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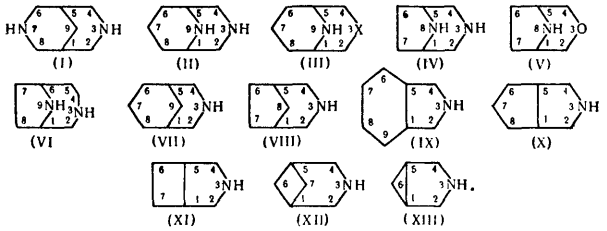
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SYNTHETIC DIAZA- AND AZA-BICYCLIC SYSTEMS WITH NON-BRIDGEHEAD NITROGEN ATOMS

M. V. Rubtsov and E. S. Nikitskaya

Introduction

Recently a large number of papers have been published on the chemical and biological studies of synthetic diaza- and aza-bicyclic systems with non-bridgehead nitrogen atoms. According to their chemical structure, these bicyclic systems may be divided into the following groups:

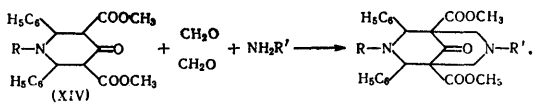


Aza- and diaza-bicyclic compounds are very interesting pharmacologically, since many of them exhibit biological activity and may be used for the investigation and preparation of new drugs. In this connection it appeared useful to give a systematic account of work dealing with the methods of synthesis of the above bicyclic systems, their chemical properties, and pharmacological activity. The present article does not include natural compounds of the tropane series and their synthetic derivatives, since a number of reviews dealing with them already exist[1-4].

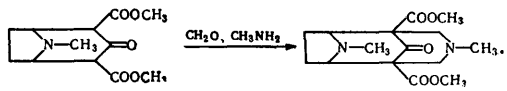
3,7-Diazabicyclo[3,3,1]nonane (I)

The derivatives of 3,7-diazabicyclo[3,3,1] nonane can be divided into two subgroups: 9-oxo-3,7-diazabicyclo[3,3,1]-nonanes or bispidones and the 3,7-diazabicyclo[3,3,1]nonanes themselves or bispidines. The methods available for the preparation of the two subgroups are different; bispidines cannot be obtained from bispidones.

Bispidones. Derivatives of 9-oxo-3,7-diazabicyclo-[3,3,1]nonane were first synthesised by Mannich and Mohs[5] by the condensation of substituted piperidonedicarboxylic ester (XIV) with formaldehyde and primary amines:

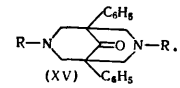


Compound (XIV) was obtained by the reaction of acetonedicarboxylic ester with the appropriate aldehyde and alkylamines[6-8]. The bicyclic system forms very readily at room temperature in aqueous alcoholic medium with a yield of 60–70%. By choosing appropriate derivatives of piperidine and alkylamines, it is possible to obtain easily various bispidones[9]†. Under these conditions the dimethyl ester of tropinonedicarboxylic acid yields a tricyclic system — the dimethyl ester of 6,8-ethylene-3,7-dimethyl-9--oxo-3,7-diazabicyclo[3,3,1]nonane-1,5-dicarboxylic acid:

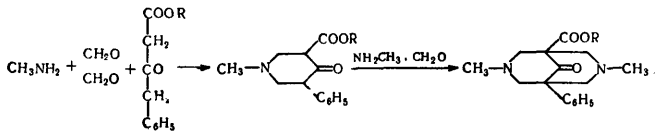


When an attempt was made to prepare a substituted γ-piperidone by the condensation of diphenylacetone, formaldehyde, and ammonia, the sole product isolated was 9-oxo-1,5-diphenyl-3,7-diazabicyclo[3,3,1]nonane[12].

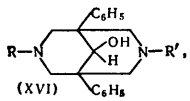
By using various alkylamines in the reaction with diphenylacetone, the authors of these investigations obtained a nunber of bispidone derivatives with the general formula (XV), where R = CH_3CO, CH_3, n-C_2H_7, $C_6H_5CH_2$, $HOCH_2CH_2$, and $ClCH_2CH_2$.



Similar results were obtained also by other workers[13], who allowed γ-phenylacetoacetic ester to react with methylamine and formaldehyde and instead of the expected product (3,5-dialkoxycarbonylphenyl-*N*-methylpiperidone), obtained bispidone derivatives, which are the products of the further interaction of the piperidone with formaldehyde and the amine:

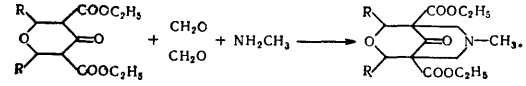


Numerous bispidone derivatives with the general formula (XVI) have been obtained by Chiavarelli and coworkers[14,15] by the condensation of diphenylacetone with formaldehyde and alkylamines followed by reduction of the ketones to alcohols with lithium aluminium hydride:

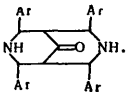


where R = R′ = C_2H_5, iso-C_3H_7, n-C_4H_9, CH_3, H, $ClCH_2CO$, R_2NCH_2CO, etc.

† A similar reaction[10] has been carried out with pyran derivatives[11]:

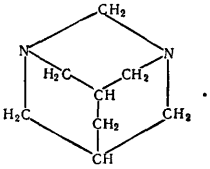


2,4,6,8-Tetraarylbispidones have been prepared by the reaction of acetone and ammonium acetate with benzaldehyde and *p*-methylbenzaldehyde[16]:

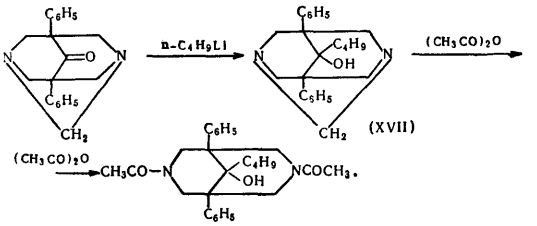


These were then reduced to the corresponding 9-bispidols.

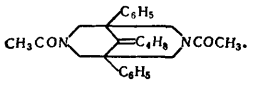
Certain diphenyl derivatives of diazaadamantane exhibit strychninelike activity[17-19]. This led to increased interest in bispidone, which is an intermediate in the synthesis of diazaadamantane:



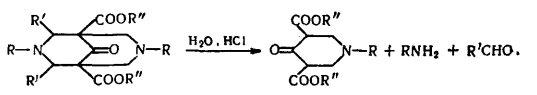
Substituted bispidones are readily obtained by the cleavage of diazaadamantane derivatives. Thus reaction of 9-oxodiazaadamantane with lithium alkyls yields tertiary alcohols, which on reaction with acetic hydride are cleaved with the formation of the *NN*-diazetyl derivative of 9-bispidol[18]:



When acetyl chloride acts upon compound (XVII), a molecule of water is split off and the ring is cleaved at the same time with the formation of an unsaturated compound[18]:



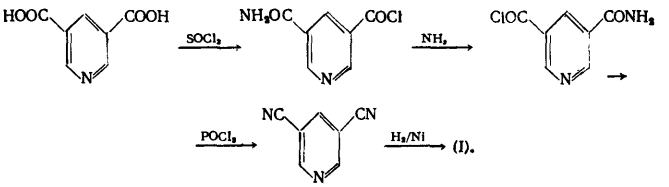
In a non-aqueous medium bispidones form dihydrochlorides, but one molecule of hydrogen chloride is easily lost (the hydrochloride "fumes"). The monohydrochloride is stable and almost insoluble in water. The carbonyl group does not undergo the characteristic reactions, and is not reduced in the presence of palladium or platinum black; on hydrogenation in methanol in the presence of palladium black, the molecule is cleaved with formation of an alkylamine and an aldehyde. Bispidones are readily hydrolysed to the corresponding piperidones, alkylamines, and aldehydes. Hydrolysis takes place even on boiling in water but the reaction is faster in the presence of acids, the substituted ring being cleaved as a rule[5,9]:



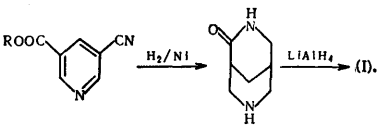
The pharmacological activity of bispidones has not been adequately investigated. Compounds with the general formula (XV) are weak anaesthetics and analgesics[12]. Among derivatives with the structure (XVI), compounds with antiarrhythmic activity have been found[14].

