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Advances in the Synthesis of 3,7,9-Heteroanalogues of Bicyclo[3,3,1]nonane

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The heteroanalogues of bicyclo[3,3,1]nonane are of great theoretical and practical interest, which has stimulated synthetic studies in this field. These compounds are used as physiologically active substances and as intermediate in organic synthesis (for example in the synthesis of heteroadamantanes); a heterobicyclononane fragment occurs in the structures of certain alkaloids. The compounds are convenient models for stereochemical and conformational studies.
Despite the very large number of novel studies on the synthesis of compounds of this type, relevant reviews are not available. The present review gives a systematic analysis of typical mechanisms of the synthesis and the synthetic scope of each method and the limits of its applicability are discussed.
The bibliography includes 140 references.

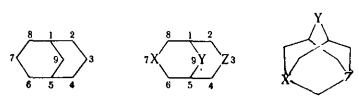
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1. INTRODUCTION

Bicyclic and skeletal compounds are now attracting increased attention owing to their unique physical or chemical properties, which makes them interesting models for the study of theoretical problems in conformational analysis, the mechanisms and the stereochemistry or reactions, the transmission of electronic effects, etc. Heteroanalogues of bicyclic systems are of special interest. The introduction of heteroatoms usually involves the retention of the general geometry characteristic of the parent hydrocarbon but can greatly modify the physical properties or the chemical behaviour of the functional groups. In many cases this leads to an extension of the range of unusual properties, which increases the scope of the application of these compounds both in theoretical studies and for important practical purposes, for example as physiologically active substances. As an example, one can point to studies using heteroanalogues of norbornane [1-4] which is one of the most widely used model compounds in theoretical studies.

This review deals with methods of synthesis of heteroanalogues of one of the bicyclic systems—bicyclo[3,3,1]-nonane (I). Derivatives of this compound are finding many applications both in conformational studies [5-10] and for synthetic purposes [11-14].



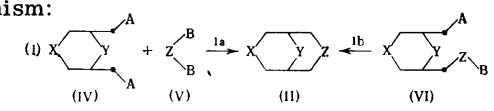
(I) (II) (III)

The methods of synthesis of bicyclo[3,3,1]nonanes are discussed exhaustively in a new review [15] and there is an extremely large literature on the synthesis of heteroanalogues of this series. Here we shall confine ourselves to a discussion of compounds with heteroatoms in the 3-, 7-, and 9-positions [compounds(II)]. Apart from the limited amount of space available, this restriction is based both on the great theoretical importance of heteroanalogues of this type and on their extensive synthetic applications, in particular in the synthesis of adamantane structures of type (III). [11-14,16-18] We may also emphasise that the 3(7)- or 9-azabicyclo[3,3,1]nonane fragment occurs in the structures of many natural alkaloids. For example, 3,7-diazabicyclononane occurs in the skeleton of alkaloids in the plant family *Papilionaceae*: lupanine, sparteine, and anagyrine; the 3-azabicyclononane fragment also occurs in the structure of certain diterpene alkaloids [20]; a series of alkaloids are also based on the 9-azabicyclononane fragment [19,21]. Special mention should also be made of the use of these compounds as physiologically active agents. Thus 3-oxa-9-azabicyclo[3,3,1]nonane and many of its derivatives have a marked effect on cholinergic systems in the organism [22]. Quaternary amino-derivatives of this series exhibit a curare-like activity [22]. Many derivatives of 3,9-diazabicyclononane exhibit similar properties [23]. A number of derivatives of 3-azabicyclononane have ganglion-blocking and hypotensive activities [24,25]. Derivatives of 1,5-diphenyl-3,7-diazabicyclonan-9-one behave as local anaesthetics [26]. Other pharmacological properties of 3,7-diazabicyclo[3,3,1]nonane ("bispidine") are described by Chiavarelly et al. [27]

The available literature data have been classified in this review on the basis of the type of the formal mechanism of synthesis and not on the basis of the type of heteroatoms. This treatment makes it possible to find typical methods of preparation, reveals the genetic relation between structures with different heteroatoms, and permits the most compact systematic account of the data. We may also note that Italian authors have published a review on 3,7-diaza-derivatives covering the literature up to 1968. [27] Therefore, in the discussion of bispidines we shall consider mainly the new literature, selecting from the older studies only those which are fundamentally essential for a systematic description.

