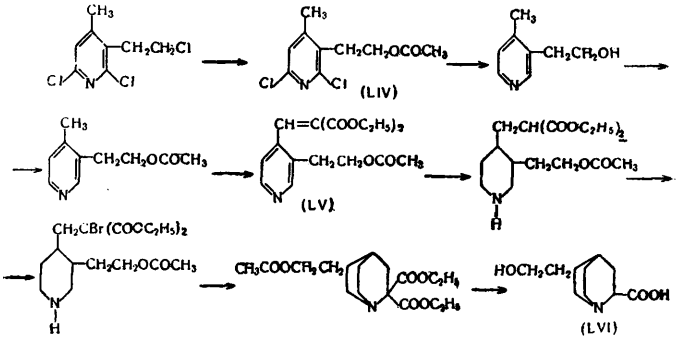
(LIII)

was not formed, demonstrating that the cyanoethyl groups were not in positions 2 and 4. Therefore, the keto-dinitrile was ascribed the structure of 2,2-di-(β-cyanoethyl)--3-quinuclidone. Compound (LII) was converted to a diacid by the Wolf–Kishner reaction.

2,5-Disubstituted Quinuclidines

Little has been published concerning the synthesis of 2,5-disubstituted quinuclidines owing to relative unavailability of 3,4-disubstituted pyridines and of suitable dihalogeno-alkylamines and trihalogeno-alkanes with a branching carbon skeleton.

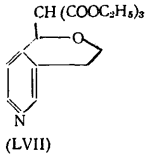
Up to now, apart from quinine alkaloids, their analogues and isomers (to which a special section of the present review is devoted), only 5-(β-hydroxyethyl)quinuclidine-2--carboxylic acid, 5-(β-methoxyethyl)quinuclidine-2-carboxylic acid, 5-quinuclidone-2-carboxylic acid, and some of their derivatives have been synthesised, using a trichloromethylethylpyridine[70,71].



(LIV) (LV) (LVI)

This trichloromethylethylpyridine, treated with potassium acetate in glacial acetic acid at 175°, gives compound (LIV) which, after dehalogenation with hydrogen in the presence of a palladium catalyst and reacetylation, condenses with mesoxalic ester to give 3-(β-acetoxyethyl)-4-(β,β-diethoxycarbonylvinyl)pyridine (LV). Catalytic hydrogenation of (LV) followed by bromination and cyclisation of the product gives 5-(β-acetoxyethyl)-2,2-diethoxycarbonylquinuclidine which, on boiling with concentrated HCl, forms 5-(β-hydroxyethyl)quinuclidine-2-carboxylic acid (LVI).

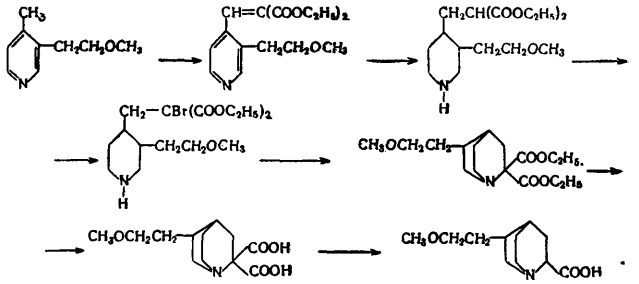
A bicyclic compound, 2-diethoxycarbonylmethylpyridino--3',4':3,4-dihydropyran (LVII), is formed when 3-(β-acetoxyethyl)-4-methylpyridine is condensed with mesoxalic ester. This compound was isolated as the hydrochloride in 11% yield; the yield of 3-(β-acetoxyethyl)-4-(β,β-diethoxycarbonylvinyl)pyridine was 36%.



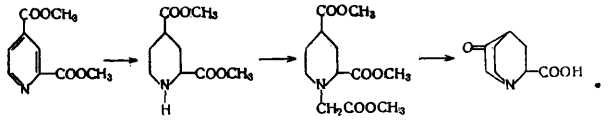
(LVII)

The authors explain the formation of compound (LVII) by the mobility of the acetoxyl group.

