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# Azaadamantanes with nitrogen atoms in the bridgehead positions

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**ABSTRACT. The methods of synthesis and properties of 1-aza-, 1,3-diaza-, and 1,3,5-triaza-adamantanes and their derivatives are discussed and treated systematically. The prospects for the employment of azaadamantanes in the solution of certain theoretical problems in the chemistry of nitrogen-containing compounds and for practical purposes—in catalysis, polymer technology and pharmacology—are demonstrated.**

**The bibliography includes 152 references.**

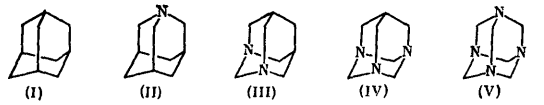
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## I. Introduction

Skeletal heterocyclic compounds with the adamantane structure (heteroadamantanes) constitute a large but so far only slightly investigated class of saturated heterocyclic compounds. They merit the continuous attention of chemists not only because of their structural relation to the unique hydrocarbon adamantane (I) but also because they have a set of specific properties resulting from the presence of heteroatoms in the adamantane nucleus. The published data on heteroadamantanes have been surveyed in a number of reviews[1–6] and in a separate chapter of a monograph on adamantanes.[7]

Azaadamantanes with nitrogen atoms in the bridgehead positions constitute a special branch of the chemistry of heteroadamantanes.



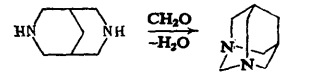
(I) (II) (III) (IV) (V)

They include 1-azaadamantane (II), 1,3-diazaadamantane (III), and 1,3,5-triazaadamantane (IV). Hexamethylenetetramine or 1,3,5,7-tetraazaadamantane (V) is also an azaadamantane. Together with this compound, azaadamantanes constitute an unusual series of compounds with identical molecular skeletons and common properties determined by the specific structure of their molecules (high melting point, volatility, thermodynamic stability, etc.) and by the presence of nitrogen atoms (basicity, high solubility in water, capacity for complex formation, etc.).[8]

| Azaadamantane | (I) | (II) | (III) | (IV) | (V) |
|---|---|---|---|---|---|
| M.p., °C | 269—272 | 250—252 | 260—264 | 260—262 | 287—288 |
| p*K* (in DMSO) | | 9.70 | 8.80 | 7.60 | 6.40 |
| p*K* (in water) | | 10.92 | 8.80 | 6.63 | 4.86 |

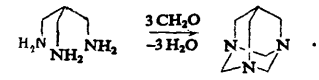
[8]

Together with common properties, there are also significant chemical differences between azaadamantanes. Whereas azaadamantanes (II) is a typical tertiary amine with a skeletal structure, in diazaadamantane (III) one of the methylene groups, located between the two nitrogen atoms, is an animal methylene group and the compound is the product of the condensation of 3,7-diazabicyclo[3.3.1]nonane (bispidine) (VI) with formaldehyde.



(VI) (III)

In triazaadamantane (IV), there are three aminal methylene groups and it is the product of the condensation of 2-aminomethyl-1,3-diaminopropane [tris(aminomethyl)methane] (VII) with formaldehyde.



(VII) (IV)

Azaadamantanes were first synthesised at the beginning of the 1950s and immediately aroused interest among investigators in different fields because of the possibility of using them in the solution of important theoretical problems in the chemistry of nitrogen-containing compounds and because of the prospect for their practical application in the synthesis of new biologically active preparations, rocket fuel components, and additives to fuel-lubricating materials, in photography, and in other fields.

The growth of the number of publications in the development of new novel methods of synthesis and the study of the properties of azaadamantanes and also the fields of their practical application which have arisen have given rise to the necessity for a survey and a separate examination of data which have accumulated on this new aspect of synthetic organic chemistry.

The review discusses literature data published up to 1987 inclusive.

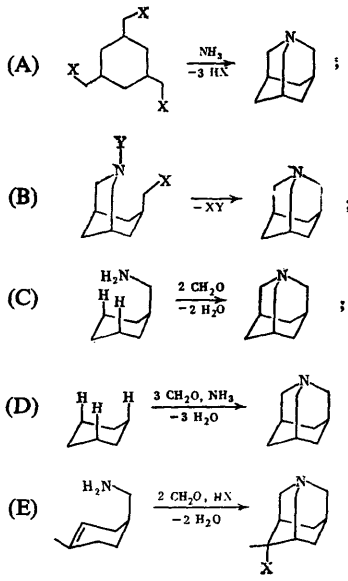
## II. Methods of synthesis

Despite the existing general approaches to the synthesis of azaadamantanes, the ways leading to the formation of the structures of different azaadamantanes are extremely specific and require separate consideration. Whereas in the initial period of the development of the chemistry of azaadamantanes they were synthesised mainly by the gradual construction of rings, methods based on the condensation of acyclic or monocyclic compounds with the single-stage closure of all three rings of the adamantane nucleus

at once have been developed in recent years. Nevertheless, the multistage methods developed previously remain of practical value for the synthesis of individual representatives.

## 1. Synthesis of 1-azaadamantane and its derivatives

The methods of synthesis of azaadamantanes (II) and its derivatives are extremely varied but most of them can be reduced to the following several formal schemes:[4]

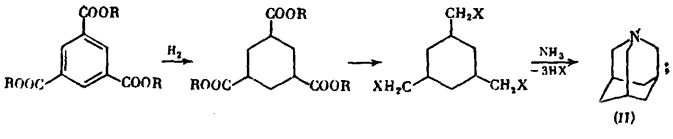



Pathway (A) represents the alkylation of ammonia, while pathway (B) represents the intramolecular alkylation of 3-azabicyclo-[3.3.1]nonane systems frequently with the simultaneous, preliminary, or subsequent elimination of the substituent at the nitrogen atom. Pathways (C) and (D) are based on the aminomethylation reaction of the type of the Mannich reaction and presuppose the presence of activating groups next to the designated hydrogen atoms. Pathway (E) is based on the condensation of alkenes with formaldehyde and amines.

The formal schemes present only the final stages of the formation of the azaadamantanes structure from the intermediates, whose synthesis is frequently a multistage process and requires special consideration.

