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Advances in the Synthesis of Heteroadamantanes

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Typical formal schemes for the synthesis of heteroadamantane structures and the limits of applicability and synthetic scope of various methods are discussed and described systematically.
The bibliography includes 207 references.

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I. INTRODUCTION

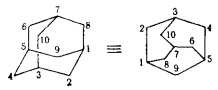
More than 1000 publications have been devoted to the synthesis and study of the properties of adamantane and its derivatives and their number has been continuously increasing. Such persistent interest by chemists is due to a set of unique properties of compounds of the adamantane series, which makes this class interesting from both theoretical and practical points of view. A large number of reviews have been devoted to the chemistry of adamantane, some of which are concerned only with synthetic aspects[1-4], while others deal more or less completely with the entire set of problems in the chemistry of adamantanes and their practical applications[5,6]. Heteroanalogues of adamantane constitute an important class of compounds. There are two reviews on heteroadamantanes covering the literature up to 1961, but these are to a large extent obsolete[1,4]. Although other reviews[7,8] were published later (partly covering the literature up to 1967), they are insufficiently complete. There has been recently a considerable growth of the number of publications dealing with the synthesis of heteroadamantanes and the search for novel methods of synthesising them and with the study of the chemical properties of the products[9-17]. Studies concerned with theoretical problems, which are solved using heteroadamantanes as model compounds, are being published systematically[18-22]. Bearing in mind also the great practical value[23-26] and physiological activity[27-42] of these compounds, it is useful to survey the new advances in this branch of synthetic organic chemistry.

We classified the literature data on the basis of the formal synthetic schemes rather than the type of heteroatoms. Such treatment makes it possible to discuss simultaneously the synthesis of adamantane heteroanalogues containing various heteroatoms and thus find the genetic relation between these structures. An undoubted advantage of this type of arrangement of data is the possibility of using a formal scheme for the synthesis of heteroadamantane which have not yet been described, containing, for example, rarely encountered heteroatoms.

II. FORMAL SCHEMES FOR THE SYNTHESIS OF HETEROADAMANTANE STRUCTURES

The formal schemes for the synthesis of adamantane heteroanalogues can be divided into several types: (1) synthesis from bicyclic structures; (2) synthesis from monocyclic structures; (3) synthesis from acyclic structures. Furthermore, methods of synthesis based on the transformation of the skeletons of other polycyclic skeletal structures constitute a class on its own to some extent. The data in this review are classified in accordance with these types.

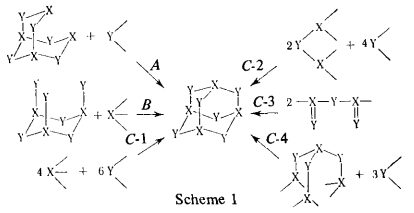
A few words must be said about the nomenclature of heteroadamantanes. According to IUPAC rules[43], the atoms of the adamantane skeleton should be numbered in a sequence such that the heteroatoms have the lowest possible numbers. The general numbering of the skeleton is the same as that adopted for adamantane itself[44,45]. When several heteroatoms of different types are present, the numbering sequence must be as follows: O, S, SE, N, P,..., Si, Ge,...



When typical synthetic schemes are considered, one must bear in mind the following characteristic of heteroadamantane structures: tervalent and quadrivalent atoms (boron, nitrogen, phosphorus, and silicon) can occupy any position in the adamantane nucleus, while bivalent atoms (oxygen and sulphur) are known *a priori* to be incapable of occupying bridgehead positions. Before oxygen or sulphur can occupy the 1-, 3-, 5-, and 7-bridgehead positions in the adamantane structure, they must be converted into the onium state. For this reason, the introduction of a heteroatom into a bridgehead position is usually fairly specific, while the methods for the introduction of heteroatoms into the 2-, 4-, etc., positions in the adamantane skeleton have much in common.

The most convenient and most frequently employed starting materials for the synthesis of the adamantane skeleton are derivatives of bicyclo[3,3,1]nonane (pathway *A*). The availability of compounds of this series[46,47] and the possibility of extensive modification of the substituents and reactive groups makes this synthetic pathway extremely promising. The method of synthesis from monocylic fragments (pathway *B*) is less general and reduces mainly to the synthesis of adamantanes with heteroatoms in the 1-, 2-, 9-, and 10-positions. Finally, there is a whole series of synthetic approaches to

heteroadamantanes based on the condensation of aliphatic compounds (pathways *C*-1–*C*-4). All these variants are presented in Scheme 1.



Scheme 1

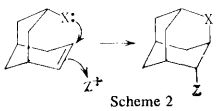
The synthetic pathways *C*-1–*C*-4 can include the formation of mono- or bi-functional compounds at intermediate stages. However, in the present review we shall not consider the detailed mechanisms of such condensations. This would be fairly difficult because their mechanisms are so far unknown in most instances and furthermore a formal treatment makes it possible to give a systematic account of data on the basis of the types of initial structures employed. Such treatment significantly facilitates the search for synthetic pathways to new heteroadamantane structures regardless of the type of heteroatom.

III. SYNTHESIS OF HETEROADAMANTANES FROM BICYCLO[3,3,1]NONANE SYSTEMS

The greatest number of heterocylic systems having the adamantane structure have been synthesised from bicyclo-[3,3,1]-nonane derivatives. This synthetic pathway may be difficult because the synthesis of the initial bicyclic structures is in many cases fairly laborious.

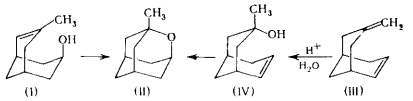
1. Synthesis Involving Multiple Bonds in the Ring

When the bicyclo[3,3,1]non-2-ene molecule contains a functional group in the *endo*-7-position, intramolecular cyclisation via Scheme 2 is possible in principle:



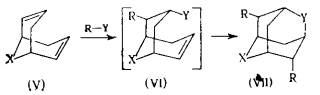
Scheme 2

By virtue of steric factors, cyclisation of this type should occur extremely readily and the problem reduces to modifications of the method for the introduction of a double bond or a functional group into the ring or to the synthesis of the bicyclononane skeleton itself. However, examples of cyclisations of this kind are so far known only for adamantane itself[48,49] and for homoadamantane heteroanalogues[50–53]. A characteristic example of reactions of this type is the cyclisation of 7-hydroxy-3-methylbicyclo[3,3,1]non-2-ene (I) to 1-methyl-2-oxa-adamantane (II) in an acid medium[54,55]:



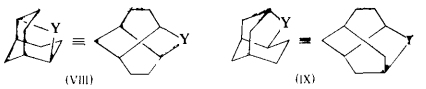
The ring closure of the diene (III) to a tricyclic system should be included in the same type of cyclisation, since oxa-adamantane (II) is formed in an acid medium via compound (IV).[56]

One of the commonest procedures for the introduction of a heteroatom involves electrophilic addition to multiple bonds in the bicyclo[3,3,1]nona-2,6-diene system via Scheme 3:



Scheme 3

In practice the reaction product is always a derivative of the adamantane structure (VII) and the intermediate monofunctional derivative of type (VI) cannot be isolated. The reaction is sometimes accompanied by the formation of twistane (VIII) and isoadamantane (IX) derivates[57]:



The initial diene structure of type (V) is usually synthesised by a method involving the transformation of the functional groups of 3,7- and 2,6-disubstituted bicyclononane derivatives. Dehydrohalogenation[58–60] or dehydration[61] reactions as well as the formation of enol or enamine derivatives from diketones[62,63] are most frequently used. Electrophilic addition to the diene (V) in water proceeds via a mixed addition mechanism and leads to 4,8-disubstituted derivatives (VII). A whole series of mono- and diheteroadamantanes, listed in Table 1, have been obtained on the basis of this reaction. The reaction of the diene (V) with sulphur dichloride proceeds via the same electrophilic addition mechanism. When the 2,6-disubstituted diene (X) is treated with sulphur dichloride, 4,8-dioxo-2-thia-adamantane (XI) is formed. It has been used as the starting material for the preparation of a series of 2-thia-adamantane derivatives[19,64,65]:

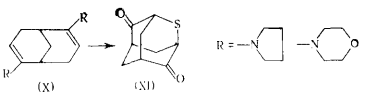
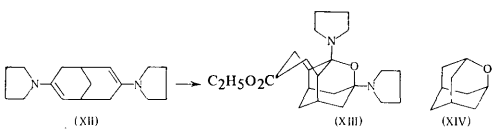


Table 1. 4,8-Disubstituted 2,6-diheteroadamantanes of type (VII) synthesised from bicyclo[3,3,1]nona-2,6-diene (V)

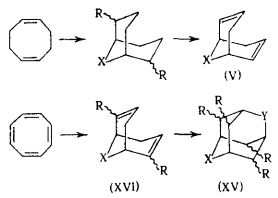
X	Y	R	R′	References
CH_2	O	HgOAc, HgI, HgCl, I, Br, OH, H	—	58, 61, 72
CH_2	N—R′	Br, H	H, CH_3, Tos	64, 73–75
CH_2	S	H, OH, Br, Cl, $=CH_2$, $=O$	—	58, 64
O	N—R′	Br, H	H, Tos	60, 64, 74, 75
O	O	HgOAc, HgI, HgCl, I, Br, H	—	59, 76, 77
O	S, SO_2	Cl, H, OCH_3, OH, OAc	—	57, 59, 76
S	S	Cl, OCH_3, H	—	78
S	Se	Cl	—	69
N—R′	S, O	Cl, Br, H, OH, OAc	$C_6H_5SO_2$, Tos, H, $CO_2C_2H_5$, CHO, CH_3	60, 64, 74, 79

The condensation of the bisenamine (XII) with ethyl bromomethylacrylate leads to the pentacyclic structure (XIII), which is based on the 2-oxa-adamantane skeleton[63]:



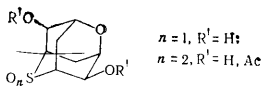
It is noteworthy that the hydration of the diene (V, X = CH_2) with sulphuric acid gives the unsubstituted 2-oxa-adamantane (XIV) in 26% yield[59]. The formation of the dioxa-adamantane (VII, X = Y = O, R = H) as a side product in the synthesis of 2,7-dioxatwistane from 9-oxabicyclo[3,3,1]nonane-2,6-diol has been explained by the same reaction of the diene (V, X = O) with sulphuric acid[66].

The synthesis of 2,6-diheteroadamantanes is based on bicyclic dienes (V) with the heteroatom in the 9-position as the starting compounds. A convenient version of the synthesis of the latter involves reactions based on unsaturated cyclo-octane derivatives via Scheme 4:

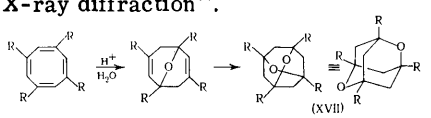


Scheme 4

When cyclo-octatetraene was treated twice with sulphur dichloride, tetrachlorodithia-adamantane (XV, X = Y = S, R = Cl) was obtained[67,68] and the addition of selenium monochloride to the dichlorothia-derivative (XVI, X = S, R = Cl) leads to the thiaselena-adamantane (XV, X = S, Y = Se, R = Cl).[69] A detailed study of the ^1H NMR spectra of oxide derivatives of 2-oxa-6-thia-adamantane (XVII, X = SO_n, Y = O, R = OR')[78] and also of heteroadamantanes of type (VII, X = O, Y = O or N-Tos; X = N-Tos, Y = CH_2, O, or N-Tos),[61,74] synthesised from *cis, cis*-cyclo-octa-1,5-diene, showed that the elementary stage is *trans*-addition, which determines the configuration of the substituted heteroadamantanes obtained:

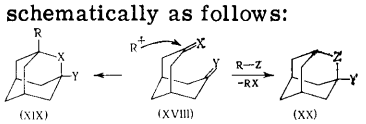


Treatment of 1,3,5,7-tetra-alkoxycyclo-octatetraene with alcohol containing a small amount of hydrogen chloride leads to the formation of 1,3,5,7-tetra-alkoxy-2,6-dioxa-adamantane (XVII),[70] the structure of which was demonstrated by X-ray diffraction[71].



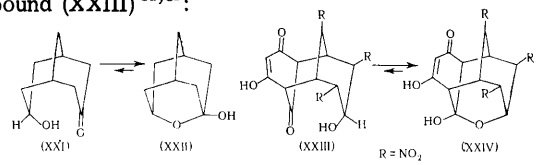
2. Condensation Involving Exocyclic Multiple Bonds

This type of formation of heteroadamantane systems can be represented schematically as follows:



Scheme 5

The basic idea of this scheme consists of the intermediate formation of *endo*-functional derivatives capable of an intramolecular reaction via the second multiple bond. The tendency towards intramolecular cyclisation is also caused by the steric proximity of the fragments at $C_{(3)}$ and $C_{(7)}$. For example, we may note that the ketoalcohol (XXI) exists in the hemiacetal form (XXII).[80] This is true also for more complex polycylic structures. For example, the derivative of 2-oxa-adamantane (XXIV) is the hemiacetal form of compound (XXIII)[81,83]:

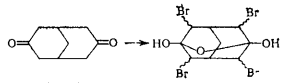


Bicyclononane derivatives with exocylic multiple bonds in the 3- and 7-positions, as in compound (XVIII, X = O or CH_2, Y = O or CH_2), are the most convenient starting compounds for condensations of this type. The difficulty of the method arises from the laborious synthesis of the initial bicyclic structures, which are obtained mainly by the cleavage of the adamantane skeleton[83-87]. A series of 2-oxa- and 2-aza-adamantanes (XIX), listed in Table 2, have been obtained from bicyclic derivatives (XVIII) via Scheme 5.

Table 2. 1,3-Disubstituted 2-heteroadamantanes of type (XIX) synthesised from unsaturated bicyclic compounds (XVIII).