In order to improve the yield of the substituted diethoxycarbonylvinylpyridine, mesoxalic ester was condensed with 3-(β-methoxyethyl)-4-methylpyridine[72] to prepare 5-(β--methoxyethyl)quinuclidine-2-carboxylic acid by a route similar to that used for the preparation of compound (LVI)[73].



5-Quinuclidone-2-carboxylic acid and some of its derivatives have been prepared using the lutidine fraction of pyridine bases as starting material[68].

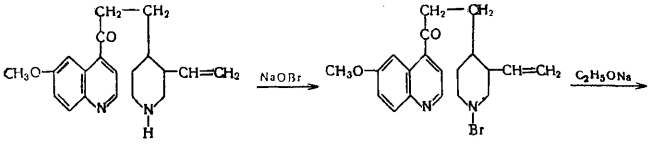


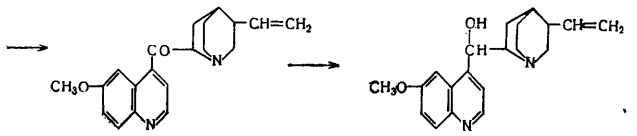
Dimethyl pyridine-2,4-dicarboxylate, obtained from 2,4--lutidine, is hydrogenated over platinum to the corresponding piperidine. This is then alkylated on the nitrogen with bromacetic ester and the product is cyclised by the Dieckmann method to 5-quinuclidone-2-carboxylic acid. The methyl and diethylaminoethyl esters of this acid, as well as the methyl esters of 5-hydroxy- and 5-acetoxyquinuclidine-2-carboxylic acid, have been described.

SYNTHESIS OF QUININE ALKALOIDS, THEIR ANALOGUES, AND ISOMERS

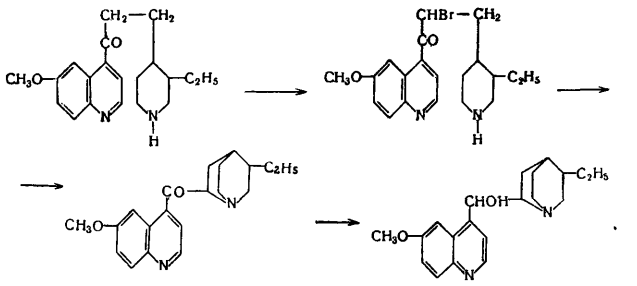
Until the last decade all research into the synthesis of quinuclidine derivatives had been directed towards methods of preparation of quinine alkaloids and their analogues and isomers. Detailed reviews of the quinine alkaloids have been published[74-76] concerning the history of their discovery and application, natural occurrence, analytical methods, isolation from cinchona bark, and investigation of structure, conversions, and stereochemistry. The present review is therefore limited to the synthesis of those quinine alkaloids and their analogues and isomers which are derived from quinuclidine.

The synthesis of quinine was attempted long before, but systematic studies only became possible after the elucidation of the structural formula of quinine alkaloids in 1908[77]. Rabe laid the foundation for these studies when he showed that quinotoxine (a fission product of natural quinine with the quinuclidine ring opened[78]) could be converted to quinine[79] as follows:



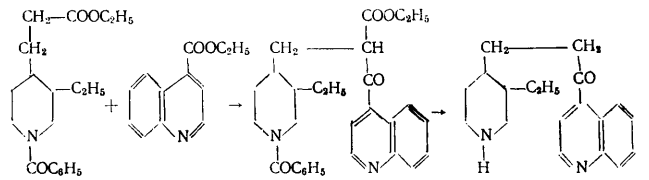


The similar conversion of hydroquinotoxine to hydroquinine gives better yields[80]. The former is brominated to give a C-bromo derivative which is cyclised to hydroquininone. The ketone is reduced catalytically, giving a mixture of stereoisomeric carbinols from which hydroquinine and hydroquinidine are isolated:



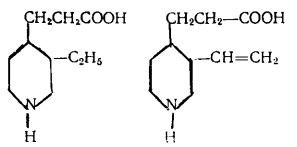
This progress in the partial syntheses of quinine and hydroquinine reduced the problem of synthesis of quinine alkaloids to the preparation of the appropriate toxines.