### (a) The synthesis of 1-azaadamantane from trimesic acid

Azaadamantane (II) was first obtained in several stages from trimesic acid.[9−11] Subsequently individual stages of this synthesis were improved.[8,12] In the first stage, the methyl or ethyl ester of trimesic acid is hydrogenated in the presence of a platinum catalyst to esters of cyclohexanetricarboxylic acid and the latter are reduced with lithium tetrahydroaluminate to 1,3,5-tri(hydroxymethyl)cyclo-hexane.

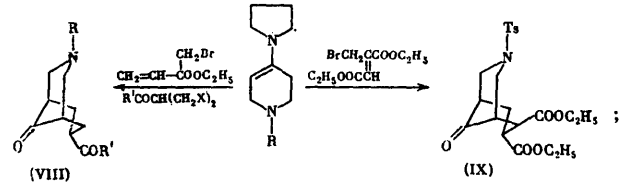



R=CH3, C2H5; X=OH, Br.

The latter is converted into azaadamantane (II) via 1,3,5-tribromo-methylcyclohexane or directly by interaction with ammonia over alumina at 375 °C.[12] Despite the low (not exceeding 10%) overall yield, this method still remains virtually the only one available for the synthesis of the unsubstituted azaadamantane (II).[8]

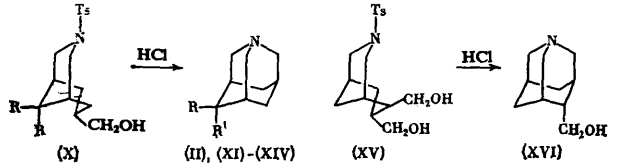
### (b) Intramolecular alkylation of 3-azabicyclo[3.3.1]nonane derivatives

The intramolecular alkylation method is based on the αα′-annelation of enamines derived from 4-piperidinones with esters of β-bromomethacrylic,[13,14] ββ′-dibromoisobutyric,[13−16] and bromomethylfumaric[17] acids or with 2-benzoyl-1,3-dichloropropane,[18] which leads to the formation of 3-azabicyclo[3.3.1]nonanes (VIII) and (IX). The initial piperidinones were obtained in several stages from available initial compounds.



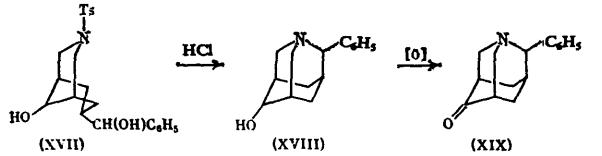

R=Ts, C6H5CO, C6H5CH2OCO; R′=C2H5O, C6H5;
X=Cl, Br.

After the modification of the keto-group in compounds (VIII) and (IX), the ester groups are reduced with lithium tetrahydroaluminate to the hydroxymethyl group. It has been observed that, when 7-hydroxymethyl-*N*-tosyl-3-azabicyclo[3.3.1]nonanes (X) and (XV), formed as a result of the reactions described above, are heated in acetic acid saturated with dry hydrogen chloride, simultaneous dissociation of the bond between the nitrogen atom and the tosyl group and intramolecular alkylation with formation of azaadamantane (II) and its derivatives (XI)−(XIV) and (XVI) take place.[14,15,17,18]



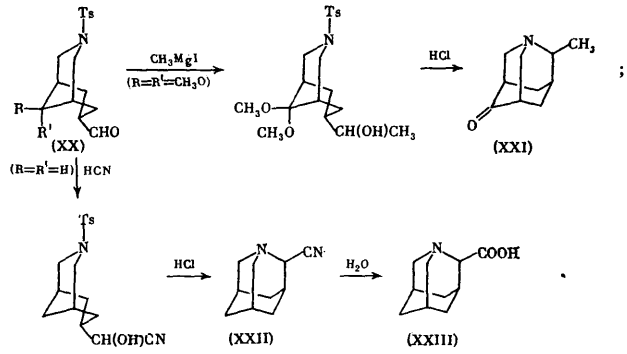

RR′ = O (XI); R = H, R′ = OH (XII);
R = OH, R′ = H (XIII); R = H, R′ = NH2 (XIV).

The diol (XVII)—the product of the reduction of the diketone (VIII, R = Ts, R′ = C6H5) (Ts = tosyl) with lithium tetrahydro-aluminate, cyclises in exactly the same way. Oxidation of 2-phenyl-1-azaadamantan-6-ol (XVIII), formed as a result of the cyclisation, with silver carbonate yields 2-phenyl-1-azaadamantan-6-one (XIX):[18]

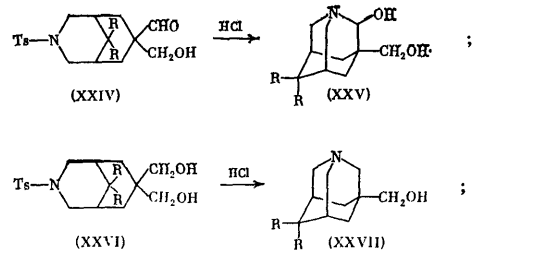



Oxidation of the 7-hydroxymethyl group in compounds (X) with R = R′ = H or $CH_3O$ or with RR′ = $SCH_2CH_2S$ affords the corresponding azabicyclononane derivatives (XX), from which azaadamantane derivatives with substituents at the C(2) atom can be obtained.[14,19] Thus treatment of the dimethoxy-derivative (XX, R = $CH_3O$) with a Grignard reagent or of the derivative (XX, R′ = H) with hydrocyanic acid, followed by treatment of the

resulting hydroxy-derivatives with hydrogen chloride in acetic acid, yielded respectively 2-methyl-1-azaadamantan-6-one (XXI) and 2-cyano-1-azaadamantane (XXII). 1-Azaadamantane-2-carboxylic acid (XXIII) was obtained from the latter by hydrolysis:[20]