2. SYNTHESIS FROM *cis*-1,3-DISUBSTITUTED HETERO-ANALOGUES OF CYCLOHEXANE

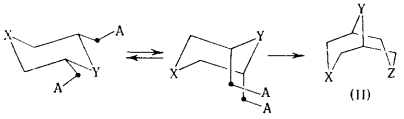
One of the commonest methods of synthesis of hetero-bicyclononanes involves the cyclisation of 1,3-disubstituted cyclohexanes and their heteroanalogues via the following mechanism:



(IV) (V) (II) (VI)

The bicyclic structure can be synthesised either by the interaction of the bifunctional compound (IV) with a suitable reagent (V) [mechanism (1a)] or via intramolecular cyclisation according to mechanism (1b). Possibly the true mechanism of the conversion of compound (IV) into (II) includes the intermediate formation of the derivative (VI). When Z = nitrogen or sulphur, the commonest procedure involves the condensation of a dihalide (IV, A = halogen), di(toluene-p-sulphonate) (IV, A = OTs), or di(methane-sulphonate) (IV, A = OMs) with an amine or sodium sulphide respectively. Although mechanism (1a) has been used to synthesise oxygen-containing compounds (II, Z = O) by the reaction of a dihalide with silver oxide[28], the commonest procedure in this case involves the intramolecular cyclisation of diols (VI, A = ZB = OH) with elimination of the elements of water[29-31].

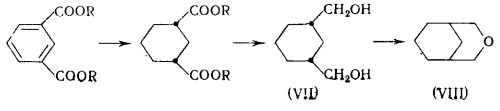
Evidently cyclisation with formation of compound (II) is possible only for *cis*-1,3-disubstituted cyclohexanes in the diaxial conformation:



(II)

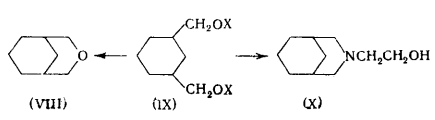
When the size of the substituent is moderate, the *cis*-isomers of 1,3-disubstituted cyclohexane usually assume the diequatorial conformation, becoming more stable in consequence than the equatorial-axial *trans*-isomers. Thus the difference between the free energies of the *cis*- and *trans*-isomers of 1,3-dimethylcyclohexane is 1.96 kcal mole^{-1} at 25°C.[32] Hence the problem of the synthesis of heterobicyclononanes reduces to the synthesis of the *cis*-isomer of a 1,3-disubstituted heteroanalogue of cyclohexane. For this purpose, one must choose either a stereoselective reaction or the mechanism must include a thermodynamically controlled stage, as a result of which the more stable *cis*-isomer predominates.

One of the commonly used reactions is catalytic hydrogenation of 1,3-bifunctional six-membered aromatic systems. Thus hydrogenation of isophthalic acid ester leads to the diol (VII), the dehydration of which yields oxabicyclononane (VIII):[29]



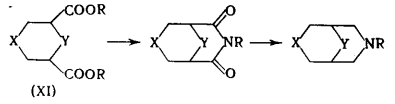
(VII) (VIII)

Catalytic hydrogenation of the ring and reduction of the methoxycarbonyl group can be carried out in stages[33]. The cyclisation has also been achieved by heating the di(methanesulphonate) (IX, X = Ms) with potassium hydroxide[33]:



(VIII) (IX) (X)

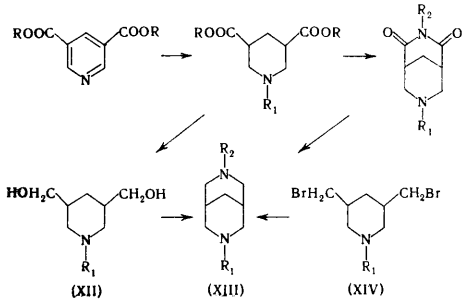
The interaction of the di(toluene-p-sulphonate) (IX, X = Ts) with ethanolamine leads to a derivative of azabicyclononane (X).[34,35] The latter is readily obtained also by the reduction of the imide of hexahydroisophthalic acid (IX, X = Y = CH_2) with lithium aluminium hydride[34]:



(XI)

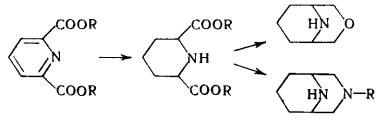
This scheme has been used to synthesise also other heteroanalogues[36-47].

The starting material for the synthesis of bispidines (XIII) may be a pyridine-3,5-dicarboxylic acid ester[12]:

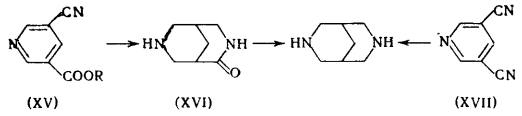


(XII) (XIII) (XIV)

Other versions of this synthesis involve the cyclisation of the dibromide (XIV)[48] or the diol (XII) in the presence of hydrogen bromide[11]. Similarly 3-oxa-9-aza[30] and 3,9-diaza-bicyclononane have been obtained from pyridine-2,6-dicarboxylic acid[46]. The same scheme has been used to synthesise 9-methyl-3,9-diaza-compounds[37]:

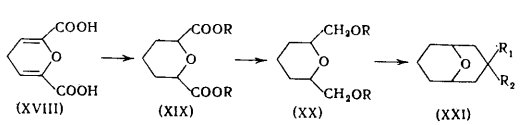


Catalytic hydrogenation of the mononitrile (XV) leads to bispidone (XVI), which is readily reduced to bispidine[49]:



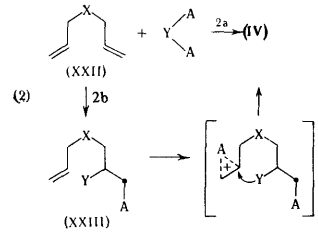
(XV) (XVI) (XVII)