Rabe[81] showed that hydrocinchotoxine (LVIII) could be obtained by Claisen condensation of ethyl cinchoninate and ethyl ester of N-benzoylhomocincholoipon followed by hydrolysis and decarboxylation of the product.



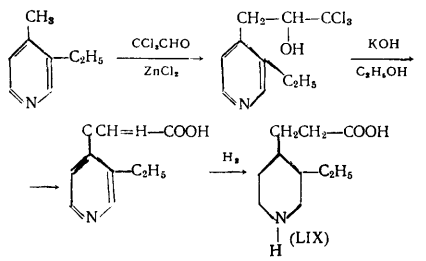
(LVIII)

The most difficult part of this synthesis is the preparation of the substituted ethyl β-(N-benzoyl-4-piperidyl)propionates: homocincholoipon (LIX) and homomeroquinene (LX)



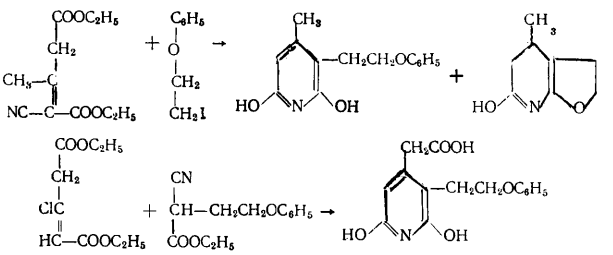
(LIX) (LX)

3-Ethyl-4-methylpyridine was used as the starting material for the synthesis of *d,l*-homocincholoipon (LIX) by Koenigs and Ottmann[82] by the route



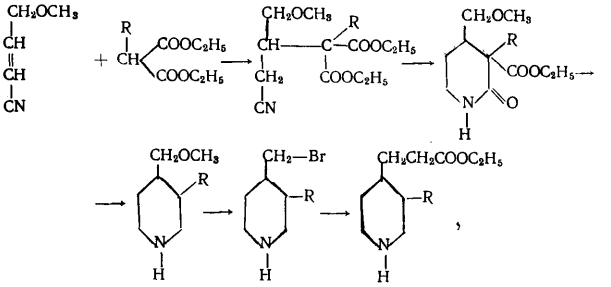
Rabe et al.[83] developed this synthesis and described the separation of ethyl ester of *d,l*-homocincholoipon into its optically active components. These studies led to the complete synthesis of the dihydro bases of some quinine alkaloids including hydroquinine and hydroquinidine.

In the synthesis of β-(3-vinyl-4-piperidyl)propionic acid (LX) the greatest difficulties were associated with the formation of the vinyl group. Matejka, Robinson, and Watt[84] were the first in this field; they condensed ethyl α-cyano-β-methylglutaconate with β-phenoxyethyl iodide and obtained 2,6-dihydroxy-3-(β-phenoxyethyl)-4-methylpyridine and 4-methyl-6-hydroxydihydrofurano-2',3' : 2,3-pyridine. They also prepared 2,6-dihydroxy-3-(β-phenoxyethyl)-4-(carboxymethyl)pyridine by condensing ethyl α-cyano-γ-phenoxybutyrate and ethyl β-chloroglutaconate:



Attempts to reduce these 2,6-dihydroxy pyridines and 6-hydroxydihydrofurano-2',3' : 2,3-pyridine to the corresponding piperidines were unsuccessful. Homomeroquinene could not be obtained from 4-methylfurano-2',3' : 2,3-pyridine since the latter's γ-methyl group does not condense with chloral[85].