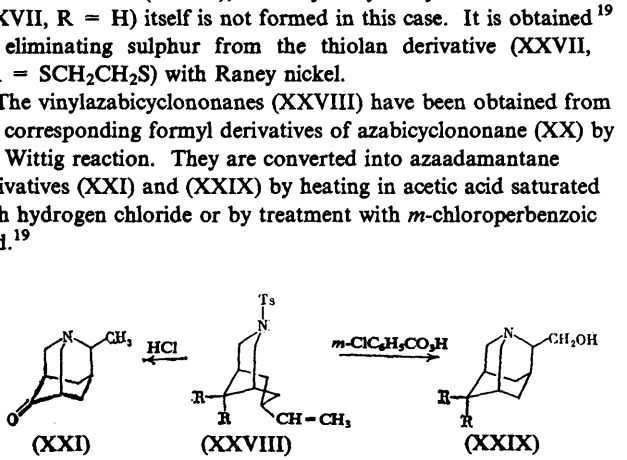
Condensation of formylazabicyclononanes (XX) with formaldehyde afforded the hydroxymethylformyl derivatives (XXIV), which cyclise on treatment with hydrogen chloride in acetic acid to 3-hydroxymethyl-1-azaadamantan-2-ol derivatives (XXV).[19] 2-Hydroxy-3-hydroxymethyl-1-azaadamantan-6-one (XXV, RR = O) obtained in this way is a rare example of a stable hemiaminal, whose stability can be explained by the incorporation of the hemiaminal nitrogen atom in the adamantane nucleus.



R=H, $CH_3O$; RR=O, $SCH_2CH_2S$.

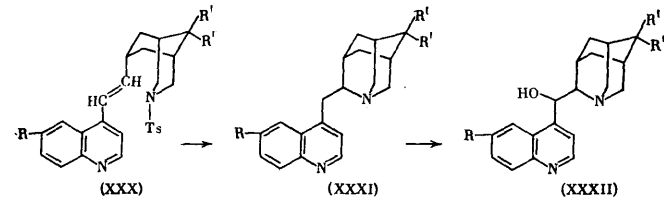
The 7,7-dihydroxymethyl derivatives of azabicyclononane (XXVI), obtained by reducing the aldols (XXIV), cyclise on treatment with hydrogen chloride in acetic acid to derivatives of 3-hydroxymethyl-1-azaadamantane (XXVII), but 3-hydroxymethyl-1-azaadamantane (XXVII, R = H) itself is not formed in this case. It is obtained[19] by eliminating sulphur from the thiolan derivative (XXVII, RR = $SCH_2CH_2S$) with Raney nickel.

The vinylazabicyclononanes (XXVIII) have been obtained from the corresponding formyl derivatives of azabicyclononane (XX) by the Wittig reaction. They are converted into azaadamantane derivatives (XXI) and (XXIX) by heating in acetic acid saturated with hydrogen chloride or by treatment with *m*-chloroperbenzoic acid.[19]



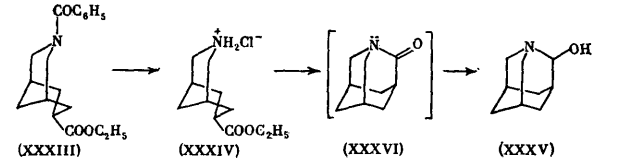
(XXVIII): R=H, $CH_3O$; (XXIX): R=H, RR=O.

Condensation of the aldehydes (XX) with the lithium derivatives of quinolinylmethylphosphonic acid esters afforded quinolinylvinylazabicyclononane derivatives (XXX), which cyclise on treatment with hydrogen chloride to azaadamantane derivatives (XXXI). These were later used to obtain analogues of the quinuclidine alkaloids (XXXII) which contain the 1-azaadamantane nucleus instead of the quinuclidine nucleus.[21]



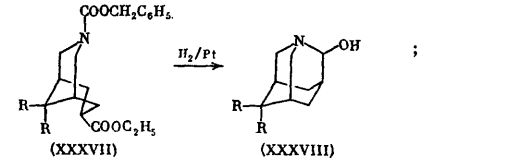
R=H, $CH_3O$; R′=H, $CH_3O$; R′R′=O, $CH_2$.

When an attempt was made to synthesise 1-azaadamantane (II) from *N*-benzoyl-7-ethoxycarbonyl-3-azabicyclo[3.3.1]nonane (XXXIII) the product of the annelation of compound (VIII, R = $C_6H_5CO$, R′ = $C_2H_5O$), i.e.



via the ester (XXXIV) (which was hydrogenated over a platinum catalyst in the form of the hydrochloride), 1-azaadamantan-2-ol (XXXV) was obtained unexpectedly instead of 1-azaadamantane (II).[16] It has been suggested that the readily reducible 2-oxo-1-azaadamantane (XXXVI) is formed as an intermediate. It is an unusual lactam, since the lone electron pair at its nitrogen atom is not conjugated with a carbonyl group but is disposed at a right angle to the C=O π-system.[16]

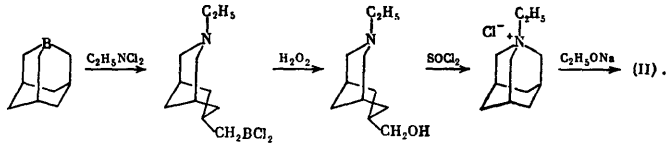
The *N*-benzyloxycarbonyl derivatives of azabicyclononane (XXXVII), obtained from the annelation product (VIII, R = $COOCH_2C_6H_5$, R′ = $C_2H_5O$), do in fact afford the corresponding derivatives of 2-hydroxy-1-adamantane (XXXVIII) on hydrogenation over a palladium catalyst.[16]



R=H; RR=$OCH_2CH_2O$.

Yet another method of synthesis of azaadamantane (II) via azabicyclononane derivatives has been developed by Soviet workers.[22] By treating 1-boraadamantane with ethyldichloroamine and subsequent oxidation of the resulting 7-dichloroboryl-methyl-*N*-ethyl-3-azabicyclo[3.3.1]nonane by hydrogen peroxide, they obtained *N*-ethyl-7-hydroxymethyl-3-azabicyclo[3.3.1]nonane (XXXIX). Its treatment with thionyl chloride in moist benzene leads

to 1-azaadamantane ethochloride. The ethyl group bound to the nitrogen atom is then removed by treatment with sodium ethoxide in alcohol.