Bispidines. As stated above bispidone derivatives do not undergo reactions characteristic of the carbonyl group and are not reduced to bispidine derivatives. For this reason, the latter must be synthesised by different methods.

In an attempt to synthesise cytisine, the molecule of which incorporates bispidine, Bohlman and coworkers[20] obtained the latter from pyridine-3,5-dicarboxylic acid:

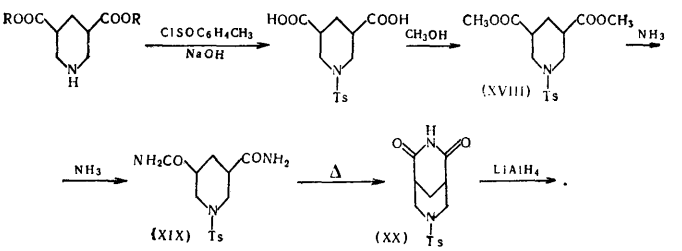


The yield of bispidine was 15%. When pyridine-3,5-dicarboxylic acid was replaced by 5-alkoxycarbonyl-3--cyano pyridine, compound (I) was again obtained[21]:



Galinovsky and Langer[22] obtained bispidine in 40% yield by heating 3,5-dibromomethylpiperidine with an alcoholic solution of ammonia in a sealed tube.

Bispidine may be synthesised from the diester of piperidine-3,5-dicarboxylic acid[23]:



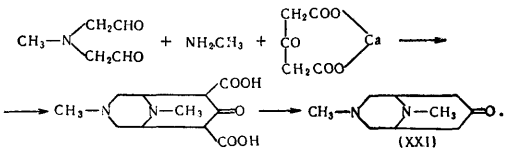
Reaction of the ester (XVIII) with boiling benzylamine gave a 95% yield of the extremely stable dibenzylamide which could not be cyclised into bispidine derivatives: for this reason the *trans*-configuration was attributed to this compound.

The ease of cyclisation of compound (XIX), which is obtained at low temperatures, and the impossibility of cyclising the dibenzylamide of *N*-tosylpiperidine-3,5-dicarboxylic acid, which is obtained at a high temperature, suggests that in the first case the formation of the diamide is preceded by the conversion of the *trans*-form of the ester (XVIII) into the *cis*-form and, conversely, in the preparation of the dibenzylamide at a high temperature the *cis*--form of the ester (XVIII) is converted into the *trans*-form. In subsequent papers the possibility of obtaining the cyclic imide (XX) directly from the ammonium salt of *N*-tosylpiperidine-3,5-dicarboxylic acid was indicated[24].

Bispidine consists of colourless crystals which avidly attract moisture and can be distilled in the form of a liquid hydrate. It is a strong diacidic base with an odour resembling that of piperidine. There are no data in the literature on the pharmacology of bispidine derivatives.

3,9-Diazabicyclo[3,3,1]nonane(II)

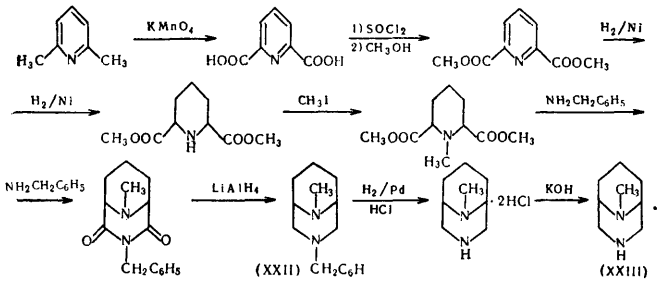
This bicyclic system was first obtained by Blount and Robinson[25] from methylaminodiacetaldehyde[26], methylamine, and the calcium salt of acetonedicarboxylic acid, the yield being 7.5%:



(XXI)

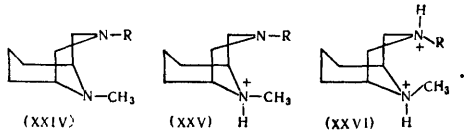
The reaction was continued to prepare the ketone (XXI).

Barnes and Fales synthesised 9-methyl-3,9-diazabicyclo[3,3,1]nonane from 2,6-lutidine[27]:



(XXII) (XXIII)

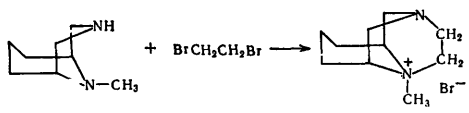
They established that the benzyl derivative (XXII) forms only the monomethiodide and the monopicrate, while 9-methyl-3,9-diazabicyclo[3,3,1]nonane (XXIII) yields both the dihydrochloride and the dipicrate. They explain this difference in behaviour by steric factors, and suggest that these compounds are most likely to have the configuration (XXIV):



(XXIV) (XXV) (XXVI)

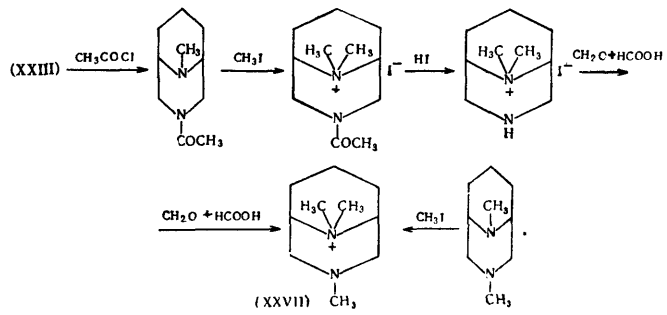
There is no steric hindrance in the formation of the mono-salt both when R = H and when R = $CH_2C_6H_5$ as in compound (XXV). However, the formation of the di-salt (XXVI) is impossible in the latter case because of steric hindrance, which occurs when methyl and benzyl groups approach one another. The steric hindrance is eliminated when the benzyl group in position 3 is replaced by hydrogen.

In order to prove the suggested configuration, Fales and Barnes synthesised 9-methyl-3,9-diazabicyclo[3,3,1,2$^{3-9}$]-undecane[28]:



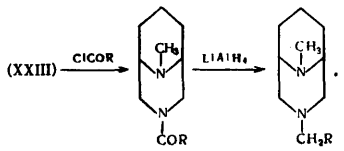
and demonstrated its structure by chemical reactions and by infrared spectroscopy.

The non-equivalence of the two nitrogen atoms in the bicyclic system (II) was noted also by other workers[29], and it has been shown that the formation of the mono-quaternary salt occurs at the nitrogen in position 9.[30] To form this salt, 9-methyl-3,9-diazabicyclo[3,3,1]nonane was acetylated, the acetyl derivative was converted into the quaternary salt, and the latter was then deacetylated and methylated with a mixture of formic acid and formaldehyde:

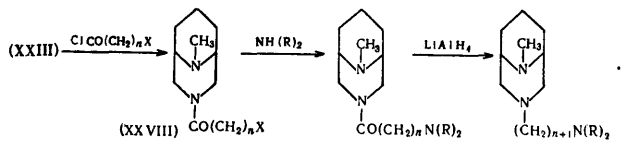


(XXVII)

The resulting quaternary salt (XXVII) proved to be identical with the methiodide of 3,9-dimethyl-3,9-diazabicyclo[3,3,1]-nonane prepared by the direct reaction of 3,9-dimethyl-3,9--diazabicyclo[3,3,1]nonane with methyl iodide. Derivatives of 9-methyl-3,9-diazabicyclo[3,3,1]nonane containing acyl, alkyl, hydroxyalkyl, carboxyalkyl, alkylaminoalkyl, and other groups at the nitrogen atom in position 3 have been synthesised recently for the purpose of pharmacological study[29]. The synthesis started with compound (XXIII) and the acid chlorides:



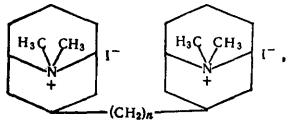
The amides thus obtained were then reduced with lithium aluminium hydride to the corresponding amines. The synthesis of 3-alkylaminoalkyl derivatives was achieved by the reaction of compound (XXIII) with the acid chlorides of halogeno-acids with subsequent substitution of the halogen in compound (XXVIII) by the dialkylamino-group and the reduction of the carbamoyl group with lithium aluminium hydride:



(XXVIII)

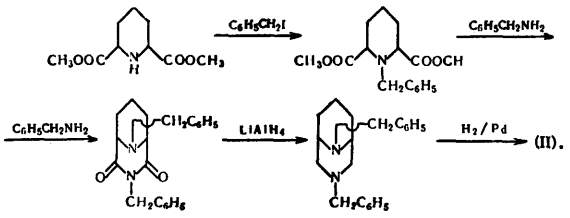
The dihydrochloride (XXIII) exhibits nicotine like activity, i.e. it stimulates ganglia[31]. Any substituent in position 3, starting with the methyl group, converts the compound into a ganglion-blocking agent. Apart from the ganglion-blocking effect, curarelike activity also appears. The greatest interest attaches to the dihydrochloride of 3,9-dimethyl-3,9-diazabicyclo[3,3,1]nonane which has approximately one twentieth of the ganglion-blocking activity of hexamethonium and is only 50% less active than the curarelike preparation diplacin which is used in the Soviet Union. When these compounds are converted into quaternary salts the ganglion-blocking and curarelike activities are intensified.