Sometimes the catalytic hydrogenation and cyclisation occur in a single stage. Thus the hydrogenation of the nitrile (XVII) under severe conditions yields bispidine at once[50]. It is readily seen that the catalytic hydrogenation method is restricted mainly to benzene and pyridine derivatives, although instances of the use of other unsaturated systems are known. Thus the reduction of pyrandicarboxylic acid (XVIII) to the tetrahydro-compound (XIX, R = H) with subsequent reduction of the ester leads to the diol (XX, R = H) with the *cis*-configuration. Tosylation of the diol followed by treatment with sodiomalonic ester leads to the oxa-derivative (XXI).[51] However, we may note that 9-oxa-derivatives are more conveniently obtained from cyclo-octadiene (see below).



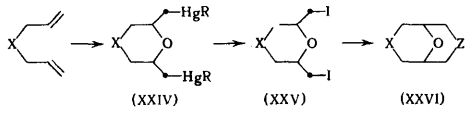
(XVIII) (XIX) (XX) (XXI)

Another general method of synthesis involves the formation of a *cis*-1,3-disubstituted cyclohexane fragment from acyclic 1,6-diene systems of type (XII) via mechanism (2):



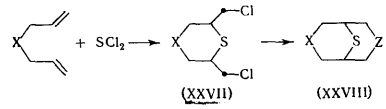
The reaction of electrophilic agents with dienes of this type can involve both double bonds [mechanism (2a)]. Another version of this process may be the addition of an electrophilic agent to one double bond with formation of the intermediate (XXIII), the functional group Y of which is capable of nucleophilic attack on the intermediate 'onium ion in the second stage of the electrophilic addition [mechanism (2b)]. Thus the second stage may be regarded as coupled addition to a multiple bond. The wide variety of electrophilic agents, the possibility of varying the heteroatom in the initial diene system, and the ease of varying the heteroatom in the last stage of the cyclisation of the 1,3-disubstituted heteroanalogue of cyclohexane make this method very convenient for the synthesis of different 3,7,9-heterobicyclononanes.

The easily available diallyl ether, diallyl sulphide, or diallylamine can be used as the diene components. The choice of the electrophilic agent is restricted by the following requirements. Firstly, it must be capable of cyclisation via two bonds and therefore the number of the usual addition products must be reduced to a minimum. Normally this condition is fulfilled by relatively weak electrophilic agents (mercury salts, sulphur dichloride). Secondly, an intermediate (XXIII) must be obtained, in which the Y group must be capable of further nucleophilic reaction or at any rate can be easily transformed into such a group. Both requirements are satisfied by the hydroxymercuration reaction. Thus hydroxymercuration of diallyl ether [52-54], diallyl sulphide [55], and diallylamine [14] leads to chloromercuri-derivatives of tetrahydropyrans of type (XXIV):



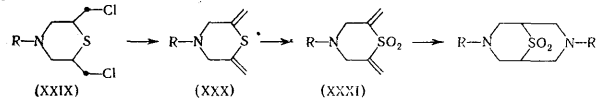
In most cases the reaction is stereoselective and leads to *cis*-isomers, although the presence of *trans*-isomers has also been established in a number of cases [53-55]. Treatment of mercuri-derivatives with iodine converts them smoothly into di-iodides (XXV). Cyclisation of the di-iodide (XXV, X = O) with silver oxide yields 3,7,9-trioxabicyclononane ("Stuehr's ether") [28]. Similarly treatment of compounds of type (XXV) with amines yielded 7-phenyl-3,9-dioxa-7-azabicyclononene (XXVI, X = O, Z = NPh) [53] and a substituted 9-oxabispidine (XXVI, X = NR_1, Z = NR_2). [14] Condensation of compounds of type (XXV) with sodium sulphide gave 9-oxa-3,7-dithia- [55] and 3,9-dioxa-7-thia-bicyclononanes [56] (XXVI, X = Z = S and X = O, Z = S respectively). It is interesting that bis-iodomethyloxathiane (XXV, X = S) reacts smoothly with sodium selenide to form 9-oxa-3-thia-7-selenabicyclononane (XXVI, X = S, Z = Se). [56]

Another widely used reaction involves the addition of sulphur dichloride. The addition of this reagent to diallyl ether [57], diallyl sulphide [57], and diallylamine [58] proceeds with formation of dichlorides of type (XXVII)

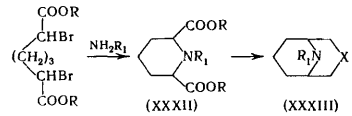


3-Oxa-7-9-dithia-, 3,7,9-trithia-, and 3-phenyl-7,9-dithia-3-azabicyclononanes were obtained by this procedure [56].