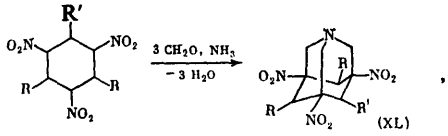

(XXXIX)

Improvement of the last two stages of the synthesis of azaadamantane (II) makes it possible to replan the synthesis of azaadamantane derivatives via azabicyclononanes.

**(c) Aminomethylation of cyclohexane derivatives**

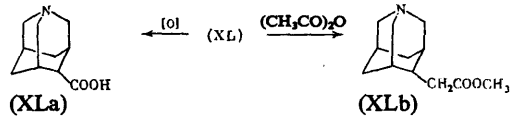
The possibility of synthesising the azaadamantane structure by condensing cyclohexane derivatives with formaldehyde and ammonia was first demonstrated in the synthesis of 3,5,7-trinitro-1-azaadamantane (XL, R = R′ = H) from trinitrocyclohexane, obtained by reducing trinitrobenzene [23] or picric acid [23–25] with sodium tetrahydroborate. Methyl- and dimethyl-trinitrocyclohexanes are obtained similarly from trinitrotoluene and trinitroxylene.[26] Trialkyltrinitrocyclohexanes are obtained by treating trinitrobenzene with Grignard reagents.[27] Hydroxymethyltrinitrocyclohexane has been obtained by reducing trinitrobenzaldehyde.[28] Treatment of trinitrobenzene with ketones in an alkaline medium followed by reduction with sodium tetrahydroborate afforded trinitrocyclohexane derivatives with a hydroxy-group in the side chain.[29,30]

The aminomethylation of trinitrocyclohexane and its derivatives is carried out in an aqueous medium using formaldehyde and ammonia or ammonium nitrate.[26,31,32] The yield of trinitroazaadamantane and its derivatives is between 10 and 50%. Instead of trinitrocyclohexanes, one can also use the hydroborate complexes, formed in the reduction of trinitroarenes, without isolating them in a pure form.[31–34] There are also other modifications of this reaction.[26,32]



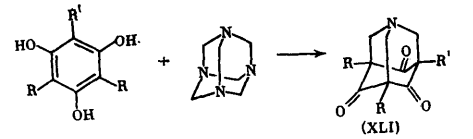

R = H, $CH_3$, $C_2H_5$, $C_3H_7$; R′ = H, $CH_3$, $C_2H_5$, $C_3H_7$, CHO, $CH_2OH$, $CH_3CH(OH)CH_2$, $(CH_2)_3CH(OH)CH$, $(CH_2)_4CH(OH)CH$.

Oxidation of hydroxymethyltrinitroazaadamantane (XL, R = H, R′ = $CH_2OH$) afforded the acid (XLa) and its acylation gave rise to the acetate (XLb).[28]




(XLa) (XLb)

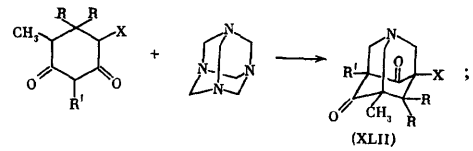
Active hydrogen atoms, which are essential for aminomethylation, are also present in phloroglucinols, but phloroglucinol itself gives rise to only tarry products of the type of phenolformaldehyde resins in its reaction with formaldehyde and ammonia. On the other hand, it has been observed [35–37] that trialkylphloroglucinols are capable of condensing with hexamethylenetetramine to form 3,5,7-trialkyl-1-azaadamantane-4,6,10-triones (XLI) in high yields.



(XLI)

R = $CH_3$, $C_2H_5$, iso-$C_3H_7$; R′ = $CH_3$, $C_2H_5$.

1-Azaadamantane-4,6-dione derivatives (XLII) are obtained by condensing cyclohexane-1,3-diones with hexamethylenetetramine.[38–40]



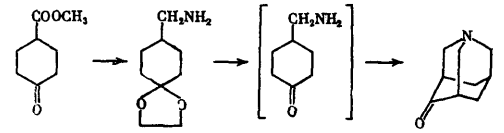
(XLII)

R = H, $CH_3$; R′ = $CH_3$, $C_2H_5$, n-$C_8H_{17}$, $C_6H_5CH_2$; X = $COOCH_3$, CN.

The initial cyclohexanediols are obtained by condensing α-vinylketones with malonic or cyanoacetic ester.

**(d) Condensation of 4-(aminomethyl)cyclohexanone with formaldehyde**

The possibility, in principle, of synthesising azaadamantane derivatives from 4-(aminomethyl)cyclohexanone derivatives has been demonstrated in relation to the synthesis of 1-azaadamantan-4-one (XI).[41]



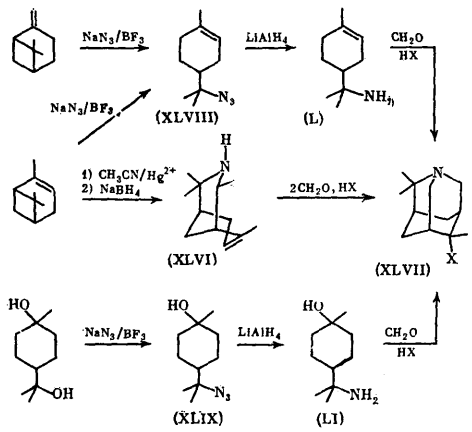
(XLIII) (XLIV) (XLV) (XI)

4-Methoxycarbonylcyclohexanone (XLIII), obtained from malonic and acrylic acid esters[41–43] or from 4-hydroxybenzoic acid,[44] was used as the starting material in this synthesis. After protecting the keto-group, the ketoester (XLIII) is converted into the amine (XLIV) (via the amide). When the latter is condensed with paraformaldehyde or trioxane in dilute sulphuric acid, the ketone protecting group is removed and the aminoketone (XLV) condenses with formaldehyde to azaadamantan-4-one (XI).[41] The value of the method is reduced by the low yield of the product (XI) in the condensation of the aminoketone (XLV) with formaldehyde.