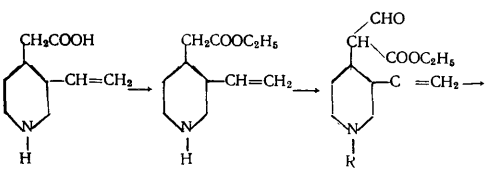
Koelsch et al. made an extensive study of methods of preparation of homomeroquinene and showed that hydrogenation of certain substituted γ-cyanobutyric esters is accompanied by cyclisation to esters of substituted 2-piperidone-3- or -5-carboxylic acids. The latter may be reduced by sodium in butanol to the corresponding piperidines. Koelsch[86,87] used these reactions for the synthesis of ethyl β-(4-piperidyl)propionate and a number of esters of 3-substituted β-(4-piperidyl)propionic acids:

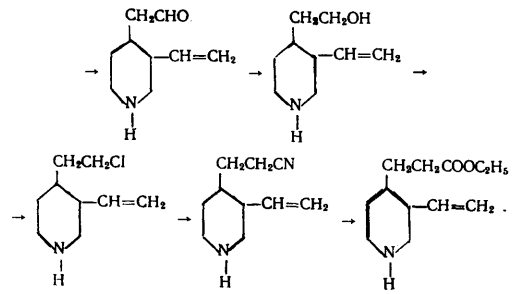


where R = H, C_2H_5, $CH_2CH_2OCH_3$, $CH_2CH_2OC_2H_5$.

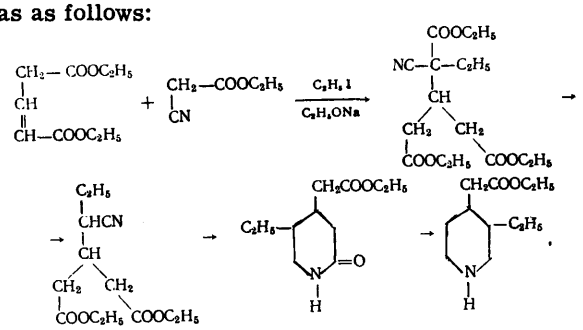
Analogues of quinine alkaloids can be prepared from these compounds in the usual way. However, further work in this field was interrupted by the Second World War.

Livshits, Preobrazhenskii, and Baryshnikova[88] proposed a method of preparation of homomeroquinene starting from meroquinene:

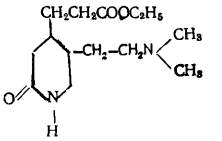




Several stages of the proposed synthesis were carried out. In 1951 Preobrazhenskii, Evstigneeva, et al.[89] suggested routes for the preparation of cincholoipon, meroquinene, and homomeroquinene which were considerably different to those of Koelsch. The suggested scheme for cincholoipon was as follows:

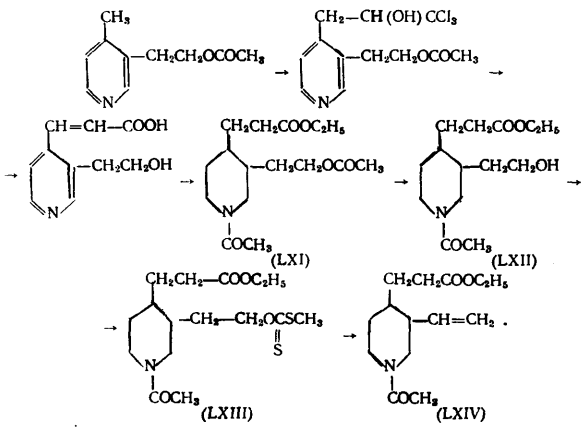


By using a β-dimethylaminoethyl halide instead of ethyl iodide these workers obtained 5-(β-dimethylaminoethyl)-4-(β-ethoxycarbonylethyl)-2-piperidone,