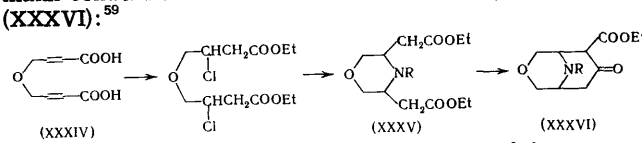
The sulphides formed can be oxidised to the sulphoxides or sulphones [57]. In many cases this permits an alternative type of cyclisation in the last stage, which can be used when the configuration of compound (XXVII) is unfavourable. For example, treatment of the bischloromethyl derivative (XXIX) with alkali yielded the diene (XXX), which was further oxidised to the sulphone (XXXI). The presence of the unsaturated sulphone fragment makes it possible to carry out nucleophilic addition to multiple bonds and thus obtain the sulphone of 3,7-disubstituted 9-thia-3,7-diazabicyclononane [58]:



Another typical reaction leading to bifunctional heteroanalogues of cyclohexane is the cyclisation of 1,5-dihalogeno-derivatives. Thus the reaction of the 2,6-dibromomopimelic ester with amines yields piperidines (XXXII), which have been used to synthesise 3,9-diaza- (XXXIII, X = NR_2) [43] and 3-oxa-9-aza-bicyclononanes (XXXIII, X = O): [31]

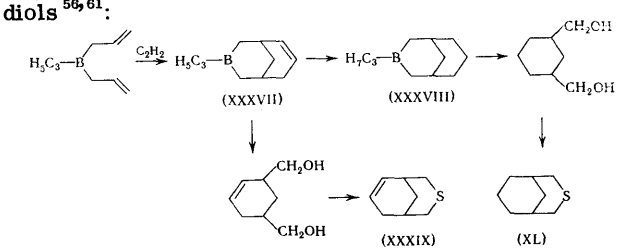


The addition of hydrogen chloride to the unsaturated acid (XXXIV) and subsequent cyclisation give rise to morpholine (XXXV). The latter was subjected to Dieckmann condensation with formation of the bicyclic ketoacid (XXXVI): [59]

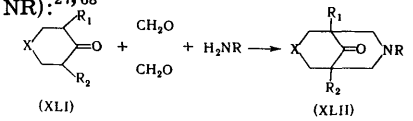


The synthesis of *cis*-1,3-disubstituted cyclohexanes from borabicyclic compounds is extremely interesting and promising. Triallylboron condenses with acetylene to give a high yield of borabicyclononene (XXXVII). [60] The latter can be converted into the saturated analogue (XXXVIII). In turn, these compounds can also be converted into *cis*-diols by the usual hydroboration method.

The 3-thiabicyclononene (XXXIX) and 3-thiabicyclononane (XL) have been obtained by the reaction of sodium sulphide with the di(toluene-*p*-sulphonates) of these diols [56, 61]:

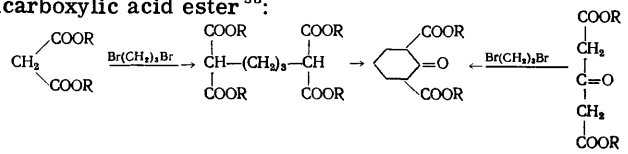


One of the typical reactions employed in the synthesis of bicyclononane structures is the Mannich condensation. With the cyclohexanones (XLI, X = CH_2), the reaction leads to 3-azabicyclononanes (XLII, X = CH_2).[38,62-67] The interaction of piperidinones (XLI, X = NR) with formaldehyde and amines results in the formation of bispidines (XLII, X = NR):[27,68]

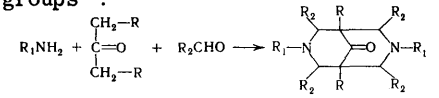


(XLI) (XLII)

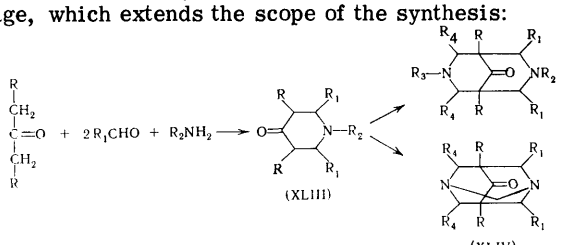
Usually R_1 and R_2 are ethoxycarbonyl groups[62,63,67,68], although the reaction takes place also when $R_1 = R_2 = H$.[65] The carboxy-groups in the aminoketone (XLII, $R_1 = R_2$ = COOH) can be readily removed by acid hydrolysis[38,63]. The corresponding diethoxycarbonylcyclohexanone can be obtained from β-dicarbonyl compounds[38] or from acetonedicarboxylic acid ester[38]:



Bispidines can also be synthesised from ketones with two methylene groups[27]:



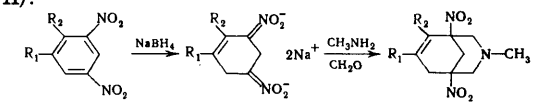
The method permits an extensive variation of the substituent, since the reaction can be carried out in stages with isolation of the intermediate monocyclic compound (XLIII). Then another aldehyde can be employed in the second stage, which extends the scope of the synthesis:



(XLIII) (XLIV)

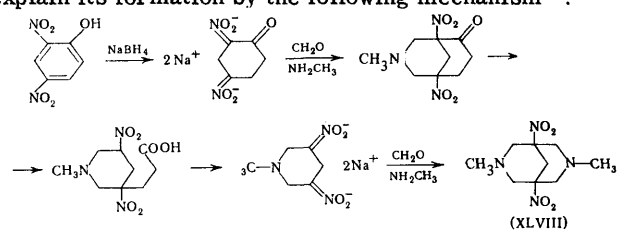
In many cases the reaction product is a compound of type (XLIV) with an adamantane structure, which can be reconverted into a bicyclic compound[69-72].