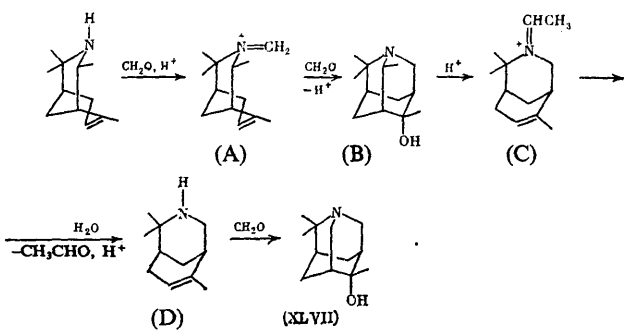
**(e) Synthesis of 1-azaadamantane derivatives from terpenes**

An unusual approach to the building of the azaadamantane structure has been developed by French investigators.[44–48] They observed that, when α-pinene is treated with acetonitrile in the presence of mercury nitrate and the resulting adduct is reduced with sodium tetrahydroborate, 2,2,4,6-tetramethyl-3-azabicyclo[3.3.1]non-6-ene (XLVI) is obtained; the latter reacts in an acid medium with formaldehyde, whereupon the process involves formally the elimination of the methyl substituents from the C(6) atom and the formation of 4,8,8-trimethyl-1-azaadamantan-4-ol (XLVII, X = OH). By carrying out the reaction in the presence of azide or acetate ions, it is possible to obtain 4-azido- and 4-acetoxy-4,8,8-trimethyl-1-azaadamantanes (XLVII, X = $N_3$, $CH_3COO$). 4-Amino-4,8,8-trimethyl-1-azaadamantane (XLVII, X = $NH_2$) has

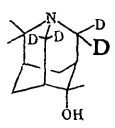
been obtained by reducing the azide with lithium tetrahydroaluminate.



The unusual elimination of the methyl group in the condensation of compound (XLVI) with formaldehyde is explained by the fact that, in the cyclisation of the methyleneimmonium cation (A) to the azaadamantane derivative (B), the methyl group at the C(4) and C(9) atoms are subjected to strong diaxial repulsion, which induces the dissociation of the C(2)–C(3)σ-bond of the type of Grob fragmentation. In the hydrolysis of the ethylideneimmonium cation (C), formed as a result of such fragmentation, a molecule of acetaldehyde is split off and the bicyclic product (D) condenses subsequently with formaldehyde, affording azaadamantanol (XLVII, X = OH).



In order to confirm the mechanism described, the deuteriated analogue of formaldehyde was employed instead of the usual formaldehyde, as a result of which deuteriated azaadamantanol was obtained.



The use of the toxic mercury nitrate in the synthesis described above creates disadvantages which can be avoided by employing a somewhat different scheme for the synthesis of azaadamantane derivatives (XLVII). Thus treatment of α-pinene with sodium azide in ether in the presence of boron trifluoride leads to the opening of the four-membered ring and the formation of the azide (XLVIII). The same product is formed under analogous conditions also from β-pinene. The azidoalcohol (XLIX) is formed from terpyne hydrate under the same conditions. Both azides, (XLVIII) and (XLIX), were reduced with lithium tetrahydroaluminate to the amines (L) and (LI), which were then condensed with formaldehyde in an acid medium to azaadamantanol (XLVII, X = OH).

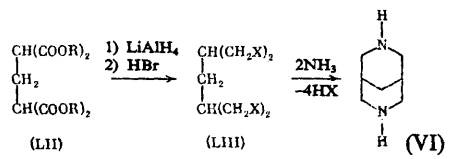
The development of methods of synthesis of azaadamantane derivatives from terpenes leads to their availability, which permits their practical employment.

## 2. Synthesis of 1,3-diazaadamantane and its derivatives

The methods of synthesis of 1,3-diazaadamantane (III) and its derivatives frequently reduce to the synthesis of bispidine (VI) and its derivatives followed by their condensation with aldehydes, in some cases without isolating the bispidines.

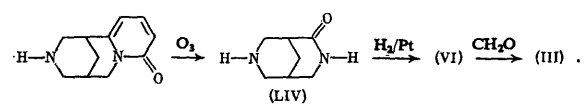
### (a) Synthesis of 1,3-diazaadamantane and its derivatives via bispidine and its derivatives

The methods of synthesis of 3,7-diazabicyclo[3.3.1]nonane (bispidine) (VI) and its derivatives have been examined in detail in other reviews.[49,50] They included data published up to 1972. The synthesis of bispidine (VI) and diazaadamantane (III) from the products of the condensation of malonic ester with formaldehyde (LII), which is subsequently reduced with lithium tetrahydroaluminate to 2,4-di(hydroxymethyl)pentane-1,5-diol (LIII, X = OH), was reported later.[51] Treatment of the last compound with hydrogen bromide in acetic acid yields 1,5-dibromo-2,4-di(bromomethyl)-pentane (LIII, X = Br). When this tetrabromo-derivative is heated in a methanol solution of ammonia, bispidine (VI) is formed.

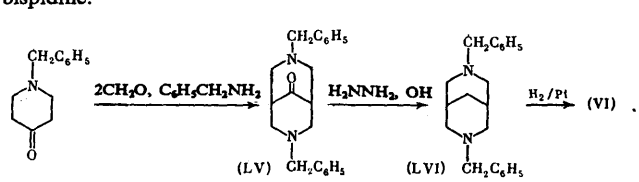


The method requires further improvement, especially in the stage involving reduction and the conversion of the tetrabromo-derivative (LIII, X = Br) into bispidine (VI), since in these stages the products are formed in a low yield, which reduces the overall yield (<7%).

The synthesis of diazaadamantane from the alkaloid cytisine has been reported.[52] In the first stage, 2-oxobispidine (LIV) is obtained by the ozonolysis of cytisine. Its hydrogenation in the presence of a platinum catalyst leads to bispidine (VI) from which diazaadamantane (III) is synthesised in its turn.