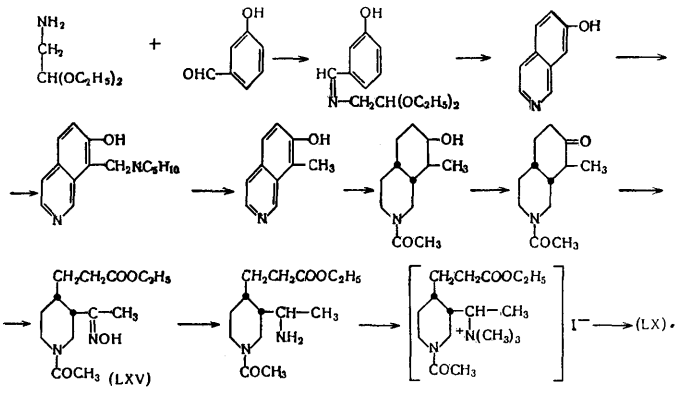
and suggested that this compound could be converted into meroquinene. A similar scheme, starting with diethyl dihydromuconate, was proposed for the synthesis of homomeroquinene. In 1958 the same workers[89] successfully synthesised cis-trans-homocincholoipon from cincholoipon via the alcohol, chloride, and cyanide.

Racemic homomeroquinene was synthesised using a trichlorocollidine (trichloro-3-ethyl-4-methylpyridine) as starting material[90]:



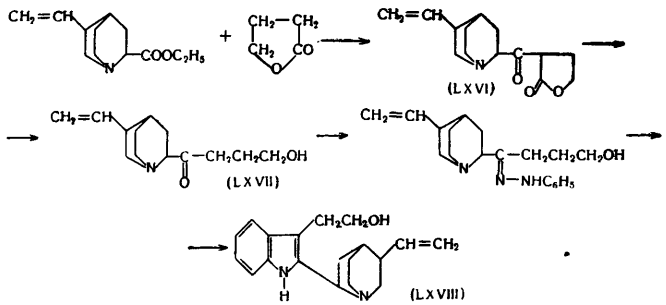
3-(β-Acetoxyethyl)-4-methylpyridine, obtained from the trichlorocollidine (see above), condenses with chloral. Hydrolysis of the product gives β-(3-hydroxyethyl-4-pyridyl)-acrylic acid which is converted by successive esterification, hydrogenation, and acetylation into 1-acetyl-3-(β-acetoxyethyl)-4-(β-ethoxycarbonylethyl)piperidine (LXI). Studies showed that under certain conditions the *O*-acetyl group could be split off selectively, with preservation of the *N*-acetyl residue, by alcoholysis of (LXI) with alcoholic hydrogen chloride. Various methods for converting the 3-(β-hydroxyethyl) group in compound (LXII) into a vinyl group were investigated: dehydration with concentrated sulphuric acid or phosphorus pentoxide, its conversion into a β-halogoethyl group with subsequent treatment with alcoholic potash, and preparation of 1-acetyl-4-(β-ethoxycarbonylethyl)-3-(β-dimethylaminoethyl)piperidine methiodide followed by Hoffman fission. These studies demonstrated that racemic *N*-acetylhomomeroquinene (LXIV) could only be obtained in small yield when methyl β-[4-(β-ethoxycarbonylethyl)-1-acetyl-3-piperidyl]ethylxanthate (LXIII) was decomposed thermally.

dl-cis-Homomeroquinene was prepared by Woodward and Doering[91] who were the first to achieve a complete synthesis of quinine:



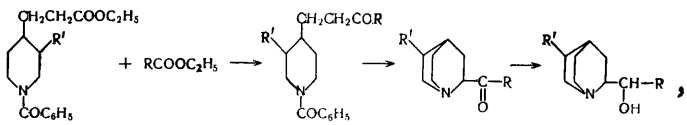
7-Hydroxyisoquinoline, obtained by the Fritsch method from *m*-hydroxybenzaldehyde and aminoacetaldehyde acetal via the Schiff's base, served as starting material. This condenses with formaldehyde and piperidine in methanol solution to 7-hydroxy-8-piperidinomethylisoquinoline which on heating to 220° with sodium methoxide yields 7-hydroxy-8-methylisoquinoline. The latter is reduced stepwise, first to the tetrahydroisoquinoline, and then (after acetylation) to a mixture of stereoisomeric 2-acetyl-7-keto-8-methyldecahydroisoquinolines from which the cis-isomer is isolated. When the latter is treated with ethyl nitrite in the presence of sodium ethoxide, the ester (LXV) is obtained, which on subsequent reduction, exhaustive methylation, and Hoffman fission, gives homomeroquinene (LX). This is converted to quinine by Rabe's method. Separation of the optically active isomers was achieved using the dibenzoyltartrates at the quinotoxine stage. This complete synthesis of quinine, achieved in 1944, was an important milestone in the chemistry of quinuclidine derivatives.