The series of symmetrical bis-quaternary salts with the general formula



is interesting. The tertiary bases were obtained by reducing the amides prepared by the reaction of compound (XXIII) with acid dichlorides[29] or the acid chlorides of halogeno--substituted acids[32]. The most active preparation, with the experimentally most pronounced curarelike activity, proved to be the symmetrical bis-quaternary salt with n = 4.[31] It is somewhat more active than decamethonium and twenty times more active than diplacin.

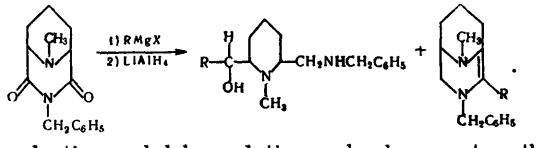
Unsubstituted 3,9-diazabicyclo[3,3,1]nonane (II) was obtained as follows[30]:



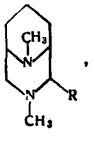
The reaction is carried out with benzyl iodide, benzyl chloride not reacting under similar conditions. The subsequent stages of the synthesis are similar to those in the synthesis of compound (XXIII).

Compound (II) is a homologue of piperazine and like the latter exhibits antihelminthic activity, which, however, is much weaker than in that of piperazine.

The synthesis of 3,9-diazabicyclo[3,3,1]nonane derivatives with substituents in position 2 does not take place smoothly[33]. The use for this purpose of the reaction between alkylmagnesium halides and cyclic imides[34] with subsequent reduction of the reaction products with lithium aluminium chloride yields mainly piperidine derivatives; unsaturated bicyclic compounds with a substituent in position 2 are obtained in only a very small yield:



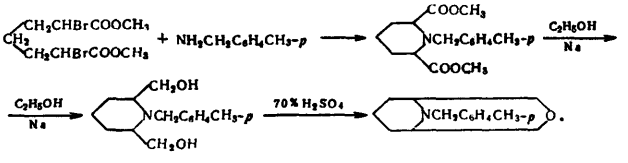
Their reduction and debenzylation and subsequent methylation at the nitrogen atom yields the compounds



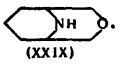
where R = CH_3 and C_2H_5.

3-Oxa(thia, selena)-9-azabicyclo[3,3,1]nonane (III)

The bicyclic system of 3-oxa-9-azabicyclo[3,3,1]nonane was obtained for the first time as 9-(p-methylbenzyl)-3--oxa-9-azabicyclo[3,3,1]nonane[35]:



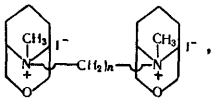
The study of 3-oxa-9-azabicyclo[3,3,1]nonane (XXIX) and its derivatives was begun in 1959 [36,37]:



(XXIX)

The starting material for its synthesis was the diethyl ester of piperidine-2,6-dicarboxylic acid[38], whose reduction with lithium aluminium hydride yielded 2,6-dihydroxymethylpiperidine, which was cyclised to compound (XXIX) with 70% sulphuric acid. The cyclisation takes place with 50% yield and is accompanied by extensive charring.

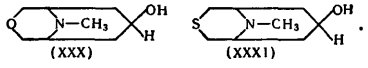
A number of derivatives of compound (XXIX) have been obtained with alkyl, acyl, alkylaminoacyl, and alkylaminoalkyl substituents at the nitrogen atom, including compounds whose acyl and alkyl substituents incorporated pharmacologically active systems such as phenothiazine, quinazolone, morpholine, and others. Ethers and esters of 9-(γ-hydroxypropyl)- and 9-(δ-hydroxybutyl)-3-oxa-9--azabicyclo[3,3,1]nonane and the symmetrical bis-quaternary salts with the general formula



have also been prepared.

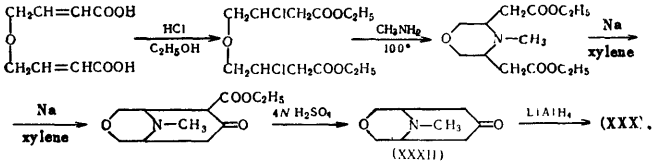
Some of these compounds exhibit nicotinelike activity and in large doses also traces of curarelike activity; none of these compounds are of practical interest.

The 7-hydroxy-derivatives of this bicyclic compound (XXX) and its thia-analogue (XXXI) proved to be more interesting[39].



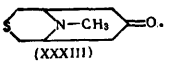
(XXX) (XXXI)

Starting from ω-carboxyallyl ether, 9-methyl-3-oxa-9--azabicyclo[3,3,1]nonan-7-one (XXXII) was obtained as follows:



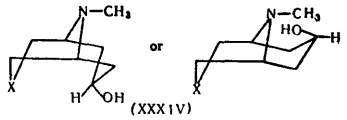
The overall yield of compound (XXXII) with respect to the ω-carboxyallyl ether was 21%. The yield is low because the diethyl ester of 1-methylmorpholine-2,6-diacetic acid is formed as a mixture of the *cis*- and *trans*-isomers and only the *cis*-isomer cyclises into the bicyclic compound. Reduction of compound (XXXII) yielded compound (XXX).

Compound (XXXI) was synthesised by the method of Blount and Robinson[26] (see p. 441). Best results were obtained when the reaction was carried out in a weakly acid medium (pH 4). The ketone (XXXIII) was reduced to the alcohol with lithium aluminium hydride, only one isomer being isolated.



(XXXIII)

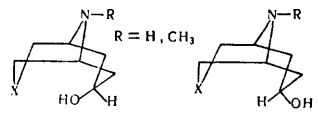
The *cis*-configuration (XXXIV) has been wrongly attributed to compounds (XXX) and (XXXI) obtained by the reduction of the ketones (XXXII) and (XXXIII):



(XXXIV)

(XXXIVa, X = O), (XXXIVb, X = S).

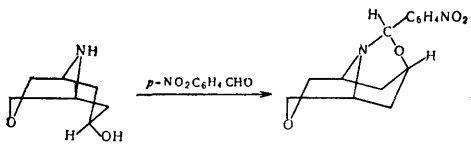
Zirkle and coworkers[40] studied the reduction of the ketones (XXXII) and (XXXIII) and the isolation in a pure form of the *cis*- and *trans*-isomers (XXX) and (XXXI). They reduced the ketones (XXXII) and (XXXIII) in different ways. When compound (XXXII) was reduced by means of a nickel catalyst in alcohol or ruthenium oxide in acetic acid, the main product was the axial (*trans*-)isomer (XXXVb, R = CH_3). The other isomer was obtained on reduction of compound (XXXII) with sodium in pentanol and on epimerisation of the axial isomer in the presence of aluminium isopropoxide. The isomer formed on epimerisation (XXXVIb, R = CH_3) is probably more stable and therefore its hydroxyl should be in the equatorial position.



(XXXV) (XXXVI)

(XXXVa, X = S), (XXXVb, X = O), (XXXVIa, X = S), (XXXVIb, X = O).

The configuration of the epimers was demonstrated by the method of acyl migration which has been used in similar cases to study the steric structure of compounds of the tropane series[41-43]. Both epimeric alcohols (XXXVb, R = CH_3) and (XXXVIb, R = CH_3), were demethylated, and the nor-compounds were benzoylated and then heated in an acid medium. In this reaction the *N*-benzoyl derivative of the equatorial (*cis*)isomer (XXXVIb, R = H) isomerised to the *O*-benzoyl derivative while the axial (*trans*-)isomer (XXXVb, R = H) remained unchanged. In addition, the equatorial isomer formed a cyclic compound with *p*-nitrobenzaldehyde[44]:

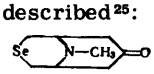


while the axial isomer charred under these conditions.