(XVIII)		(XIX)				References
X	Y	X	Y	R	R'	
O	O	O, N—R'	OH, Cl	CH_3, C_6H_5	H, CH_3, Tos, C_6H_5CO	62, 80, 87, 88
O	CH_2	O	CH_3, C_6H_5, CH_2R'	H, OH	HgOAc, I	88–90
O	N—R'	O, N—R'	OH, NHR'	—	H, O ‖ $NHCNHSO_2C_6H_4R'$	89, 90
N—OH	N—OH	N—H	NH_2, OH	—	—	87
O	CHOH	O	CH_3	—	—	91

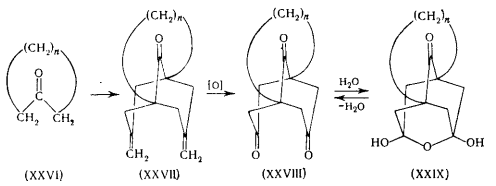
Bromination of the diketone (XVIII, X = Y = O) in acetic acid with four equivalents of bromine yields 4a, 8a, 9a, 10a-tetrabromo-1,3-dihydroxy-2-oxa-adamantane (XXV). On the other hand, bromination with 4.5 equivalents of trimethylphenylammonium tribromide in CH_2Cl_2 leads to a mixture of 4e, 8e, 9a, 10a-tetrabromo-derivative (XXV) and 2,6-dibromotriasterane-3,7-dione, which are separated chromatographically[92]. The authors assume that the oxa-adamantane system is formed via a tetrabromodiketone stage:



The presence of bromine atoms in both positions adjoining the C=O groups can enhance the electrophilic properties of these groups so much that the hydrated forms are stabilised and the latter can subsequently cyclise spontaneously to the oxa-adamantane system.

A study of the condensation of the cycloalkanones (XXVI, n = 9 or 10) and $\alpha\alpha'$-dichloroisobutene demonstrated[93] the formation of a considerable amount of the dimethylene derivative (XXVII). The oxidation of the olefin (XXVII) with potassium permanganate followed by treatment with lead

tetra-acetate gives a 13% yield of the triketone (XXVIII), which is converted into the oxa-adamantane (XXIX):

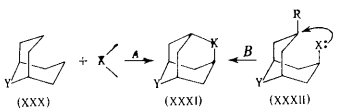


(XXVI) (XXVII) (XXVIII) (XXIX)

The authors concluded that the mobile decamethylene chain not only does not interfere with the formation of the oxa-adamantane system but actually promotes it, since it should favour the double chair conformation in the conformational equilibrium of the bicyclo[3,3,1]nonane system[94].

3. Condensation Without the Involvement of Multiple Bonds and Heteroatoms

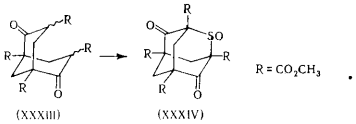
The reactions involving cyclisation to the adamantane structure of initial bicyclo[3,3,1]nonane derivatives without multiple bonds or heteroatoms participating in the formation of a tricyclic system are presented in Scheme 6.



(XXX) (XXXI) (XXXII)

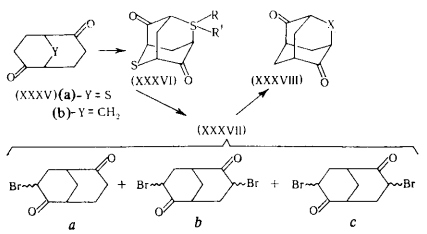
Scheme 6

This scheme (pathway *A*) applies when the so called "Meerwein ester" (XXXIII) reacts with thionyl chloride[62]. This gives rise to a 71% yield of the 2-thia-adamantane system (XXXIV):



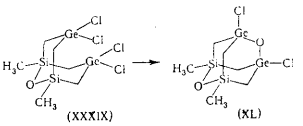
(XXXIII) (XXXIV)

An analogous tricylic system [XXXVI, (RR') = CH_2; R = CH_3, R' = OH or OAc] has been obtained by the reaction of the diketone (XXXVa) with acetic anhydride in a highly acid medium[95]. On bromination with pyridine hydrobromide perbromide, the diketone (XXXVb) gives a mixture of the mono- and di-bromo-derivatives (XXXVII, a–c).[98] On treatment with ammonia in absolute dioxan, 2-aza-adamantane-4,8-dione (XXXVIII, X = NH) was obtained from this mixture of bromo-derivatives:



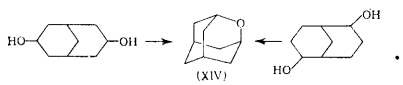
(XXXV)(a)- Y = S (XXXVI) (XXXVIII)
(b)- Y = CH_2
(XXXVII)
a b c

The replacement of ammonia by methylamine leads to the *N*-methyl derivative of 2-aza-adamantane (XXXVIII, X = NCH_3). Reduction of the dibromo-derivative (XXXVIIc) with sodium tetrahydroborate in aqueous alcoholic solutions leads to 2-oxa-adamantane-4,8-diol and, in the presence of catalytic amounts of alkali, to the oxa-adamantane (XXXVIII, X = O).[97] Heteroadamantanes (XL) containing O, Si, and Ge have been obtained via the same pathway *A* by treating the chlorogermane (XXXIX) with water[98]:



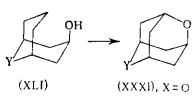
(XXXIX) (XL)

The formation of mono-oxa-adamantane (XIV) from bicyclo[3,3,1]nonane-3,7-diol under the influence of concentrated sulphuric acid is an example of type *B* condensations of bicylic compounds[83,84]. 2-Oxa-adamantane can be obtained by the same pathway from the readily available bicyclo-[3,3,1]nonane-2,6-diol[99,100]. Evidently the formation of 2-oxa-adamantane in the latter case requires a series of hydride shifts:



(XIV)

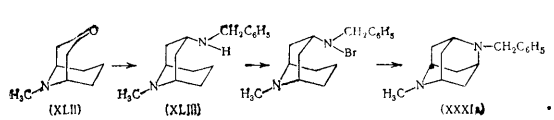
Treatment of the *endo*-alcohol (XLI, Y = CH_2) with lead tetra-acetate in boiling benzene or its oxidation with a mixture of iodine and mercury(II) oxide in carbon tetrachloride give rise to oxa-adamantane (XIV)[101] in yields of 89 and 60% respectively. The *exo*-isomer (XLI, Y = CH_2) is unreactive with respect to lead tetra-acetate and the main product of its oxidation with mercury(II) oxide was the corresponding ketone:



(XLI) (XXXII), X = O

6-Oxa-2-phospha-adamantane (XXXI, X = O, Y = PC_6H_{11}, O ‖ PCH_2PH, or $PPhCH_2$)[102] and 6-oxa-2-aza-adamantane (XXXI, X = O, Y = $NCOCH_3$)[103] skeletons have been obtained by a similar method. The attempts to synthesise the oxa-aza-adamantane system by the cyclisation of the benzylamino-derivative (XLI, Y = NCH_2Ph) have been unsuccessful, while refluxing of the acetamido-derivative (XLI, Y = NCH_3CO) in benzene in the presence of lead tetra-acetate leads smoothly to 6-oxa-2-aza-adamantane (XXXI, X = O, Y = $NCOCH_3$). The same heteroadamantane system (XXXI, X = O, Y = NCH_3) was obtained at 85% yield by the acid cyclisation of 7-ethoxy-*N*-methyl-3α-granatanol (XXXII, X = OH, Y = NCH_3, R = OC_2H_5) with hydrobromic acid[104].