Chen' Chan-bai, Evstigneeva, and Preobrazhenskii[92] carried out a partial synthesis of cinchonamine — a quinine alkaloid containing a quinuclidine and an indole nucleus — starting from ethyl 5-vinylquinuclidine-2-carboxylate:



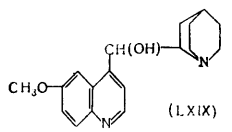
The acid had been prepared earlier by oxidation of naturally occurring quinamine[93]; the ethyl ester condenses with γ-butyrolactone to give the compound (LXVI). When the latter is heated with sulphuric acid, the lactone ring opens and the product undergoes decarboxylation to form (LXVII), the phenylhydrazone of which was converted by a modified Fischer reaction into cinchonamine (LXVIII), identical with the natural alkaloid.

Some syntheses of quinine alkaloid analogues and isomers, based chiefly on Rabe's scheme, consisted of condensation of esters of β-(1-benzoyl-4-piperidyl)propionic acid, or its derivatives, with an acid, followed by closure of the quinuclidine ring and reduction of the ketone thus formed to a corresponding substituted quinuclidine-2-carbinol:

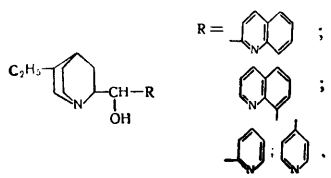


where R' = H, C_2H_5.

This method was used for the synthesis of 6-methoxy-9--rubanol (LXIX)[94,95], which differs from quinine in the absence of a vinyl group on the quinuclidine nucleus. Two stereoisomers of this compound (which correspond in configuration to quinine and quinidine) and their racemate proved very close to quinine in their anti-malarial activity:

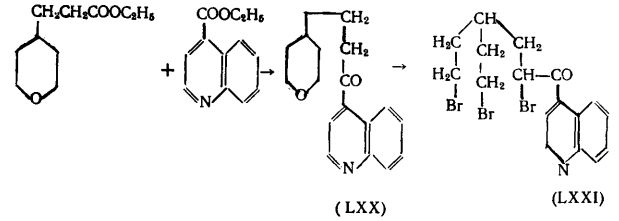


A similar route was used in the preparation of the following compounds. (5-Ethyl-2-quinuclidyl)(6'-methoxy-8'--quinolyl)carbinol[96] and (5-ethyl-2-quinuclidyl)(6'-methoxy--2'-quinolyl)carbinol[97] are isomers of hydroquinine with a quinuclidylhydroxymethyl group in the 2- and 8-positions of the quinoline nucleus. (5-Ethyl-2-quinuclidyl)(4'-pyridyl)-carbinol[98] and (5-ethyl-2-quinuclidyl)(2'-pyridyl)carbinol[99] are analogues of hydrocinchonine, containing a 2- or 4-substituted pyridine ring instead of the quinoline nucleus. (2-Quinuclidyl)(4'-pyridyl)carbinol[100], (2-quinuclidyl)(2'--pyridyl)carbinol[101] and (2-quinuclidyl)(1'-naphthyl)carbinol[102] and isoquinoline analogues of quinine alkaloids (as the ketones)[103] were also prepared.