Because of the presence of sulphur, the thia-bicyclic ketone (XXXIII) does not undergo catalytic hydrogenation, but it is reduced with sodium in pentanol, the product being the equatorial (*cis*-)isomer (XXXVIa, R = CH_3). Reduction of the ketones (XXXII) and (XXXIII) with lithium aluminium hydride yields the axial (*trans*-)isomers (XXXVa, R = CH_3) and (XXXVb, R = CH_3).

A number of esters of compounds (XXX) and (XXXI) with diphenylacetic, benzilic, and other acids have been obtained[39,40]. Among these compounds the benzylic acid ester of compound (XXX), which exhibits considerable spasmolytic and high anaesthetic activity, is the most interesting[45]. In addition, it proved effective in the treatment of gastric ulcers and Parkinson's disease[40,45].

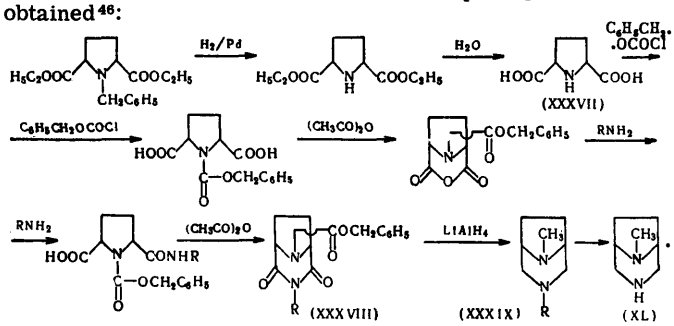
The synthesis of 9-methyl-3-selena-9-azabicyclo[3,3,1]-nonan-7-one has been described[25]:



No data concerning its biological properties have been given.

3,8-Diazabicyclo[3,2,1]octane (IV)

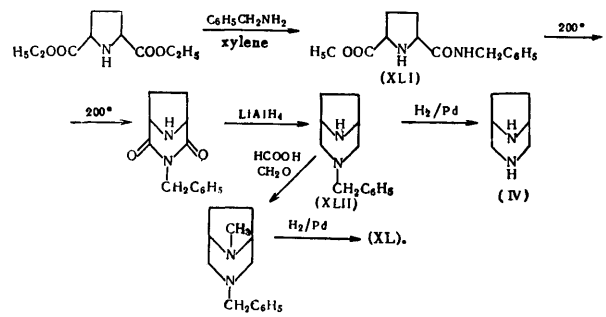
Bicyclic systems containing the pyrrolidine and piperidine rings are biologically very interesting, since they are similar to tropane and contain the piperazine ring, which is a component of many physiologically active substances. Numerous attempts to synthesise compounds of this series remained unsuccessful for a long time. It was not until 1961 that 8-methyl-3,8-diazabicyclo[3,2,1]octane was obtained[46]:



The acid (XXXVII) could be obtained from the ester only by using water as the hydrolytic agent In acid and alkaline media the pyrrolidine ring is cleaved. Since the acid (XXXVII) is very soluble in water and virtually insoluble in alcohol, it was isolated as the 1-benzyloxycarbonyl derivative, which was then converted into the anhydride using acetic anhydride. Reaction of the anhydride with alkylamines yielded monoamides, which on boiling with acetic anhydride were converted into the cyclic imides (XXXVIII). The imides were reduced with lithium aluminium hydride, the benzyloxycarbonyl group being converted into the methyl group.

Benzylamine was used to prepare 8-methyl-3,8-diazabicyclo[3,2,1]octane (XL). In this case reduction with lithium aluminium hydride gave 3-benzyl-8-methyl-3,8-diazabicyclo[3,2,1]octane (XXXIX, R = $CH_2C_6H_5$), which was debenzylated in the presence of palladium.

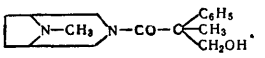
Later a simpler synthesis was developed for compound (XL), which permitted also the preparation of the unsubstituted bicyclic compound (IV)[47]:



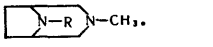
While in the first procedure, involving seven stages, the yield of compound (XL) was 16%, in the second procedure, consisting of five stages, the yield increased to 25%.[48] A more detailed study of the thermal cyclisation of the ester-amide (XLI) led to the isolation from the reaction mixture of two other substances[49]. One of these was the benzylimide of 1-ethylpyrrolidine-2,5-dicarboxylic acid and the other proved to be the *trans*-form of the ester-amide (XLI).

Derivatives of compound (XL) containing alkyl, aralkyl, and acyl groups in position 3 have been obtained. Like the derivatives of 3,9-diazabicyclo[3,3,1]nonane, the 3-alkyl derivatives of compound (XL) give only mono-quaternary salts, the quaternary nitrogen being in position 8.

Pharmacological study has established that 3-substituted derivatives of compound (XL) are antagonists of acetylcholine, 8-methyl-3-(α-methyltropoyl)-3,8-diazabicyclo[3,2,1]octane showing the greatest activity[50]:



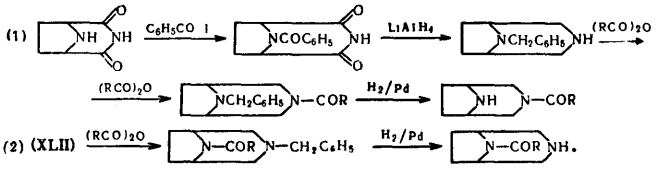
To compare the pharmacological activity of the 3-substituted derivatives of compound (XL) with their 8-isomers, a number of compounds having the following general formula were obtained[51]:



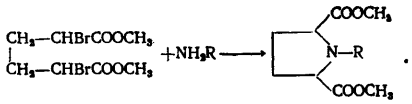
Here R is an acyl or an alkyl group. It was found that, in contrast to the 3-isomers, the 8-acyl derivatives exhibit analgesic activity, 3-methyl-8-propionyl-3,8-diazabicyclo[3,2,1]octane being the most effective.

Investigation of the properties of the 3- and 8-acyl derivatives of 3,8-diazabicyclo[3,2,1]octane showed that the acyl residue in position 8 migrates to position 3 under the influence of temperature or alkaline reagents[52]. The opposite migration has not been observed.

The 3- and 8-acyl derivatives required for this purpose can be obtained as follows:



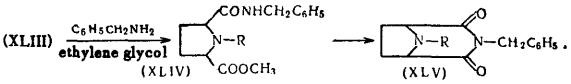
In the synthesis of the derivatives of 3,8-diazabicyclo[3,2,1]-octane a special study was made of the pyrrolidine ring closure reaction[53]:



(XLIII)

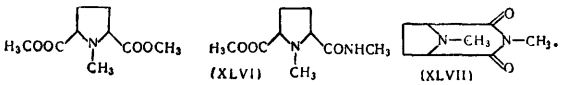
$\alpha\alpha'$-Dibromoadipic acid is shown to be a mixture of isomers[54-56]. In order to obtain from this acid 1-substituted *cis*-pyrrolidine-2,5-dicarboxylic ester (XLIII), the *meso*-form must be used in the reaction, the racemate being less suitable. In the reaction of the *meso*-form of $\alpha\alpha'$-dibromoadipic acid with aniline in a mixture of benzene and nitromethane 1-phenylpyrrolidine-2,5-dicarboxylic ester forms in 70% yield. The *cis*- and *trans*-isomers, in the proportions of three to one, can be separated by fractional crystallisation and by chromatography. Under the same condition the racemate of $\alpha\alpha'$-dibromoadipate gives compound (XLIII) in 10% yield, which can be separated into equal amounts of the *cis*- and *trans*-isomers.

Study of the synthesis of the imide (XLV) showed[53] that not only cyclisation but also the formation of the ester--amide (XLIV) proceeds with considerable difficulty:



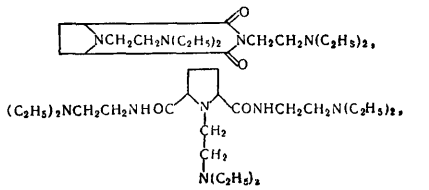
The product required can be obtained only when the reaction with benzylamine is carried out in boiling ethylene glycol in the presence of metallic sodium, followed by distillation of the reaction mixture without prior removal of the catalyst. During the distillation the cyclisation with the formation of compound (XLV) goes to completion, the yield of (XLV) being 40% from *cis*- (XLIII) and 12% from *trans*-(XLIII).