An interesting method for the synthesis of 3-azabicyclononanes is based on the use of *m*-dinitrobenzenes. The reduction of the latter leads to compounds (XLVI), the Mannich condensation of which yields the aza-derivatives (XLVII):[73-75]



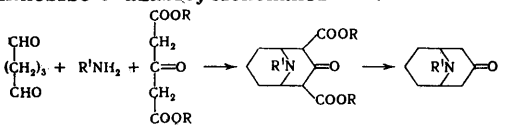
(XLV) (XLVI) (XLVII)

It is interesting that the dinitrophenol (XLV, R_1 = H, R_2 = OH) gives rise under these conditions to an anomalous product—the dinitrobispidine (XLVIII). The authors explain its formation by the following mechanism[75]:

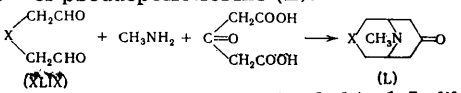


(XLVIII)

The Robinson–Schopf condensation can be used extensively to synthesise 9-azabicyclononanes[76,77]:

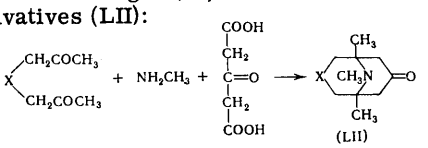


We may note that the synthesis of N-methyl-9-azabicyclo[3,3,1]nonan-3-one ("pseudopelletierine") plays an important role in the determination of the structure of cyclo-octatetraene[78,79]. This reaction makes it possible to vary the substituents, is convenient for preparative purposes, and usually takes place with a high yield[13,80-87]. It can be extended to glutaraldehydes with functional substituents, for example 3-phenyl[83] or 3-ethoxy-derivatives[13]. Heteroanalogues of glutaraldehyde (XLIX) have also been used in this reaction, which permitted the synthesis of thia-,[88,89] oxa-,[89] selena-,[88] and *N*-methylaza-analogues[88] of pseudopelletierine (L):



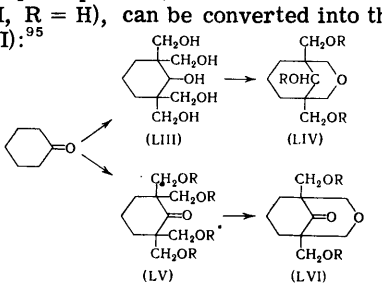
(XLIX) (L)

Recently this condensation was extended to 1,5-diketones[90]. Thus the condensation of heptane-2,6-dione (LI, X = CH_2) and its 4-thia-analogue (LI, X = S) leads smoothly to the aza-derivatives (LII):



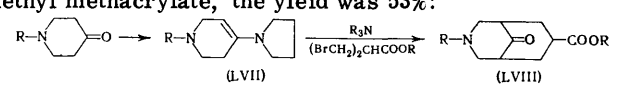
(LII)

As early as 1891, Tollens showed that the condensation of aliphatic aldehydes and ketones with formaldehyde in the presence of calcium oxide yields polyhydric alcohols[91]. Under these conditions, cyclohexanone forms the pentahydric alcohol (LIII),[92] which is dehydrated by hydrogen chloride to form the cyclic ether (LIV, R = H).[92,93] Treatment with acetic acid yields the acetate (LIV, R = Ac).[94] When the condensation is carried out under milder conditions, the carbonyl group is not involved and the tetra(toluene-*p*-sulphonate) obtained from the tetrahydric alcohol (LVI, R = H), can be converted into the cyclic product (LVI):[95]



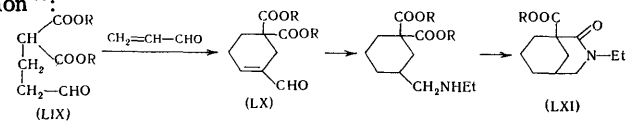
(LIII) (LIV) (LV) (LVI)

In synthetic studies on steroids, it was found that the concentration of unsaturated ketones and cyclic ketones and diketones can proceed via the intermediate formation of compounds with the bicyclo[3,3,1]nonane skeleton[96]. Similarly cyclisation of enamines of cyclic ketones with unsaturated carbonyl compounds or β-halogenocarbonyl compounds likewise constitutes a general method of synthesising bicyclononanes[15]. These reactions can be achieved also when the initial compounds contain heteroatoms. Thus the aza-compound (LVIII) was obtained in 80% yield from the enamine (LVII) by condensation with ββ-dibromoisobutyrate[97]. In the reaction with β-bromomethyl methacrylate, the yield was 53%:[97]