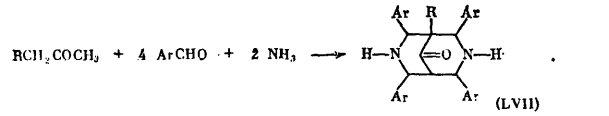


Perhaps the most effective method of synthesis of bispidine (VI) is based on the condensation of the readily available *N*-benzyl-4-piperidinone with paraformaldehyde and benzylamine, which leads to the formation of the unstable *NN'*-dibenzylbispidinol (LV). It is reduced, without isolation, by the Huang-Minlon method to *NN'*-dibenzylbispidine (LVI). Hydrogenation of the latter in acetic acid under pressure in the presence of a palladium catalyst leads to bispidine.[53]

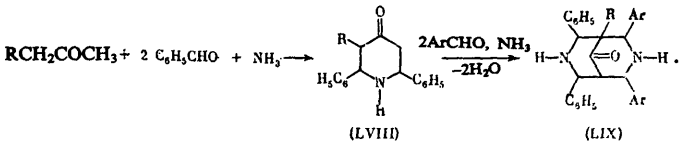


The overall yield of bispidine (VI) recalculated in terms of *N*-benzylpiperidinone is about 60%.

Condensation of acetone or ethyl methyl ketone (but not other ketones) with various aromatic aldehydes and ammonia or their reaction products affords exceptionally readily tetraarylbispidinones (LVII, R = H, $CH_3$) with aryl substituents at the bridging carbon atoms. In order to obtain bispidinones with various aryl substituents, the reaction is carried out in two stages: the first stage yields diphenylpiperidinones (LVIII, R = H, $CH_3$), while the second stage gives rise to the bispidinones (LIX):[54-58]

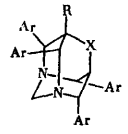


(LVII)



(LVIII) (LIX)

The keto-group in tetraarylbispidinones (LVII) and (LIX) is then reduced to the methylene or hydroxy-group. The condensation of tetraarylbispidines with paraformaldehyde in carbon tetrachloride, dichloroethane, dimethylformamide, or dioxane gives rise to the corresponding tetraaryldiazaadamantanes (LX).



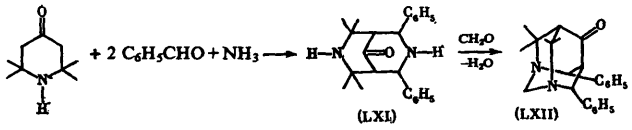
(LX)

R = H, $CH_3$; X = $CH_2$, CHOH, CO; Ar = $C_6H_5$, 4-$CH_3OC_6H_4$, 4-$ClC_6H_4$, 2-$ClC_6H_4$, 3,4-$(CH_3O)_2C_6H_3$, 4-$CH_3C_6H_4$, α-$C_5H_4N$.

Tetraaryldiazaadamantanols (LX, X = CHOH) and tetraaryldiazaadamantanes (LX, X = $CH_2$) are also obtained by reducing diazaadamantanones (LX, X = CO) with lithium tetrahydroaluminate or by the Wolff–Kishner method.

It has long been assumed,[59,60] that only formaldehyde can condense with diarylbispidine, but it has been found that aromatic aldehydes also react similarly;[56,58] however, the reaction is very slow (45 days) and the yield does not exceed 10%.

By a procedure similar to that used for tetraaryldiazaadamantanes (LX), tetramethyldiphenyldiazaadamantanone (LXII) can be obtained from triacetoneamine via a substituted bispidinone (LXI).[61,62]



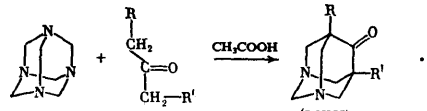
(LXI) (LXII)

Despite the ease of their synthesis, tetraaryldiazaadamantanes (LX) are apparently not very promising because of the cumbersome nature of their molecules, only a small proportion of which corresponds to the diazaadamantane nucleus.

**(b) Synthesis of 1,3-diazaadamantan-6-ones**

The most convenient and readily available intermediates for the synthesis of various diazaadamantane derivatives are at present 1,3-diazaadamantan-6-ones (LXIII). Until recently, they were obtained by condensing the corresponding ketones with formaldehyde and ammonia. Mainly ketones with activated α- and α′-hydrogen atoms were used in the reaction. 5,7-Diphenyl-,[63-65] 5,7-dimethoxy- and 5,7-diethoxy-,[65,66] 5,7-di(phenylthio)-,[63] 5-phenyl-7-phenylthio- and 5-phenyl-7-*p*-tolylthio-,[67,68] 7-ethoxycarbonyl-5-phenyl-,[69] and 7-methoxycarbonyl-5-phenylthio-1,3-diazaadamantan-6-ones[70] have been obtained in this way. It was shown later that 5,7-dimethyl-1,3-diazaadamantan-6-one can also be obtained by the same method but in a low yield.[71]

A more effective and a more general method of synthesis of diazaadamantanones (LXIII) is based on the condensation of ketones with hexamethylenetetramine.[72-74]



(LXIII)

The replacement of formaldehyde and ammonia by hexamethylenetetramine makes it possible to increase the yield of dimethyldiazaadamantanone (LXIII, R = R′ = $CH_3$) from 20 to 74% and that of diphenyldiazaadamantanone (LXIII, R = R′ = $C_6H_5$) from 59 to 90%; however, the most significant feature is that the new method makes it possible to obtain diazaadamantanones not only with two hydrocarbon substituents virtually of any kind but also with one substituent.

The increase in the yield of diazaadamantanones (LXIII) when hexamethylenetetramine is used can be explained by a change in the chemistry of the process. When ketones are condensed with formaldehyde and ammonia, the diazaadamantane structure is formed as a result of a large number of intermolecular reactions,[75] each of which may be accompanied by the formation of side products. On the other hand, in the condensation with hexamethylenetetramine, diazaadamantanones can be formed as a result of a single intermolecular interaction of the protonated form of hexamethylenetetramine with a ketone and subsequent intramolecular rearrangements with elimination of the methylenediamine fragment in one of the concluding stages and the formation of diazaadamantone.