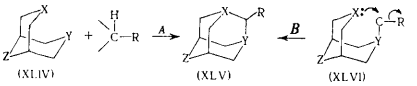
The Hofmann–Löffler reaction was used for the first time in 1973 to synthesise the 2,6-diaza-adamantane system[105]. Reductive amination of the ketone (XLII) in the presence of benzylamine leads to the amine (XLIII), which is converted into the diaza-adamantane derivative (XXXIIa) by subsequent bromination and cyclisation in sulphuric acid:



(XLII) (XLIII) (XXXIIa)

4. Condensations Involving the Heteroatoms of Bicyclo-[3,3,1]nonane Derivatives

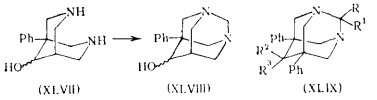
Reactions of this type are used to synthesise mono- and di-heteroadamantanes with heteroatoms in the 1- and 3-positions, which can be represented schematically as follows:



(XLIV) (XLV) (XLVI)

Scheme 7

Reactions of this kind are used most typically in the synthesis of diaza-adamantane systems (pathway *A*). The simplest instance is the condensation of 3,7-diazabicyclo[3,3,1]nonane (bispidine) (XLIV, X = Y = NH, Z = CH_2) with formaldehyde. The problem of the synthesis of the diaza-adamantanes essentially reduces therefore to the problem of the synthesis of bispidine and similar structures. Likewise the condensation of bispidinol (XLVII) with paraformaldehyde in alcohol yields 1,3-diaza-adamantanol (XLVIII)[106]:



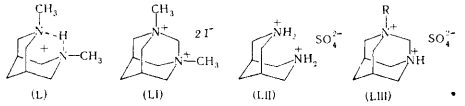
(XLVII) (XLVIII) (XLIX)

When 1,5-diphenylbispidin-9-ol and 1,5-diphenylbispidin-9-one were treated with the corresponding aldehydes or ketones, a series of biologically active 2-substituted diaza-adamantanes of type (XLIX) were obtained[107] (listed in Table 3).

Table 3. 1,3-Diaza-adamantanes (XLIX) obtained by the condensation of bispidine derivatives with formaldehyde[107]

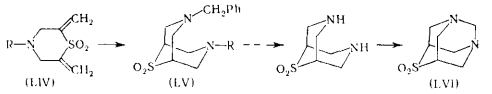
R^2	R^3	R	R^1
H (R^2R^3) = O	OH	H, Me, Et H, Me, Et	Me, Et, Pr, iso-Pr, Ph, *p*-$MeOC_6H_4$, 2-furyl, Me, Et, Pr iso-Pr, Ph, *p*-$MeOC_6H_4$, 2-furyl, 4,3-HO(MeO)C_6H_3

A flattened double chair conformation has been found for *NN'*-dimethylbispidines[108], which promotes the formation of intramolecular hydrogen bonds in salts of bispidine derivatives (for example, perchlorates) and this results in the formation of the adamantane-like structure (L). When *NN'*-dimethylbispidine was treated with methylene iodide, a high yield of diaza-adamantane (LI) was obtained[109]:



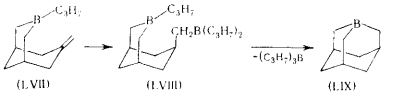
(L) (LI) (LII) (LIII)

Products having a similar structure, i.e. (LIII, R = H or CH_3), are also obtained when bispidine salts (LII) are treated with formaldehyde and formic acid[110]. 6-Oxa-1,3-diaza-adamantane (XLV, X = Y = N, Z = O, R = H) has been synthesised from diallylamine via the intermediate formation of 9-oxabispidine (XLIV, X = Y = NH, Z = O).[111] The reaction of the diallylamide of benzenesulphonic acid with mercury acetate gives rise to the morpholine system, which is converted into 9-oxabispidine on treatment with ammonia. The condensation of the bispidine derivative with paraformaldehyde leads to the oxadiazo-adamantane (XLV, X = Y = N, Z = O, R = H). The 6-thia-1,3-diaza-adamantane system has been synthesised by an analogous sequence of reactions[112]. The reaction of sulphur dichloride with *NN*-diallylbenzenesulphonamide results in cyclisation to the thiomorpholine system (LIV). Similar cyclisation reactions have been described previously[113]. Subsequent interaction with benzylamine leads to the cyclisation of the thiomorpholine system to the thiobispidine system (LV), which is converted in several stages, involving subsequent condensation with formaldehyde, into 6-thia- 1,3-diaza-adamantane (LVI):



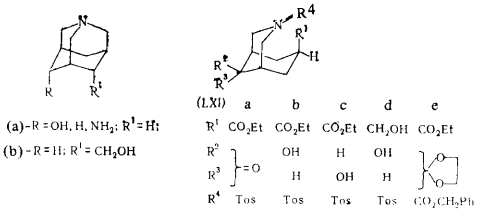
(LIV) (LV) (LVI)

1-Heteroadamantane systems are mainly synthesised via pathway *B* (Scheme 7). Bicyclononane derivatives (XLVI) substituted in the 3- (at the heteroatom) and 7-positions of the bicyclononane molecule are convenient starting materials for this pathway. The synthesis of 1-bora-adamantanes is an example of condensations of this kind. The hydroboration of 7-methylene-3-propyl-3-borobicyclo[3,3,1]nonane (LVII) with tetra-n-propyldiborane leads to compound (LVIII), the cyclisation of which with elimination of 3-propylborane yields 1-bora-adamantane (LIX).[114,115] When compound (LVIII) interacts with pyridine, the pyridine adduct of 1-bora-adamantane is formed[116]. We may note that the geometry of bora-adamantane should simulate the structure of the 1-adamantyl carbonium ion:



(LVII) (LVIII) (LIX)

The starting compound for the synthesis of the aza-adamantane (LXa) is the 3-azabicyclononane derivative (LXI), synthesised by the condensation of ethyl α-bromomethacrylate or its precursor $\beta\beta'$-dibromoisobutyrate with the enamine derived from *N*-toluenesulphonylpiperidin-4-one[117] or other *N*-substituted piperidin-4-ones[118,119]. The reduction of the ketoester (LXIa) with lithium tetrahydroaluminate gives the diol (LXId), which is smoothly detosylated under the influence of a mixture of hydrochloric and acetic acids to give 4-hydroxy-1-aza-adamantane (LX, R = OH). Catalytic hydrogenolysis of the readily available ethylene acetal (LXIe) gives a high yield of 2,6-disubstituted 1-aza-adamantane[118]:



(LX) (a)-R = OH, H, NH_2; R^1 = H;
(b)-R = H; R^1 = CH_2OH

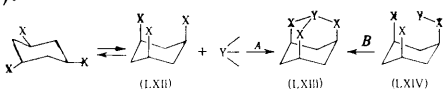
(LXI)

	a	b	c	d	e
R^1	CO_2Et	CO_2Et	CO_2Et	CH_2OH	CO_2Et
R^2	} =O	OH	H	OH	
R^3		H	OH	H	
R^4	Tos	Tos	Tos	Tos	CO_2CH_2Ph

IV. CONDENSATION AND INTRAMOLECULAR CYCLISATION OF *CIS*, *CIS*-1,3,5-TRISUBSTITUTED CYCLOHEXANES

The general scheme for the synthesis of 2,4,10-triheteroadamantanes involves the condensation of *cis*, *cis*-1,3,5-trisubstituted cyclohexanes with compounds containing a fragment Y capable of condensing with three functional groups

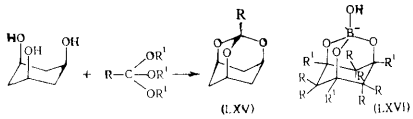
at once to form single bonds in accordance with Scheme 8 (pathway *A*):



Scheme 8

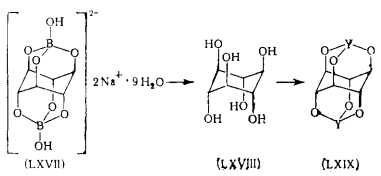
It is possible to suggest a version of the general scheme where the tervalent component is already combined with one of the functional groups, as shown in Scheme 8 (pathway *B*). Possibly in the synthesis of triheteroadamantanes via pathway *A*, stage *B* is included as an intermediate step and the two versions are indistinguishable. However, it is methodologically useful to distinguish pathway *B*, since it is suitable also for the synthesis of 2,4-diheteroadamantanes.