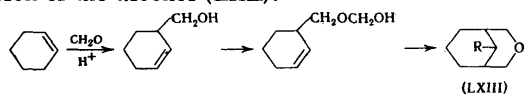
(LVII) (LVIII)

The reaction with acrolein proceeds similarly [98]. An example of the condensation of an unsaturated aldehyde with an aliphatic carbonyl compound leading to a cyclic product is the interaction of the diethoxycarbonylaldehyde (LIX) with acrolein. The resulting unsaturated aldehyde (LX) cyclises to the lactam (LXI) after reductive amination [99]:



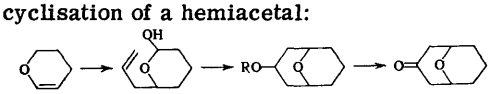
(LIX) (LX) (LXI)

The reaction of formaldehyde with cyclic olefins (the Prins reaction) has found some application in the synthesis of oxygen-containing bicyclononanes. According to Blomquist and Wolinsky [100] and Dolby and Schwarz [101], the formation of substituted 3-oxabicyclononanes from cyclohexane is stereoselective and proceeds via the intermediate formation of the alcohol (LXII):



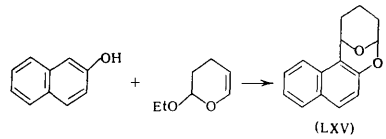
(LXII) (LXIII)

Various substituted oxabicyclononanes of type (LXIII) have been obtained by means of this reaction [100-103]. When the condensation is carried out in the presence of hydrochloric acid, the main product is the *anti*-9-chloro-derivative (LXIII, R = Cl). [104] This chloride is readily reduced to 3-oxabicyclo[3,3,1]nonane [104]. 9-Oxabicyclononane (LXIV) was obtained from dihydropyran by a procedure [105] involving the cyclisation of a hemiacetal:



(LXIV)

Here it is also appropriate to describe the formation of the tricyclic compound (LXV) with the 2,9-dioxabicyclo[3,3,1]-nonane moiety from ethoxydihydropyran and β-naphthol [106]:

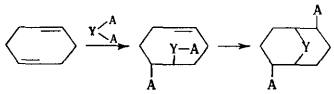


(LXV)

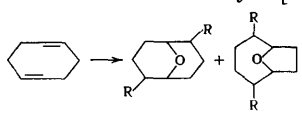
3. SYNTHESIS FROM CYCLO-OCTANE DERIVATIVES

One of the versions of the synthesis of the above bicyclic compounds under consideration involves the cyclisation of compounds which already contain an eight-membered ring in their structure. Such cyclisation can be achieved by electrophilic addition to cyclo-octa-1,5-diene via the following procedure:

(3)



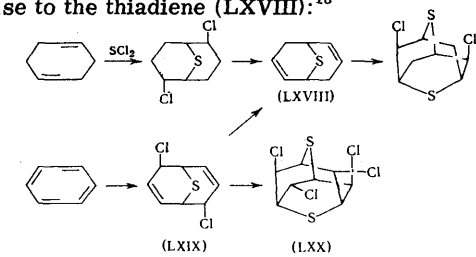
Evidently all the remarks made above concerning the addition to the 1,5-diene system are valid also for this type of addition. Indeed the hydroxymercuration reaction readily yields derivatives of 9-oxabicyclo[3,3,1]nonane [107-110]:



(LXVI) (LXVII)

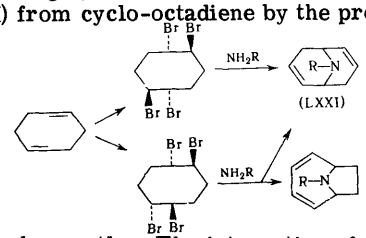
A detailed study of this reaction showed that, together with compounds having the structure of bicyclo[3,3,1]nonane, derivatives of bicyclo[4,2,1]nonane (LXVII) are also formed [108,109]. Their proportions depend sometimes on the reaction conditions, which makes it possible to drive the process towards the preferential formation of compounds of the bicyclo[3,3,1]nonane series (LXVI). [109]

The reaction with sulphur dichloride [111,112] and Se_2Cl_2 (Lautenschlaeger [16]) takes place similarly. It is interesting that cyclo-octatetrane can be introduced into the reaction with SCl_2. [18,113] The reaction can be stopped at the stage of the diene (LXIX), the subsequent interaction of which with a second mole of SCl_2 yields dithia-adamantane (LXX). The reduction of the dichloride (LXIX) gives rise to the thiadiene (LXVIII): [18]



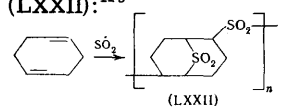
(LXVIII) (LXIX) (LXX)

An interesting synthesis of 9-azabicyclononane-2,6-diene (LXXI) from cyclo-octadiene by the procedure [114]