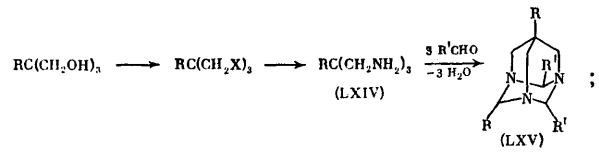
## 3. Synthesis of 1,3,5-triazaadamantane and its derivatives

1,3,5-Triazaadamantane (IV), which represents, as already mentioned, the products of the condensation of tris(aminomethyl)-methane (VII) with formaldehyde, was first obtained by this reaction in 1952.[76] The initial tris(aminomethyl)methane (VII) is difficult to obtain; it is synthesised by a complex multistage method from malonic and acetonedicarboxylic acid esters via methanetriacetic acid and its amide:[76]

$$HC(CH_2COOH)_3 \rightarrow HC(CH_2CONH_2)_3 \rightarrow HC(CH_2NH_2)_3.$$
(VII)

The homologues of tris(aminomethyl)methane (LXIV) can be obtained much more readily. They are obtained from the available

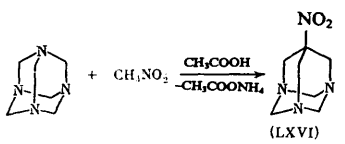
tris(hydroxymethyl)ethane and its homologues via the tribromo-derivatives by the phthalimide method[71] or via the tritosylate and the triazide:[78]




$R = CH_3$, $C_{12}H_{25}$; X = Br, $N_3$; $\mathbf{R' = H, C_6H_5}$ α-$C_5H_4N$.

Condensation of the triamines (LXIV) with formaldehyde affords triazaadamantane (LXV, R′ = H) derivatives with substituents at the bridgehead carbon atom,[77,79] while condensation with benzaldehyde and 2-formylpyridine gives rise to tribenzyl- and tri-α-pyridyl-triazaadamantanes (LXV, R = $CH_3$, R′ = H, $C_6H_5$, α-$C_5H_4N$) containing substituents also at the aminal carbon atoms.[80,81]

Triazaadamantane derivatives with functional groups at the bridgehead carbon atom are obtained from 7-nitro-1,3,5-triazaadamantane (LXVI), which was first synthesised[82] by condensing nitromethane with formaldehyde and ammonia. A number of modifications of this process were proposed later.[83–92] The best method involves the condensation of hexamethylenetetramine with nitromethane in the presence of acetic acid[83,88,90] first proposed by Kuznetsov et al.[83]




By optimising the process, it was found[93] that the highest yield of the target product (LXVI) is obtained for the molar ratios hexamethylenetetramine : nitromethane : acetic acid = 1 : 1.1 : 2.3. The proposed mechanism of the formation of nitrotriazaadamantane (LXVI) has been described.[94]

The simple and convenient methods of synthesis of azaadamantane derivatives developed in recent years, especially those based on the condensation of hexamethylenetetramine with nitro-compounds and carbonyl compounds, make them extremely readily available for study and for use in the synthesis of other azaadamantane derivatives.

## III. Chemical properties

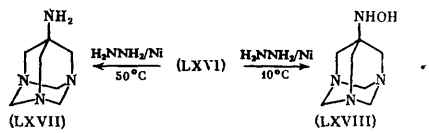
The chemical properties of azaadamantanes are determined primarily by the presence and mutual influence of the nitrogen atoms in the bridgehead positions in the adamantane nucleus. The presence of aminal methylene groups in di- and tri-azaadamantanes is responsible for the tendency of these compounds to react with certain electrophiles. The similarity to adamantane (I), which increases as the number of nitrogen atoms is reduced, suggests that such derivatives, especially azaadamantane (II), have properties characteristic of adamantane, in particular those associated with the increased reactivity of hydrogen atoms at the bridgehead positions.

The mutual influence of nitrogen atoms affects primarily the basicity of azaadamantanes, which decreases with increase in the number of nitrogen atoms in the molecule.[8] Protonation of one of the nitrogen atoms leads to the distribution of the charge between the remaining nitrogen atoms of the molecule. Polyazaadamantanes usually behave as monoacidic bases in their reactions with acids. The aminal character of the methylene groups linking the nitrogen atoms in di- and tri-azaadamantanes is manifested to a much lesser extent than for the usual aminals or hexamethylenetetramine. Thus, whereas the latter readily breaks down on heating with inorganic acids, di- and tri-azaadamantanes do not decompose even on prolonged heating with concentrated hydrochloric acid.

### 1. Reactions of functional groups

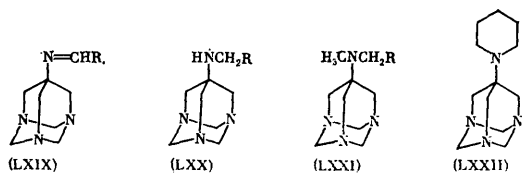
The method of synthesis of azaadamantane described in the previous Section lead as a rule to the formation of derivatives with functional groups which serve as intermediates in the synthesis of other azaadamantane derivatives.

One of such available intermediates is nitrotriazaadamantane (LXVI). It is reduced to 7-amino-1,3,5-triazaadamantane (LXVII) with lithium tetrahydroaluminate,[82] with hydrogen in the presence of nickel,[82,84,85,91] cobalt,[91] rhodium[86,92] or platinum[89,92] catalysts, with zinc in an alkaline medium,[87,92] and with iron or tin in an acid medium.[87,92] The most convenient method involves reduction with hydrazine hydrate at atmospheric pressure in the presence of a nickel catalyst at 50 °C.[94]




At a lower temperature (+10 °C), 7-hydroxyamino-1,3,5-triazaadamantane (LXVIII) is obtained in 67% yield.[94]

Aminotriazaadamantane (LXVII) has also been used as an intermediate in the synthesis of a large number of derivatives. Its reactions with aromatic and aliphatic aldehydes afford the azomethines (LXIX).[95–97] Their hydrogenation in the presence of a platinum catalyst yielded alkyl- and aryl-methylaminotriazaadamantanes (LXX). The reductive methylation of the latter leads to methylalkylaminotriazaadamantanes (LXXI).[86,92]

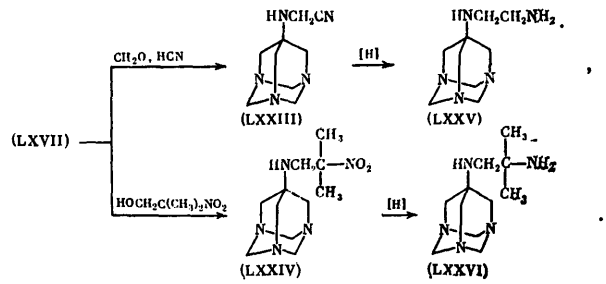



R = $C_6H_5$, 4-$CH_3C_6H_4$, 4-$ClC_6H_4$, 2-$HOC_6H_4$, 4-$CH_3OC_6H_4$, 4-$(CH_3)_2NC_6H_4$, α-$C_5H_4N$, α-$C_4H_3O$, $CH_3$, $C_2H_5$, n-$C_3H_7$, n-$C_4H_9$, iso-$C_4H_9$, n-$C_5H_{11}$, H.