Schipper and Boehme[57] published interesting observations in 1961. They showed that in the reaction of dimethyl $\alpha\alpha'$-dibromoadipate with methylamine in the ratio 1 : 3 three products are formed:

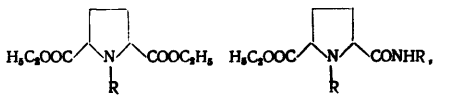


Compound (XLVII) can also be obtained in 50% yield on heating the ester-amide (XLVI) to 180°. Reduction of compound (XLVII) with lithium aluminium hydride yields, 3,8--dimethyl-3,8-diazabicyclo[3,2,1]octane.

The reaction of $\alpha\alpha'$-dibromoadipate proceeds in different ways with different alkylamines. For example, when β-diethylaminoethylamine is used, a mixture of the bicyclic compound and the diamide is formed:



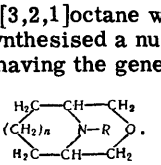
whereas with benzylamine or n-butylamine the reaction products are the ester and the ester-amide:



where R = n-C_4H_9 or $C_6H_5CH_2$.

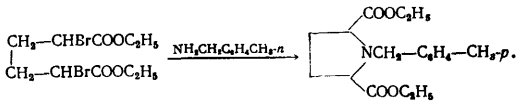
3-Oxa-8-azabicyclo[3,2,1]octane (V)

3-Oxa-8-azabicyclo[3,2,1]octane was obtained by Braun and Leistner[35], who synthesised a number of bicyclic derivatives of morpholine having the general formula

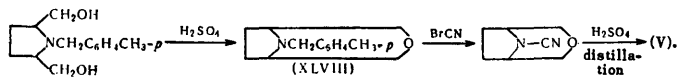


The simplest representative of this series, morpholino-pyrrolidine or 3-oxa-8-azabicyclo[3,2,1]octane, was synthesised from diethyl *meso*-$\alpha\alpha'$-dibromoadipate and

p-methylbenzylamine via the 1-(*p*-methylbenzyl)pyrrolidine-2,5-dicarboxylic ester:



The latter was reduced with sodium in alcohol to the corresponding diol which was cyclised with 70% sulphuric acid at 175° into 8-(*p*-methylbenzyl)-3-oxa-8-azabicyclo[3,2,1]-octane (XLVIII):

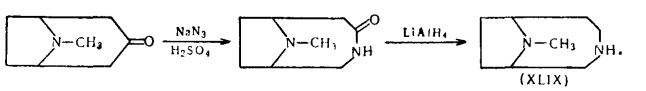


To prepare the nor-compound, the *p*-methylbenzyl derivative (XLVIII) was allowed to react with cyanogen bromide, the cyano-derivative being subsequently saponified with 25% sulphuric acid.

Like morpholinopiperidine (XXIX), morpholinopyrrolidine (V) shows little pharmacological activity[35].

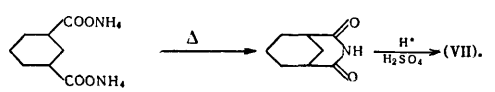
3,9-Diazabicyclo[4,2,1]nonane (VI)

In 1960 a short note was published concerning the synthesis of 9-methyl-3,9-diazabicyclo[4,2,1]nonane (XLIX) as the starting material for the preparation of pharmacologically active substances[58]. The synthesis was achieved by treating tropinone with sodium azide in sulphuric acid with subsequent reduction of the cyclic amide formed with lithium aluminium hydride. The yield of compound (XLIX) was 51% with respect to tropinone.



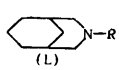
3-Azabicyclo[3,3,1]nonane (VII)

Compound (VII) was first prepared by the dry distillation of ammonium hexahydroisophthalate, the imide formed being subsequently reduced at a lead cathode in 65% sulphuric acid[59]:

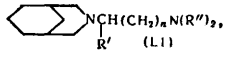


The yield of compound (VII) was only 17%, probably as a result of the hydrolysis of the imide during the reduction process.

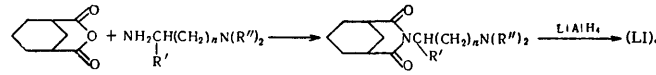
In recent years a number of papers have been published on the synthesis of derivatives of compound (VII). Compounds having the general formula (L) have been obtained[60]:



where R = CH_3, C_2H_5, $CH(CH_3)_2$, $CH_2CH{=}CH_2$, NO, etc., and also the mono- and bis-quaternary salts (LI)[61]:

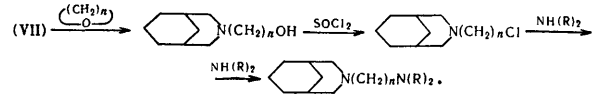


where n = 1, 2, and 3, R′ = H and CH_3, and $N(R'')_2$ = $N(CH_3)_2$, $N(C_2H_5)_2$, pyrrolidyl, morpholinyl, etc. These compounds were synthesised by the reaction of compound (VII) with alkyl halides[60] or by the reaction of hexahydroisophthalic acid or its anhydride with the corresponding amines and subsequent reduction of the resulting imides with lithium aluminium hydride[61,62]:



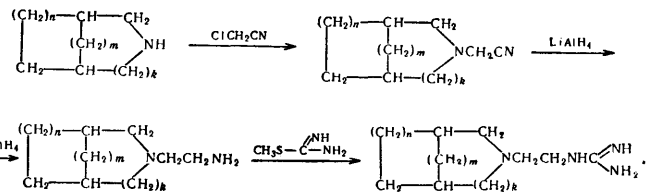
Later it was shown that substituted derivatives of (VII) can form from the di(*p*-toluenesulphonate) ester of 1,3-dihydroxymethylcyclohexane and the corresponding amine[63].

Compounds (LI) in which n = 1 and R′ = CH_3 do not form bis-quaternary salts because of steric hindrance. The other compounds form mono-quaternary salts at 20° and bis-quaternary salts at 80–90°. Compounds (LI) in which n = 1 or 2 and R′ = H can be obtained by the reaction of compound (VII) with epoxyethylene and epoxypropene followed by treatment of the resulting alcohols with thionyl chloride and secondary amines[61]:



The compounds obtained[61] exhibit considerable ganglion-blocking activity, the most interesting being 3-(γ-dimethylaminopropyl)-3-azabicyclo[3,3,1]nonane methiodide[61] and 3-(ω-dimethylaminopentyl)-3-azabicyclo[3,3,1]nonane[64]. It is noteworthy that similar compounds containing an even number of methylene groups have been found by Rice and Grogan to have little activity[65].

Later studies showed[66-68] that certain derivatives of compound (VII) and also of its structural isomer 3-azabicyclo[3,2,2]nonane exhibit hypotensive properties. Among these 3-(β-guanidinoethyl) derivatives proved to be especially active, preliminary data showing that in the intensity and duration of the activity they are not inferior to guanethidine[66]‡. The synthesis of 3-(β-guanidinoethyl)-3-azabicyclo[3,3,1]nonane and its analogues were achieved as follows:

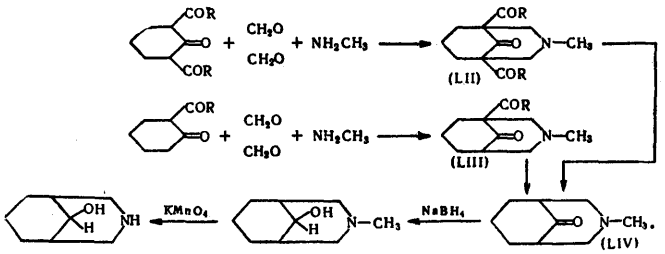


The azabicycloalkanes were converted into *N*-cyanomethyl derivatives and the latter were reduced with lithium aluminium hydride and then allowed to react with *S*-methylisothiourea.