This type of condensation was used for the first time to synthesise the 2,4,10-trioxa-adamantane system (LXIII, X = O, Y = CH).[120] The synthesis involves the esterification of *cis*-phloroglucitol by orthoesters via the mechanism



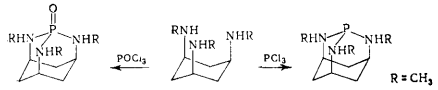
cis-Phloroglucitol has proved to be a very readily available starting compound and is frequently used in similar syntheses[30,31,121-124]. For example, we may note that its condensation with the tetraethyl ester of orthomalonic acid in the presence of boron trichloride yielded 3-ethoxycarbonylmethyl-2,4,10-trioxa-adamantane (LXV, R = $CH_2CO_2C_2H_5$). Using different condensing agents, a series of trisubstituted trioxa-adamantanes (LXV) have been obtained via a similar mechanism[30,31].

This type of condensation is very suitable for the synthesis of 1-hetero-derivatives of 2,4,10-trioxa-adamantane. In particular, *cis*, *cis*-cyclohexane-1,3,5-triols form stable complexes of type (LXVI) on reaction with sodium metaborate[121]. Evidently this type of condensation is analogous to the well known reaction involving the formation of borate complexes of carbohydrates and polyhydroxy-compounds[125]. It is of interest that *trans*-hexahydroxycyclohexane (scyllitol) (LXVIII) forms a borate complex having the diadamantane structure (LXVII). This reaction is used to isolate scyllitol from natural sources. Scyllitol reacts with triethyl orthoformate in dimethyl sulphoxide (DMSO) to form a polymeric intermediate, which can be converted by pyrolysis into hexaoxadiadamantane (LXIX, Y = CH) in 15% yield. The reaction of compound (LXVIII) with trimethyl phosphite in DMSO or hexamethylphosphoramide yielded diadamantane (LXIX, Y = P)[126]:

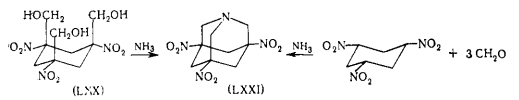


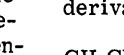
One can also use in this reaction trimethyl phosphate, which reacts with phloroglucitol to give 2,4,10-trioxa-1-phosphaadamantane (LXIII, X = O, Y = P)[122]. The same cyclic system was obtained on treating the *cis*-isomers of cyclohexane-1,3,5-triol derivatives with phosphorus trichloride[121]. The structure of compounds (LXIII, X = O, Y = CH, P, or P=O) has also been studied by ^{1}H NMR.[127-129]

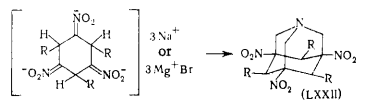
Similarly to the reaction with *cis*-phloroglucitol, the *cis*-isomer of the triamine (LXII, XR = $NHSO_2C_6H_5$, $NHCH_2C_6H_5$, or $NHCH_3$) condensed with orthoformate in the presence of sulphuric acid to a compound with a 2,4,10-triaza-adamantane structure (LXIII, Y = CH, X = $NSO_2C_6H_5$,[130] $NCH_2C_6H_5$, or NCH_3.[131] Treatment of compound (LXII) with phosphoryl chloride or phosphorus trichloride leads to 2,8,9-triaza-1-phospha-adamantane structures (LXIIIa and LXIIIb):[131]



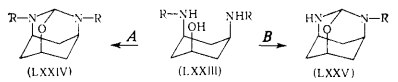
A report[132] of a study of the structure of 1,3,5-trihydroxymethyl-1,3,5-trinitrocyclohexane isomers (LXX) and the synthesis of 3,5,7-trinitro-1-aza-adamantane (LXXI) by the condensation of the triol (LXX) with ammonia in an alkaline medium was published in 1972:

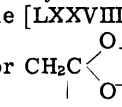


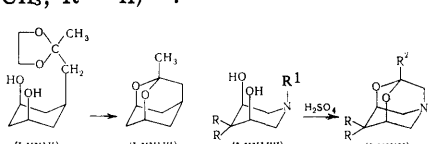
The condensation of 1,3,5-trinitrocyclohexane with ammonia and formaldehyde also led to compound (LXXI). 3,5,7-Trinitro-1-aza-adamantane (LXXI) and a number of its derivatives [LXXII, R = CH_3, C_2H_5, $CH(CH_3)_2$, n-C_4H_9, $CH_2CH(OH)CH_3$, , or ][133] have been obtained by the reduction of 1,3,5-trinitrobenzene with sodium tetrahydroborate or Grignard reagents followed by treatment of the reduction products with formaldehyde and ammonium chloride:



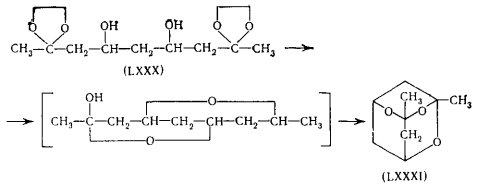
The condensation of the hydroxyamine (LXXIII) with triethylorthoformate leads to the formation of derivatives of 2-oxa-4,10-diaza-adamantane (LXXIV):[134]



The starting compound (LXXIII) is interesting because its *N*-acyl derivative (R = $COCH_3$) can be converted by intramolecular cyclisation into oxadiaza-adamantane (LXXV) (Scheme 8, pathway *B*). This mechanism can also be illustrated by the following example. Treatment of the ethylene ketal (LXXVI) with sulphuric acid leads to 1-methyl-2,6-dioxa-adamantane (LXXVII)[135] and cyclisation of the *N*-substituted 3,5-dihydroxypiperidine [LXXVIII, R = H, or CH_3, R^1 = $CH_2CH(OC_2H_5)_2$, CH_2Ph, or ] under the influence of sulphuric acid yields a derivative of 4,9-dioxa-1-aza-adamantane (LXXIX, R^1 = R^2 = H; R^1 = H, R^2 = CH_3; R^1 = CH_3, R^2 = H)[136]:

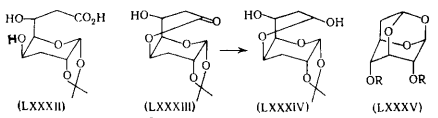


3,5-Dimethyl-2,4,6-trioxa-adamantane (LXXXI) has been obtained by the hydrolysis of the diethylene ketal (LXXX) with a dilute inorganic acid followed by the elimination of water from the non-isolated bicyclohemiketal form[137]:



(LXXX) (LXXXI)