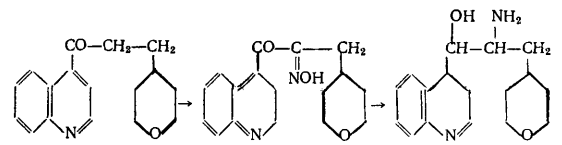


Chemotherapeutic investigations revealed that substitution of a 4-pyridyl ring for the quinoline nucleus in hydroquinine gives a compound which retains the antimalarial properties of hydroquinine.

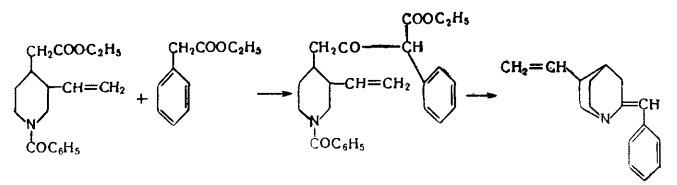
Prelog attempted to obtain quinine alkaloid analogues from compounds of the tetrahydropyran series[104] by a method similar in principle to that of Rabe:



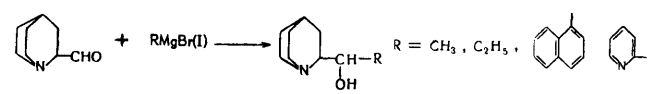
Ethyl cinchoninate was condensed with 4-(β-ethoxycarbonylethyl)tetrahydropyran and the condensation product (LXX) was converted to the tribromide (LXXI) by fuming hydrobromic acid, but attempted cyclisation of (LXXI) failed. (4'-Quinolyl)(2-quinuclidyl)carbinol was not obtained by "double intramolecular alkylation" of the amino alcohol synthesised as follows:



Kenner and Nandi[105] made use of Rabe's scheme for the preparation of 2-benzylidene-5-vinylquinuclidine, an analogue of dehydrated quinine alkaloids, from ethyl esters of N-benzoylmeroquinene and ethyl phenylacetate:



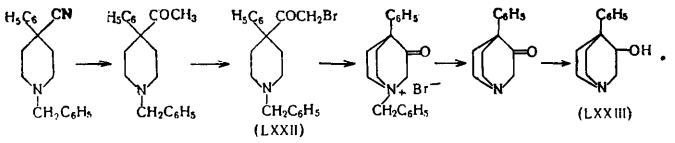
Recently a new method has been described for the synthesis of substituted quinuclidine-2-carbinols[106], based on the reaction between 2-formylquinuclidine with Grignard reagents:



This method has been used for the preparation of the following compounds: (2-quinuclidyl)methylcarbinol, (2-quinuclidyl)ethylcarbinol, (2-quinuclidyl)(1'-naphthyl)carbinol and (2-quinuclidyl)(2'-pyridyl)carbinol. (2-Quinuclidyl)-methylcarbinol has also been prepared by catalytic reduction of 2-acetylquinuclidine (synthesis described above) in the presence of platinum. Both this reduction in an alcoholic medium and the method employing Grignard reagents give a mixture of diastereoisomeric (2-quinuclidyl)methylcarbinols. By reduction in an aqueous medium, only one diastereoisomer of this compound was obtained.

3,4-Disubstituted Quinuclidines

Only one report has been published[107] on the synthesis of 3,4-disubstituted quinuclidines. It described the synthesis of 4-phenyl-3-hydroxyquinuclidine:



1-Benzyl-4-phenyl-4-cyanopiperidine reacts with lithium methyl to form 1-benzyl-4-phenyl-4-acetylpiperidine which is converted to the bromide (LXXII) by bromine in glacial acetic acid. The bromide cyclises to 1-benzyl-4-phenyl--3-ketoquinuclidinium bromide. By eliminating benzyl bromide and reducing the product with lithium aluminium hydride, 4-phenyl-3-hydroxyquinuclidine (LXXIII) is obtained. The alcohol (LXXIII) was esterified with acetic and propionic anhydrides but the esters obtained showed no analgesic properties.

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