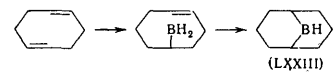
(LXXI)

was described recently. The interaction of cyclo-octa-1,5-diene with sulphur dioxide in the presence of radical initiators takes place in an interesting way. The reaction product is a polymer, the structural unit of which is a bicyclic sulphone (LXXII): [115]



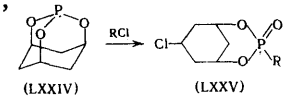
(LXXII)

Evidently the range of electrophilic agents which react according to this mechanism can be extended. For example, it is known that diborane reacts with cyclo-octadiene to form 9-borabicyclononane (LXXIII) [116]:



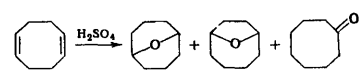
(LXXIII)

Probably one can select conditions for the synthesis of other organic derivatives of the elements using suitable selenium, phosphorus, etc. compounds as electrophilic agents. We may note that bicyclic phosphonates of type (LXXV), which are formed by the Arbuzov reaction between the heteroadamantane (LXXIV) and an alkyl chloride [117],

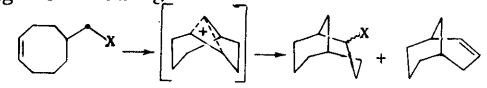


(LXXIV) (LXXV)

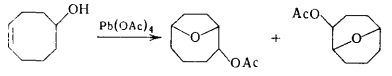
have been described. The interaction of cyclo-octadiene with sulphuric acid can also be included among reactions of this type [118]:



A second set of reactions includes transannular processes in eight-membered rings, for example those involving the following mechanism:

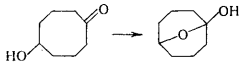


We shall not consider the mechanism of these reactions, which has been dealt with fairly thoroughly in the literature [119–122], and shall discuss the synthetic aspect of the problem. These reactions are usually employed to synthesise 9-oxa-derivatives. Thus cyclisation of the unsaturated alcohol (LXXVI) lead tetra-acetate yields smoothly the bicyclic compounds (LXXVII) and (LXXVIII):[123]

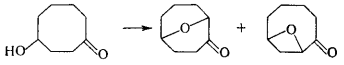


(LXXVI) (LXXVII) (LXXVIII)

According to Cope et al. [108], 5-hydroxycyclo-octanone exists in the hemiacetal form:

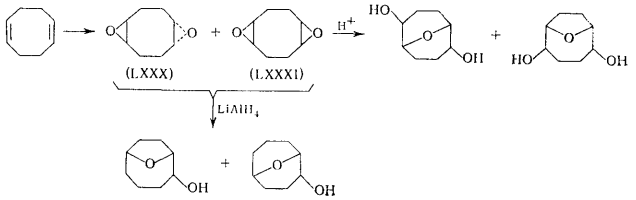


A transannular reaction was observed when the hydroxyketone (LXXIX) was brominated and the crude product was treated with potassium hydroxide [108]:



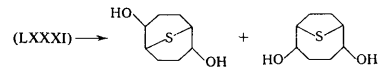
(LXXIX)

The formation of derivatives of isomeric bicyclononanes as a result of ring opening in the epoxides (LXXX) and (LXXXI) [124] belongs to reactions of the same type:

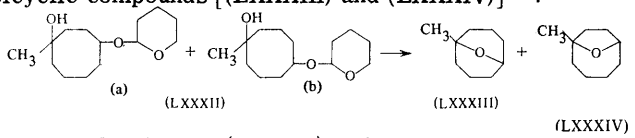


(LXXX) (LXXXI)

When the *cis*-diepoxide (LXXXI) is treated with sodium sulphide, a 9-thia-derivative is formed [124]:

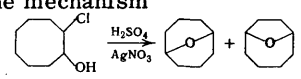


On treatment with acid, a mixture of cyclic tetrahydropyranyl ethers (LXXXII, a and b) also give a mixture of bicyclic compounds [(LXXXIII) and (LXXXIV)] [125]:



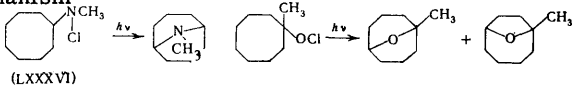
(a) (LXXXII) (b) (LXXXIII) (LXXXIV)

The chlorohydrin (LXXXV) undergoes transannular cyclisation via the mechanism [126]



(LXXXV)

Chloroamines are known to be cyclised under the influence of sulphuric acid or on heating into cyclic amines [127]. Similarly irradiation of the chloroamine (LXXXVI) is accompanied by transannular cyclisation according to the mechanism [128]

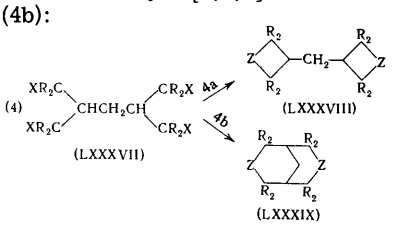


(LXXXVI)

A similar transannular rearrangement is observed for 1-methylcyclo-octyl hypochlorite [125]. There is no doubt that photochemical transannular cyclisation is extremely promising.