The 2,4,6-trioxa-adamantane system has also been obtained by the intramolecular cyclisation of compound (LXXXIV)[138,139]. On refluxing with molecular sieves in toluene, the ammonium salt of the acid (LXXXII) yields the lactone (LXXXIII), the hemiacetal (LXXXIV) of which is converted into 6-deoxy-*D*-glucodealdoheptose on hydrolysis. 50% of the latter exists in the cyclic trioxa-adamantane form (LXXXV, R = H):

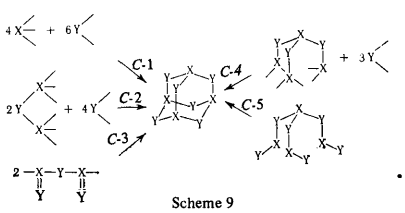


(LXXXII) (LXXXIII) (LXXXIV) (LXXXV)

like *D*-glucuronic acid, 6-deoxy-*D*-glucohepturonic acid is capable of being converted into a lactone[140]. The hemiacetal of this lactone also gives rise to the trioxa-adamantane structure (LXXXV), as shown by ^{1}H NMR.[141,142]

V. SYNTHESIS FROM ACYCLIC COMPOUNDS

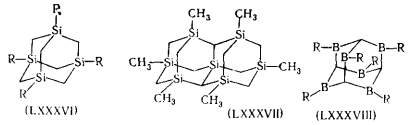
One should note in the first place that almost any heterocyclic system with the adamantane structure can be constructed from acyclic fragments, but the later must contain both atoms capable of occupying the 1-, 3-, 5-, and 7-positions in the adamantane skeleton and bivalent atoms known on *a priori* grounds to be incapable of occupying bridgehead positions. The ratio of the reactants depends on the number of atoms in the initial fragments involved in the construction of the adamantane skeleton. Condensation of this type can therefore be represented by several formal schemes (Scheme 9):



Scheme 9

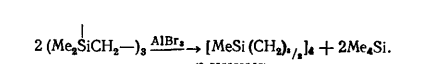
The simplest initial structures are ammonia and formaldehyde (pathway *C*-1). Their condensation was achieved for the first time in 1860 in the synthesis of hexamethylenetetramine (urotropine or 1,3,5,7-tetra-aza-adamantane)[143], to which the adamantane structure was attributed as early as 1895.[144] The methods of synthesis of urotropine derivatives are not considered in this review, since the chemistry of urotropine constitutes an independent field.

The *C*-2 pathway is frequently followed in the synthesis of sila-adamantanes by the pyrolysis of simple halogenosilanes and silanes with carbon-containing substituents. For example the pyrolysis of tetramethylsilane at 650°C led to the isolation of tetramethyltetrasila-adamantane (LXXXVI, R = Me) from a complex mixture of reaction products[145-149]:



(LXXXVI) (LXXXVII) (LXXXVIII)

In addition, compound (LXXXVII)[148,150], the structure of which was demonstrated by ^{1}H NMR, was isolated by chromatography. The yield of the tetrasila-adamantane derivative (LXXXVI, R = Me) increased greatly (sometimes to 80%), when 1,3,5-hexamethyl-1,3,5-trisilacyclohexane was introduced into the reaction[151]:

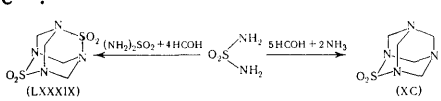


(LXXXVI)

Pyrolysis of chlorotrimethylsilane at 700°C leads to a mixture of compounds ranging from fully chlorinated derivatives (LXXXVI, R = Cl) to fully methylated sila-adamantanes (LXXXVI, R = Me), which can be separated chromatographically[149,152]. The tetrachloro-derivative (LXXXVI) was also obtained from chlorotrimethylsilane and tetrachlorosilane in the presence of aluminium chloride at 500°C but in very low yields[153]. The interaction of carbon-containing silanes incorporating Si–Cl groups with $ZnCl_2$ in organic solvents leads to cyclic fluorinated carbon-containing silanes (LXXXVI, R = F) where all the hydrogen atoms can be replaced by chlorine on photochemical chlorination[154]. Boraadamantanes with a structure of type (LXXXVIII, R = Me) can be obtained via similar reactions on pyrolysis of trimethylboron at 450°C.[155]

Thus pathway *C*-2 is extremely convenient for the synthesis of various tetrasila-adamantanes with structures of type (LXXXVI, R = Cl, Br, or Me) and possibly also structures with heteroatoms such as germanium and tin, when starting compounds having structures containing the $SiCh_2$, CH_2Si, Si_3CH, $GeCH_2$, or $SnCH_2$, etc. fragments are used.

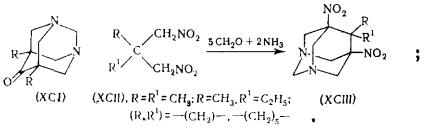
The *C*-3 type of condensation can be illustrated by the synthesis of tetramethylenetetramine disulphone (LXXXIX) on reaction between sulphamide and formaldehyde in proportions of 2 : 4.[156] It is noteworthy that the cyclic disulphone (LXXXIX) is extremely toxic and its action on the central nervous system is five times as potent as that of strychnine[157]:



(LXXXIX) (XC)

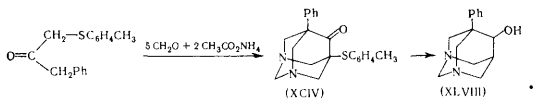
The synthesis of the sulphone (XC) is a kind of combination of pathways *C*-1 and *C*-2 in a single reaction. The condensation of sulphamide, formaldehyde, and ammonia is carried out in an acid medium to give a 90% yield of the sulphone (XC).[158] This type of condensation of acyclic fragments, involved in the construction of the adamantane molecule, constitutes a modified Mannich condensation. The mechanism of the condensation reactions may involve in the initial stages the formation of mono- and bicyclic structures. Although mono- and bicyclic intermediates can be isolated in the Mannich condensation as the main products, depending on the reaction conditions, nevertheless heteroadamantane structures are usually synthesised without the isolation of the intermediates. We therefore regard this type of condensation as an independent process, bearing in mind the real initial structural units.

The condensation of diethyl acetonedicarboxylate in the presence of ammonium acetate[159] leads to the diaza-adamantane (XCI, R = $CO_2C_2H_5$). The Mannich reaction, which employs dibenzyl ketone and ammonium acetate or dibenzyl ketone, alkylammonium acetate, and ammonium acetate as the starting compounds, gives rise to the diaza-adamantane (XCI, R = Ph) together with a certain amount of bicyclic products[160]:



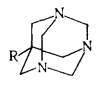
(XCI) (XCII, $R = R^1 = CH_3$; $R = CH_3$, $R^1 = C_2H_5$; $(R,R^1) = -(CH_2)_4-$, $-(CH_2)_5-$) (XCIII)

One of the simplest and most convenient methods for the synthesis of 1,3-diaza-adamantane derivatives involves the aminomethylation of compounds containing two active methylene groups with formaldehyde and ammonia salts of weak acids. Thus 2,2-dialkyl-1,3-dinitropropanes (XCII) condense with formaldehyde and ammonium acetate in the presence of ammonium carbonate to form substituted 1,3-diaza-adamantanes (XCIII).[161] Tolylthiophenylacetone is converted by a similar reaction into the diaza-adamantane (XCIV), which is easily reduced by Raney nickel to compound (XLVIII).[105]



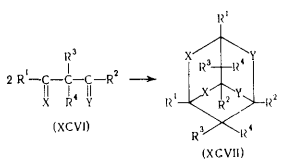
(XCIV) (XLVIII)

The starting compounds used as structural units in the synthesis of substituted 1,3,5-triaza-adamantanes (XCV, R = NO_2 or NH_2) are nitromethane, paraformaldehyde and ammonium acetate[162].