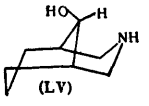
Derivatives of compound (VII) may be synthesised also by the Mannich reaction[71-75]. 9-Hydroxy-3-azabicyclo-

‡ Among the derivatives of 3-azabicyclo[3,2,2]nonane, a structural isomer of compound (VII), compounds have been obtained recently capable of giving rise to hypotonia, salivation, and convulsions[69,70].

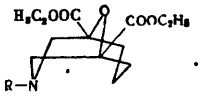
[3,3,1]nonane was obtained by this method from cyclohexanone derivatives[71]:



Condensation of diethyl cyclohexanone-2,6-dicarboxylate and ethyl cyclohexanone-2-carboxylate with formaldehyde and methylamine yields the diethyl ester (LII) and the ethyl ester (LIII). The amides of the acids can be used in the reaction instead of the esters. Hydrolysis and decarboxylation of compounds (LII) and (LIII) give compound (LIV); this can be reduced with sodium borohydride to the corresponding alcohol, which can be demethylated with an alkaline solution of potassium permanganate to 9-hydroxy-3-azabicyclo[3,3,1]nonane or isopseudogranatoline, the latter compound probably having the *trans*-configuration (LV), since it does not form a cyclic product with *p*-nitrobenzaldehyde[44]:

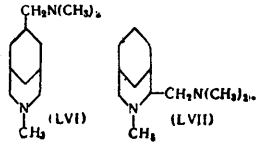


Study of the formation of compound (LII) by the Mannich reaction[72,73] showed that, depending on the temperature (25° or 100°), one of two compounds, differing in their boiling points but identical in all other properties and having the composition of compound (LII), is obtained. They are probably the *cis*- and *trans*-isomers with respect to the ethoxycarbonyl groups§. Compounds of this type must have the chair–chair structure:

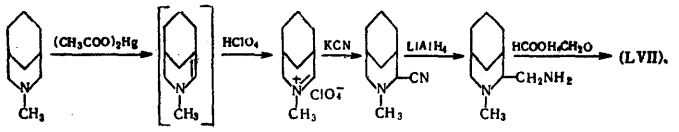


Their carbonyl groups do not give the characteristic reactions, which is evidently due to steric hindrance[73]. Hydrolysis and decarboxylation of both isomers yield the same ketone (LIV), which forms an oxime and can be reduced by the Wolff–Kishner method to compound (L, R = CH_3).

Other derivatives of 3-azabicyclo[3,3,1]nonane which have been synthesised are the 7- and 2-dimethylaminoethyl compounds[76]:

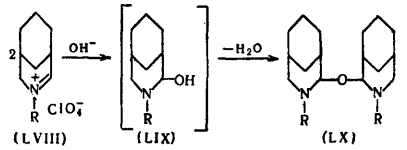


Compound (LVI) was obtained from cyclohexane-1,3,5-tricarboxylic acid, which was converted by dry ammonia at 200–220° into its monoamide, monoimide. The latter was reduced with lithium aluminium hydride and methylated with a mixture of formic acid and formaldehyde to give compound (LVI). Compound (LVII) was synthesised as follows:

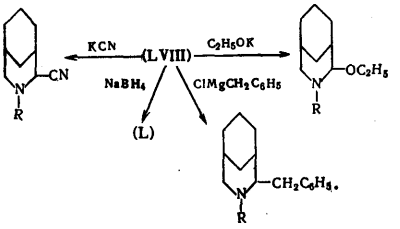


3-Methyl-3-azabicyclo[3,3,1]nonane was dehydrogenated at 80° with a solution of mercury acetate in 5% acetic acid; the unsaturated compound, isolated as the perchlorate, was converted by the action of an aqueous solution of potassium cyanide into 2-cyano-3-methyl-3-azabicyclo[3,3,1]nonane. The latter was reduced with lithium aluminium hydride and methylated with a mixture of formic acid and formaldehyde to give compound (LVII). No data on the pharmacological activity of thesecompounds have been published.

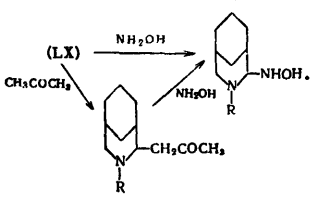
Schneider and Götz[77] found that, on being acted upon by sodium hydroxide, perchlorates of the type of (LVIII) do not form the hydroxy-derivative (LIX) but the dimeric compound (LX):



Reaction of compound (LVIII) with various nucleophilic agents gives 2-substituted derivatives of 3-alkyl-3-azabicyclo[3,3,1]nonane: 2-ethoxy-derivative with potassium ethoxide, 2-cyano-derivative with potassium cyanide, and 2-benzyl derivative with benzylmagnesium chloride. Reduction of compound (LVIII) with sodium borohydride gives compound (L).



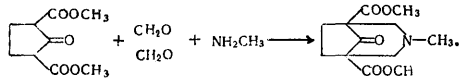
The dimer (LX) also reacts with nucleophilic agents, forming monomeric 2-substituted derivatives: reaction with hydroxylamine in absolute alcohol gives 3-alkyl-2--hydroxyamino-3-azabicyclo[3,3,1]nonane and the reaction with acetone gives a ketone which on being acted upon by hydroxylamine does not give an oxime but the hydroxylamino-derivative:



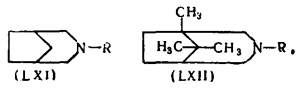
§ This does not appear to be possible (Ed. of Translation).

3-Azabicyclo[3,2,1]octane (VIII)

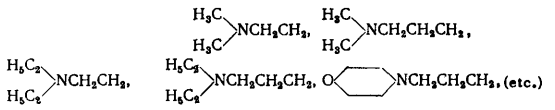
Derivatives of compound (VIII) can be obtained by the Mannich reaction from the cyclopentanone-1,5-dicarboxylic ester[75,78]:



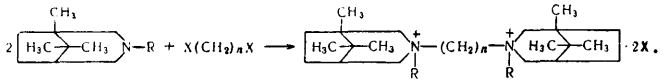
Another synthetic pathway for compound (VIII) is based on the use of the anhydride of *cis*-1,3-cyclopentanedicarboxylic acid[79] or the camphoric anhydride, which is converted into bicyclic amines via the corresponding imides[80-82]. Depending on the initial anhydride and amine, compounds having the structures (LXI) and (LXII) are formed:



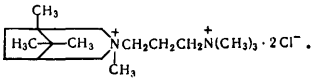
where R = alkyl,



Reaction of 3-alkyl-1,8,8-trimethyl-3-azabicyclo[3,3,1]-nonane with $\alpha\omega$-dihalogenoalkanes gave symmetrical bis--quaternary salts[80]:



Pharmacological investigation of the compounds synthesised showed that the tertiary bases are inactive, while the quaternary salts show hypotensive activity[83,84]. No differences were observed between the (+)- and (±)-forms. 3-(γ-Diethylaminopropyl)-1,8,8-trimethyl-3-azabicyclo-[3,2,1]octane was found to have the greatest activity[84]:

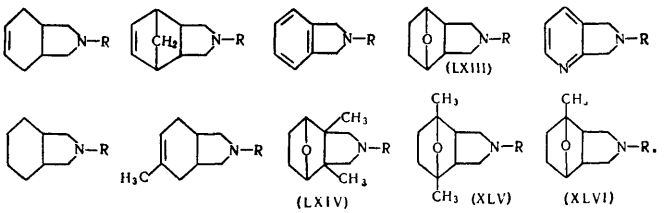


This substance exhibits pronounced hypotensive activity and also depressive activity on the central nervous system.

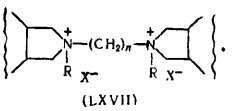
3-Azabicyclo[4,3,0]nonane (IX)

3-Azabicyclo[4,3,0]nonanes or isoindolines have been synthesised in different ways. Thus Tiffeneau and coworkers[85] obtained *N*-isopentylisoindoline by the reaction of *o*-bromomethylbenzyl bromide with diisopentylamine. In a similar way Braun and coworkers[86,87] obtained isoindoline and a number of its derivatives.