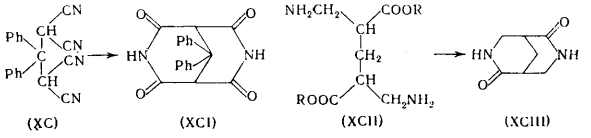
4. SYNTHESIS FROM 1,1,3,3-TETRASUBSTITUTED PROPANES

Symmetrical 1,1,3,3-tetrasubstituted propanes (LXXXVII) can be converted into bicyclo[3,3,1]nonanes (LXXXIX) via mechanism (4b):



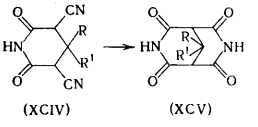
(LXXXVII) (LXXXVIII) (LXXXIX)

However, the cyclisation can also follow the alternative mechanism (4a) with formation of cyclobutane derivatives (LXXXVIII). The relative contributions by these two mechanisms depend on the type of reaction. Thus the cyclisation of the tetra(toluene-*p*-sulphonate) of 2,4-di-(hydroxymethyl)pentane-1,5-diol (LXXXVII, R = H, X = OTs) by reaction with disodiomalonic ester proceeds via mechanism (4a) with formation of the tetraester [(LXXXVIII), Z = C(COOR')$_2$]. [129] On the other hand, acid hydrolysis of the tetranitrile (XC) leads to the diimide (XCI), which has a bicyclononane skeleton [130]:



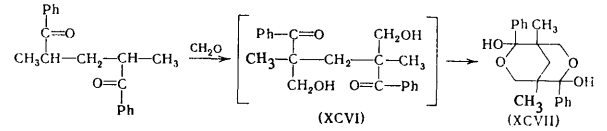
(XC) (XCI) (XCII) (XCIII)

The formation of the dilactam (XCIII) from the bis-aminoester (XCII) proceeds similarly [131]. In these cases the cyclisation can probably be carried out in stages. At any rate, acid hydrolysis of the dinitrile (XCIV) also yields compound (XCV) with a bispidine structure [132–134]:



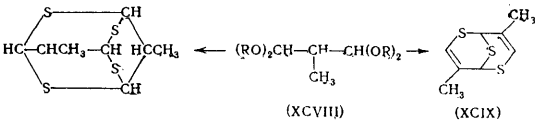
(XCIV) (XCV)

The cyclisation of the intermediate ketol (XCVI), leading to the formation of a derivative of 3,7-dioxabicyclononanediol (XCVII), takes place in a similar manner [135]:



(XCVI) (XCVII)

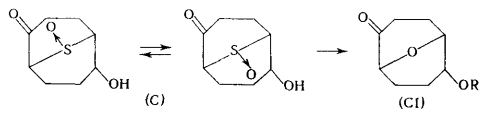
In the synthesis of tetrathia-adamantane from the diacetal (XCVIII) and hydrogen sulphide, the diene (XCIX) is formed as a side product [136]:



(XCVIII) (XCIX)

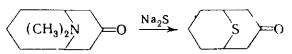
5. SPECIAL METHODS OF SYNTHESIS

In conclusion we shall describe several unique reactions involving changes in the heteroatoms in the bicyclic system under consideration. Thus the β-ketosulphoxide (C) is converted into the 9-oxa-derivative (CI) on irradiation [137]:



(C) (CI)

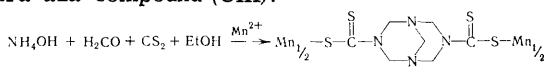
The reaction of pseudopelletierine methiodide (CII) with sodium sulphide, which leads to a smooth replacement of the heteroatom, is very interesting [138,139]:



(CII)

It is possible to put forward several versions of the mechanism of this reaction, in particular an elimination–addition mechanism; however, it would be interesting to make an experimental study of this problem.

Examples of polycondensations leading to structures with a bicyclononane skeleton are known. For example, the reaction of formaldehyde with ammonia and carbon bisulphide in the presence of manganese(II) sulphate yields the tetra-aza-compound (CIII):[140]



(CIII)

The mechanism of this condensation is not known in detail and it maybe that the reaction involves one of the mechanisms described above.

---o0o---

The foregoing data show that synthetic methods leading to heteroanalogues of bicyclo[3,3,1]nonane are fairly varied and include many procedures of preparative organic chemistry. It is quite evident that in future one may expect an increase in the number of studies in this field in view of the practical importance of compounds of this series and the enormous advances in the development of synthetic methods in general. The development of methods in the chemistry of organic derivatives of the elements gives rise to the self-evident possibility of extending the range of heteroatoms in this bicyclic system. The appearance of many new reactions involving coupled addition to a multiple bond greatly extends the scope of the heterocyclisation of diene systems. Finally, the new photochemical reactions which have been developed are also promising for the synthesis of heterobicyclononanes.

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