(XCV)

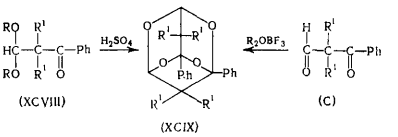
The condensation of β-dicarbonyl compounds and their thioanalogues has a great scope for the synthesis of polyheteroadamantanes. Reactions of this type can be represented schematically as follows:



(XCVI) (XCVII)

Depending on the nature of X and Y, a number of heteroadamantane structures can be synthesised by the "dimerisation" of the initial dicarbonyl compounds or by condensation with other β-dicarbonyl compounds.

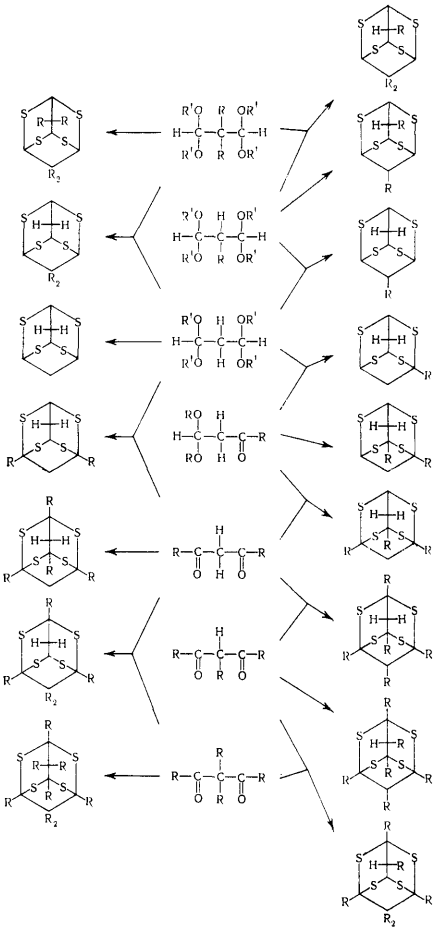
The synthesis of α-formylisobutyrophenone (XCVI, X = Y = O, R^1 = Ph, R^2 = H, $R^3 = R^4$ = Me)[163] from the acetal (XCVIII, R = C_2H_5, R^1 = CH_3) was described in 1959. It was later established[164] that the compound, to which the structure of α-formylisobutyrophenone had been erroneously attributed in the previous study, is in fact the dimer of this aldehyde. The tetraoxa-adamantane structure (XCIX, R^1 = Me) was proposed for it on the basis of spectroscopic data. It was found that the dimer (XCIX) is obtained in almost quantitative yield when the acetal (XCVIII) is treated with 80% sulphuric acid:



(XCVIII) (XCIX) (C)

The dimerisation of certain β-dicarbonyl compounds in the presence of boron triluoride-ether or zinc chloride in glacial acetic acid leads to only slight yields of tetra- and penta-methyl derivatives of tetraoxa-adamantane, the structures of which have been identified by mass spectrometry. In contrast to this, the dimerisation of the ketoaldehyde (C) leads to an almost quantitative yield of tetraoxa-adamantane (XCIX).[165] This type of dimerisation is also characteristic of thioanalogues[166]. All possible versions of the synthesis of polythia-adamantanes are most clearly illustrated by Scheme 10 of Olsson and Almqvist[166], which is reproduced here.

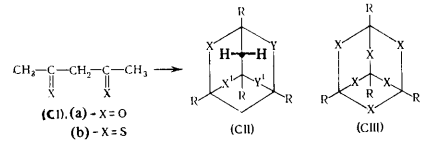
The Syntheses of 2,4,6,8-Tetrathia-adamantane Derivatives[166]



Scheme 10

In a strongly acid medium in the presence of hydrogen sulphide, β-diketones, and particularly pentane-2,4-dione (CIa) are converted into derivatives of tetrathia-adamantane (CII, X = Y = X^1 = Y^1 = S) and its mono-oxa- (X = O), dioxa- (X = Y = O), and trioxa-analogues (X = Y = Y^1 = O)

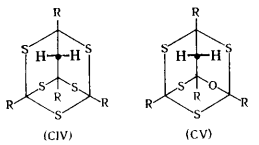
(CII, R = Me).[167] The main product of the reaction of dithioacetylacetone (CIb) was a tetrathia-adamantane (CII, X = Y = X^1 = Y^1 = S, R = Me).[168] The selenium analogue (CII, X = Y = X^1 = Y^1 = Se) was synthesised for the first time in 1969[169] by passing hydrogen selenide through a solution of pentane-2,4-dione in glacial acetic acid in the presence of zinc chloride. In addition the hexaselena-adamantane (CIII, X = Se) was isolated from the mixture of reaction products.



(CI), (a) - X = O
(b) - X = S

(CII) (CIII)

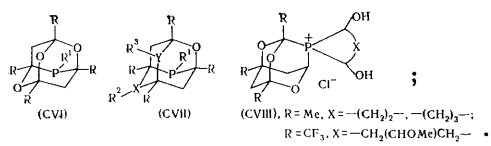
Thiocarboxylic acids and their salts have been used as convenient substitutes of hydrogen sulphide in the synthesis of oxathia-adamantanes. The reaction of β-dicarbonyl compounds with thioacetic acid was carried out for the first time by Brändström[170]. Apart from the tetrathia-adamantane (CII), he obtained two substances, which he regarded without proof as its oxa-analogues (CII, X = O and X = Y = O). The same reaction of β-dicarbonyl compounds (XCVI, X = Y = O; X = Y = S; X = O, Y = S) with thioacetic acid in the presence of zinc chloride led to the synthesis of tetrathia-adamantanes (XCVII), pentathia-adamantanes (CIV), and hexathia-adamantanes (CIII, X = S) in proportions determined by the molar ratios of the initial reactants. Mono-, di-, and tri-oxa-analogues of compound (CII) and the oxatetrathia-adamantane (CV, R = Me) are formed simultaneously[171].



(CIV) (CV)

Thus β-dicarbonyl compounds react with hydrogen sulphide or thiocarboxylic acids to give isomeric mixtures of thia- and oxathia-adamantanes[2,170], which can be separated by preparative gas–liquid chromatography (GLC) and identified by mass spectrometry[166,172-174].

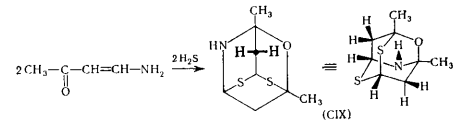
Using phosphine or primary substituted phosphines instead of hydrogen sulphide, it is possible to obtain by a similar reaction phosphorus analogues having structures of type (CII, X = Y = Y^1 = O, X^1 = P)[175] as well as a series of tetra-alkyl-substituted 2,6,9-trioxa-10-phospha-adamantanes (CVI).[176] By varying the amounts of phosphine or primary substituted phosphine taken for the reaction with an alkyl-β-diketone, it is possible to obtain a series of compounds with a structure of type (CVII):



(CVI) (CVII) (CVIII), R = Me, X = —$(CH_2)_2$—, —$(CH_2)_3$—; R = CF_3, X = —CH_2(CHOMe)CH_2—

where X and Y may be oxygen or phosphorus[177]. Thus, when two equivalents of the β-diketone react with one equivalent of phosphine, compound (CVII, X = Y = O) is the product; the reaction with two equivalents of phosphine yields the oxaphospha-derivative (CVII, X = P, Y = O) and the reaction with three equivalents of phosphine gives rise to the phospha-derivative (CVII, X = Y = P). The compounds obtained in this way are listed in Table 4.