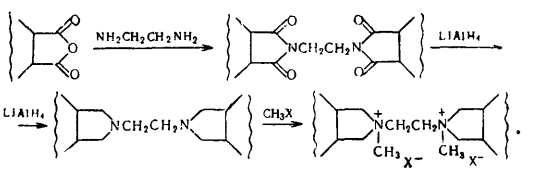
Substituted isoindolines are most simply obtained by the reduction of the imides of 1,2-dicarboxylic acids[88-91] which in turn are synthesised from the anhydrides of the corresponding dicarboxylic acids and alkylamines[92]. The following derivatives of isoindoline have been synthesised:



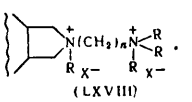
The amines used were dimethylamino-, diethylamino-, morpholino-, and piperidino-ethylamines, and others. The resulting bicyclic amines were converted into asymmetric and symmetric bis-quaternary salts (LXVII)[93] by standard methods[80]:



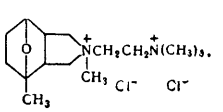
The quaternary salts are readily obtained when n = 3 and more; when n = 2 only one end of the dihalogenoalkane reacts with the amine. In this case, in order to obtain symmetric bis-quaternary salts, the corresponding anhydride of the dicarboxylic acid is allowed to react with ethylenediamine, the condensation product being reduced with lithium aluminium hydride and converted into the quaternary salt by means of methyl iodide:



Substituted acid imides and their methiodides are pharmacologically inactive. The isoindoline bases are only weakly active, but their conversion into bis-quaternary salts yields compounds with pronounced hypotensive activity and low toxicity. Compounds (LXVII) and (LXVIII), with n = 2 or 3 and R = CH_3 or C_2H_5, and compounds with an oxygen bridge (LXIII–LXVI) exhibit very powerful hypotensive properties.

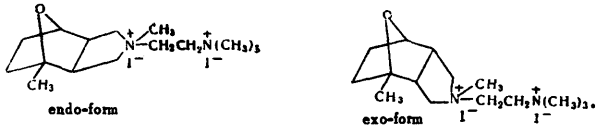


Among all the compounds of this series which have been investigated, preparation H-2 proved to be the most effective[94,95]:

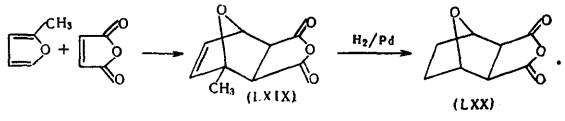


It is much more active and less toxic than hexamethonium. From their study of the structure of preparation H-2 (as

the dimethiodide), Rice and Grogan concluded that this compound can exist in one of two forms[96]:

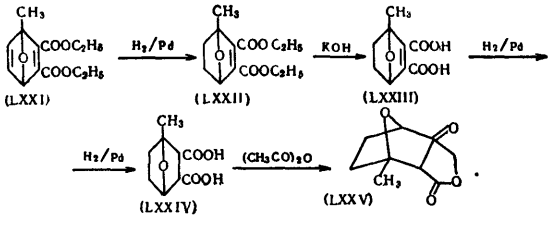


They synthesised both isomers and investigated their pharmacological properties. The synthesis was based on phthalic anhydride derivatives of different configurations. Condensation of maleic anhydride and 2-methylfuran gave the addition product (LXIX)[97] with the *exo*-configuration[98]:



Its reduction yields *exo*-perhydrophthalic anhydride (LXX).

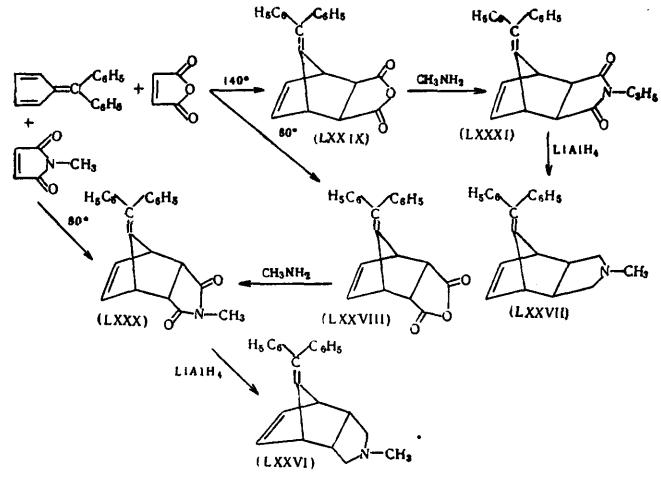
The condensation of diethyl acetylene-1,2-dicarboxylate acid with 2-methylfuran gives the addition product (LXXI)[99,100]:



On catalytic hydrogenation of compounds (LXXI), one mole of hydrogen adds on to give compound (LXXII), which can be hydrolysed to the acid (LXXIII). Reduction of compound (LXXIII) yields *endo-cis*-perhydrophthalic acid (LXXIV), which can be converted into the anhydride (LXXV) by treatment with acetic anhydride and acetyl chloride. The acid obtained from the anhydride (LXX) is not identical with the acid (LXXIV), just as the anhydride (LXX) is not identical with the anhydride (LXXV). Taking into account the work of Woodward and Baer[98], it may be assumed that the anhydride (LXXV) has the *endo*-form.

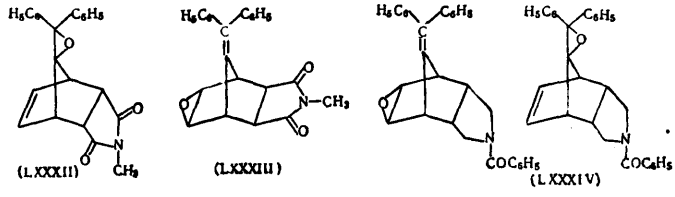
The anhydrides (LXX) and (LXXV) were allowed to react with dimethylaminoethylamine, the resulting imides being reduced with lithium aluminium hydride and converted into bis-quaternary salts. The pharmacological activity of the two compounds proved to be equally high[94].

In 1962 Poos and coworkers[101] synthesised the *endo*- and *exo*-isomers of 8-diphenylmethylene-2-methyltetrahydro-4,7-methanoisoindoline (LXXVI) and (LXXVII) and a number of its derivatives, starting from the corresponding fulvenes, by a method similar to that described above. Condensation of diphenylfulvene and maleic anhydride at 80° gives predominantly the *endo*-form of the addition product (LXXVIII), and at 140° the *exo*-form (LXXIX).[102] Condensation of diphenylfulvene with *N*-methylmaleimide at 80° gave only one addition product (LXXX), which proved to be identical with the compound formed on reaction of compound (LXXVIII) with methylamine, i.e. it has the *endo*-configuration. Subsequent reduction of compound (LXXX) with lithium aluminium hydride gave *endo*-8-diphenylmethylene-2-methyltetrahydro-4,7-methanoisoindoline (LXXVI):



The *exo*-derivative (LXXVII) was synthesised in a similar way via the *exo*-form of the addition product (LXXIX), by the reaction of the latter with methylamine followed by the reduction of *exo*-8-diphenylmethylene-2-methyltetrahydro-4,7-methanoisoindoline-1,3-dione (LXXXI), with lithium aluminium hydride to give compound (LXXVII).

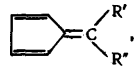
The unusual features of the reactions of compounds (LXXX) and (LXXXI) with perbenzoic acid are also noteworthy[103]. Compound (LXXX) forms an oxygen bridge at the double bond outside the ring to give compound (LXXXII), while compound (LXXXI) forms only the ring epoxide (LXXXIII):



However, the reaction of *endo*-8-diphenylmethylene-2-benzoyltetrahydro-4,7-methanoisoindoline with perbenzoic acid yields a mixture of epoxides (LXXXIV). Selective epoxide formation is probably due to the configuration of the molecule and the presence of the amide group.

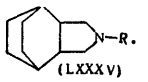
Compound (LXXVI) exhibits pronounced peripheral and central anticholinergic activity. Compound (LXXVII) is somewhat less active.

The authors also prepared a number of compounds, predominantly of the *endo*-series, using different fulvenes having the general formula



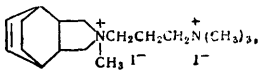
where R′ = R″ = CH_3(1), R′ = C_6H_5 and R″ = CH_3(2), R′ = = C_6H_5 and R″ = *p*-C_6H_4Cl(3), R′ = C_6H_5 and R″ = *m*-$CF_3C_6H_4$(4), R′ = C_6H_5 and R″ = *o*-$CH_3C_6H_4$(5), and R′ = C_6H_5 and R″ = 2-C_5H_4N(6). The compounds obtained included some with anticholinergic activity, but much weaker than that of compound (LXXVI).