The condensation of secondary substituted phosphines with aldehydes (for example glutaraldehyde) leads to structures of type (CVI), (CVII), and (CVIII).[178] The reaction of α-aminovinyl ketone with hydrogen sulphide leads to the polyheteroadamantane (CIX),[179] the positions of the N, O, and S atoms in which were determined by spectroscopic methods:

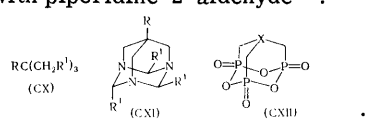


(CIX)

Table 4. Heteroadamantanes with a structure of type (CVII).[177]

X	Y	R	R^1	R^2	R^3
O	O	Me	H, iso-Bu, Octyl, Pr	—	—
O	O	trifluoromethyl	R^1 = R^2 = tris-(2-hydroxyethyl)		
O	O	Pr	dodecyl	—	—
O	O	1,5-diethyl-3,7-dimethyl	benzyl	—	—
O	O	Bu	2-carboxyethyl	—	—
P	O	Me, Et	R^1 = R^2 = bis-(2-cyanoethyl), allyl, cyclohexyl, bis-(*p*-chlorophenyl)		—
P	P	Me	Ph	Ph	Ph
P	P	trifluoromethyl	R^1 = R^2 = tris(2-hydroxyethyl)		H

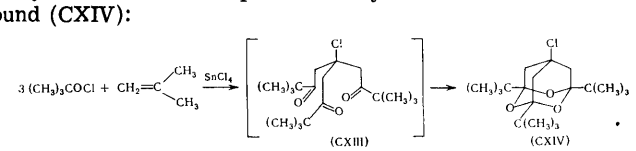
Synthetic schemes for the preparation of heteroadamantanes via pathway *C*-4 are based on the use as starting compounds of trifunctional derivatives containing in their structure both atoms capable of occupying bridge-positions and atoms occupying the 2-, 4-, and other analogous positions in the adamantane skeleton. Thus the initial fragment already contains seven atoms needed for the construction of the adamantane skeleton. The missing three units are introduced by condensation or intramolecular cyclisation from the substituents present in the initial molecule (see Scheme 9, pathway *C*-5). The triaza-adamantane structure (CXI, R = Me, R^1 = 2-C_5H_4N) was demonstrated in 1967 for the product of the condensation of tri(aminomethyl)methane (CX, R = CH_3, R^1 = NH_2) with piperidine-2-aldehyde[180]:



(CX) (CXI) (CXII)

It was shown with the aid of ^{1}H NMR that two pyridyl groups in compound (CXI) are located in equatorial positions and one is in an axial position. A number of mono-substituted derivatives of compound (CXI) with the substituents R = H and R^1 = NO_2, NH_2, HNOH, $N(CH_3)_3$, $HNCOCH_3$, HNCOPh, or $HNCH_2C(NO_2)(CH_3)_2$ have been obtained[181] from tri-(hydroxymethyl)nitromethane (CX, R = NO_2, R^1 = OH) ammonia, and formaldehyde. Oxaphospha-adamantane derivatives of type (CXII, X = N, P = O) are formed on intramolecular degradation of nitrilotrimethylenephosphonic acid $N(CH_2.PO_3H_2)_3$ or $OP(CH_2PO_3H_2)_3$ by acetic anhydride[182].

A new type of triacylation in the reactions of pivaloyl halides with isobutene was discovered in 1972.[183] In the presence of tin tetrachloride, this reaction gives rise to the trioxa-adamantane derivative (CXIV), which is probably formed via the triketone (CXIII). The latter is apparently unstable and is spontaneously converted into compound (CXIV):

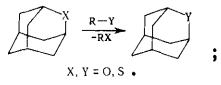


(CXIII) (CXIV)

The data presented show that the pathways to the synthesis of heteroadamantanes from acyclic compounds are extremely varied and numerous and constitute a large field in the synthesis of various heteroanalogues of adamantane.

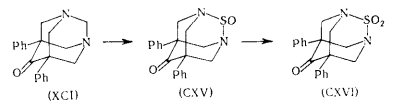
VI. SYNTHESIS BY THE TRANSFORMATION OF POLYCYCLIC STRUCTURES

So far there are few instances in the literature of the formation of heteroadamantane derivatives as a result of the transformation of the skeletons of other polycyclic molecules. However, this method appears fairly promising bearing in mind the advances in the synthesis of a wide variety of polycyclic and skeletal structures. One of the methods formally resembles the Yur'ev reaction[184] (Scheme 11):

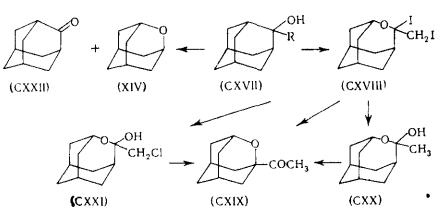


Scheme 11

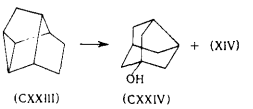
Reactions leading to the substitution of the heteroatom in rings are known also for bicyclo[3,3,1]nonane systems[185-187]. The formation of thiadiaza-adamantane (CXV) from diaza-adamantane (XCI)[188] by treating the latter with $SOCl_2$ in anhydrous pyridine is an example of reactions of this kind involving adamantane structures:



A new pathway to the synthesis of the 2-oxa-adamantane system from derivatives of 2-substituted adamantanols was discovered in 1971.[189] When 2-methyladamantan-2-ol (CXVII, R = Me) was treated with lead tetra-acetate in the presence of iodine, the oxahomoadamantane derivative (CXVIII) was obtained. The di-iodoether (CXVIII) is readily decomposed by dilute hydrochloric acid in DMF to the oxa-adamantane derivative (CXIX). The ketone (CXIX) was also obtained from both homoadamantanes (CXX) and (CXXI) by treatment with iodine in the presence of hydrogen chloride in DMF. Treatment of the adamantanol (CXVII, R = H) with a mixture of yellow or red mercury(II) oxide and iodine, the reaction system being heated or irradiated, leads to a mixture of unsubstituted 2-oxa-adamantane (XIV), and the adamantanone (CXXII).[190] The ratio of the reaction products depends on the molar ratios of the adamantanol, mercury(II) oxide, and iodine and on the reaction temperature:



The unsubstituted oxa-adamantane (XIV) has also been obtained in a low yield (10%) in the reaction of deltacyclane (CXXIII) with concentrated sulphuric acid. Depending on the conditions, the main reaction product is 1-noradamantanol (CXXIV) or 2-noradamantanol[191]:



During the preparation of the manuscript for the press and while it remained with the editors, a number of studies have been published on the synthesis[192-201], properties[202-205], and structure[206-207] of heteroadamantanes containing between one and five heteroatoms in the adamantane structure.

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