Introduction of an ethylene group across positions 4 and 7 of the isoindoline system somewhat alters the mode of action of the substances. For example, among compounds with the general formula (LXXXV), which were obtained by Japanese investigators [104-106],

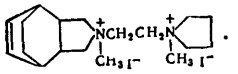


(LXXXV)

Some were found to have ganglion-blocking activity, for example the dimethiodide of 2-(γ-dimethylaminopropyl)--4,7-ethanotetrahydroisoindoline:



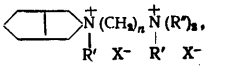
and the dimethiodide of 2-(β-pyrrolidin-1-ylethyl)-4,7--ethanotetrahydroisoindoline:



3-Azabicyclo[3,3,0]octane (X)

Hypotensive activity, ranging from moderate to high, is shown by the following systems: 3-azabicyclo[3,2,1]-octane, 1,8,8-trimethyl-3-azabicyclo[3,2,1]octane, 3-azabicyclo[3,2,0]heptane, and also various modifications of the cyclic systems of isoindoline — 3-azabicyclo[4,3,0]-nonane [80,81,92,93,96,107]. However, the derivatives of 3-azabicyclo[3,3,1]nonane proved to have little or no activity [65]. The sharp difference in activity between compounds (IX) and (VII) led investigators to synthesise derivatives of compound (X) [108] to compare their pharmacological activity with that of 3-azabicyclo[3,2,1]octane.

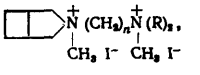
The starting material was the anhydride of *cis*-cyclopentane-1,2-dicarboxylic acid [109], which was converted into the corresponding derivative of compound (X) in the usual way — by reaction with amines followed by reduction with lithium aluminium hydride. The bis-quaternary amines obtained in this way were readily converted into bis-quaternary salts:



with marked hypotensive activity. Thus there is no difference in the mode of action and activity of 3-azabicyclo-[3,2,1]octanes and 3-azabicyclo[3,3,0]octanes.

3-Azabicyclo[3,2,0]heptane (XI)

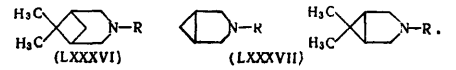
Derivatives of this bicyclic compound were first obtained in 1957 [107] from the anhydride of cyclobutane-1,2--dicarboxylic acid [110], which was converted in the usual way, by reaction with appropriate amines, into a substituted imide and then the corresponding amine. The bis--quaternary salts of this series of compounds exhibit hypotensive activity, the most active among them being, as in the case of isoindolines, substances with the general formula



where n = 2 or 3 and R = CH_3 or C_2H_5.

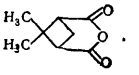
3-Azabicyclo[3,1,1]heptane (XII) and 3-Azabicyclo[3,1,0]-hexane (XIII)

The pharmacologically active bicyclic monoaza-systems which have been described above, can be classified as polymethylenepiperidines and polymethylenepyrrolidines with bridges consisting of 2, 3, and 4 methylene groups. Rice and coworkers synthesised the piperidine (LXXXVI) and pyrrolidine (LXXXVII) derivatives with a bridge containing one methylene group only [111]:



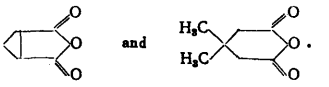
(LXXXVI) (LXXXVII)

The derivative (LXXXVI) was obtained in the usual way from the norpinic anhydride (LXXXVIII). [112]

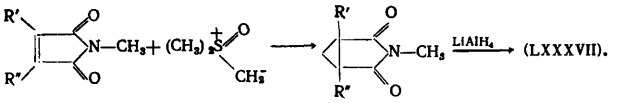


(LXXXVIII)

The synthesis of compound (LXXXVII) was based on the anhydrides [113,114]



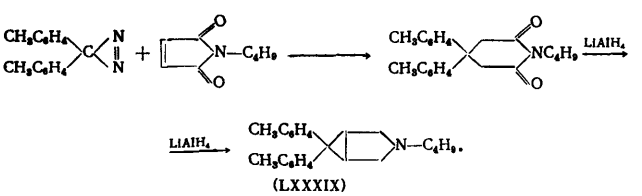
A recent paper describes a new synthesis of cyclopropane-1,2-dicarboximides [115], which consisted in the reaction of substituted *N*-methylmaleimides with trimethylsulphoxonium ylid [116]:



The 3-substituted derivatives of compound (LXXXVII) readily yield bis-quaternary salts, in contrast to the 3-substituted derivatives of compound (LXXXVI) which form bis-quaternary salts only at high temperatures and pressures. A similar difference in behaviour as regards quaternisation was noted earlier for other bicyclic systems containing pyrrolidine and piperidine rings [61,65,81,93].

Among the derivatives of the bicyclic compounds considered here, only the quaternary ammonium salts proved to be active. The dimethiodide of 3-(γ-dimethylaminopropyl)-3-azabicyclo[3,1,0]hexane shows no activity, that of its 6,6-dimethyl homologue is higher, but the highest activity is shown by derivatives of compound (LXXXVI).

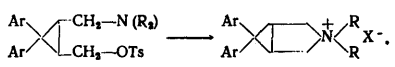
The synthesis of 3-butyl-6,6-ditolyl-3-azabicyclo[3,1,0]-hexane (LXXXIX), involving the reaction of diaryldiazomethane, with *N*-substituted maleimide followed by reduction with lithium aluminium hydride to compound (LXXXIX), was described in 1962. [117]



(LXXXIX)

Similar compounds can be obtained as quaternary salts by the cyclisation of 3-aminoalkyl-1,1-diaryl-2-hydroxy-

methylcyclopropane in the presence of *p*-toluenesulphonyl chloride:



If the tertiary amino-group consists of a piperidine or morpholine residue, spiro-quaternary salts are formed.

Pharmacological study of these compounds showed that the bicyclic imides are inactive; their reduction to the amines results in the appearance of some local anaesthetic and analgesic activity. The quaternary salts are somewhat more active than the tertiary bases, but they are not of practical interest either.

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POLYMERISATION CONCEPTS IN THE CHEMISTRY OF CEMENTS

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1. INTRODUCTION

The chief chemical elements present in cements are silicon, aluminium, oxygen, and calcium. In the inorganic world, silicon exhibits a remarkable ability to form polymeric chains[1]. These include the homochain polymer formed by elementary silicon, and a large number of heterochain polymers, of which the silicic acids and their salts — the silicates — are most widely encountered in nature and also in practical applications[2-8].

Aluminium is a metallic element but the great majority of its oxygen compounds, e.g. compounds such as corundum and hydrargillite, are heterochain polymers[2,9-13].

Oxygen in the polymeric chains formed by various elements acts as a bridge, and only in the peroxides is it capable of forming a homochain, consisting of two atoms[1].

Calcium on the other hand behaves as a cation.

Since the chief elements present in cements are capable of forming inorganic polymer chains, there is every justification for assuming that polymerisation and depolymerisation processes will also take place in the preparation and hardening of cement.

The ideas of Le Châtelier, subsequently developed by many workers, made it possible to understand the basis of the mechanism of the hardening of inorganic binding agents. In most work devoted to this question, the substance taken as standard model was gypsum — a compound which is not polymeric in character. In some cases, macromolecular compounds were also used as models. While drawing the analogy between the mechanisms of the hardening of cement and joiners' glue or silica gel, however, the supporters of the colloid theory (Michaelis and Kühl) saw in these substances only the high degree of dispersion, the high specific surface, and the ability to take part in sorption processes[14,15].

Modern theoretical views on the mechanism of the hydration hardening of cement are based on the concepts of physicochemical mechanics, whose basis principles were developed by Rebinder[16,17].

Work by Bernal[18], Belov and coworkers[19,20], and others established that the products of the hydration hardening of Portland cement contain isolated units of calcium hydrosilicates and compounds containing chains of condensed silicon–oxygen tetrahedra, i.e. polysiloxane chains. The periodicity of the manifestation of binding properties, related to Mendeleev's Table, was established by Zhuravlev[21] and confirmed by Moshchanskii[22].

In an examination of cement and concrete from the viewpoint of the chemistry of macromolecular compounds, Korshak and Mozgova[2] put forward the idea that "cement and concrete contain inorganic silicate polymers". The suggestion that silicate cements be regarded as three-dimensional polymers had been put forward earlier, in