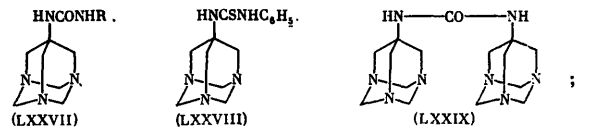
Methylaminotriazaadamantane (LXX, R = H) cannot be obtained by the reductive methylation of aminotriazaadamantane (LXVII), since dimethylaminotriazaadamantane (LXXI, R = H) is formed immediately.[84,86] Treatment of the amine (LXVII) with glutaraldehyde under reductive conditions yields 7-(1-piperidinyl)-1,3,5-triazaadamantane (LXXII).[86]

When aminotriazaadamantane (LXVII) is used as the amine component in aminomethylation reactions, only one hydrogen atom of the amino-group in compound (LXVII) participates in the reaction. The products of the condensation of compound (LXXVII) with formaldehyde and hydrocyanic acid [compound (LXXIII)] or

with 2-nitropropane [compound (LXXIV)] were reduced to the corresponding aminoethyl derivatives (LXXV) and (LXXVI).[84,89,98]




Triazaadamantanylureas (LXXVII) have been obtained by the reaction of the amine (LXVII) with isocyanates,[84,87,99,100] while the reaction with phenyl isothiocyanate afforded thiourea (LXXVIII). Heating of aminotriazaadamantane (LXVII) with urea gives rise to 1,3-bis(triazaadamantyl)urea (LXXIX).[99,101]




R = $C_6H_5$, 3-$ClC_6H_4$, 4-$ClC_6H_4$, $C_6H_{11}$.

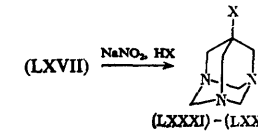
The synthesis of the amides (LXXX) from aminotriazaadamantane (LXVII) involves certain difficulties because acylating agents such as carboxylic acid anhydrides and chlorides can decompose the triazaadamantane skeleton. Therefore, in order to obtain 7-acetamido-1,3,5-triazaadamantane (LXXX, R = $CH_3$), the amine (LXVII) was heated with isopropyl acetate,[86] while the benzamido-derivative (LXXX, R = $C_6H_5$) and the nitrobenzamido-derivatives (LXXX, R = 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$) were obtained by heating the methyl benzoate and nitrobenzoate.[99] The nitrobenzamido-derivatives were reduced to the aminobenzamido-derivatives (LXXX, R = 3-$H_2NC_6H_4$, 4-$H_2NC_6H_4$).[99]




R = $CH_3$, $C_6H_5$, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 3-$H_2NC_6H_4$, 4-$H_2NC_6H_4$, $C_6H_5CONHCH_2$, $C_2H_5OCONHCH_2$, $CH_3OCONHCH_2$, $H_2NCH_2$.

The benzamido-derivative (LXXX, R = $C_6H_5$) has also been synthesised by the carbodiimide method and the mixed anhydride method.[102] The acylglycinamido-derivatives (LXXX, R = $C_6H_5CONHCH_2$, $C_2H_5OCONHCH_2$, $CH_3OCONHCH_2$) have been obtained by the mixed anhydride method.[102] Their hydrolysis led to the glycinamido-derivative (LXXX, R = $H_2NCH_2$).[102]

In order to convert the readily available aminotriazaadamantane (LXVII) into other triazaadamantane derivatives, its diazotisation with sodium nitrite was investigated in different acids.[83,87,94] Triazaadamantanol could not be synthesised by this procedure, but, when the reaction was carried out in concentrated hydrochloric and hydrobromic acids, 7-chloro- and 7-bromo-1,3,5-triazaadamantanes (LXXXI) and (LXXXII) were obtained in preparative yields.

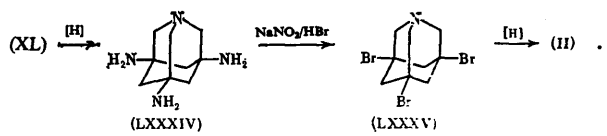



X=Cl (LXXXI), Br (LXXXII), SCN (LXXXIII).

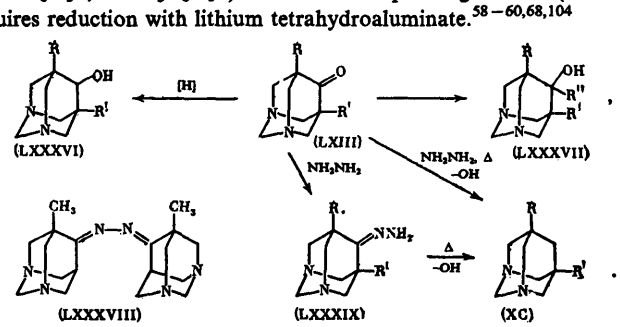
The diazotisation of compound (LXVII) in sulphuric acid in the presence of potassium thiocyanate leads to 7-thiocyanato-1,3,5-triazaadamantane (LXXXIII).[94] Heating of the latter with Raney nickel affords the unsubstituted triazaadamantane (IV).

Triazaadamantane (IV) has been synthesised in a virtually quantitative yield by reducing bromotriazaadamantane (LXXXII) with hydrazine hydrate in the presence of a nickel catalyst.[94] This is the last stage in what is nowadays the most convenient three-stage scheme for the synthesis of 1,3,5-triazaadamantane (IV) from the available nitrotriazaadamantane (LXVI).[94]

The unsubstituted 1-azaadamantane (II) can be obtained via a similar scheme from 3,5,7-trinitro-1-azaadamantane (XL), since it has been shown[103] that the diazotisation of 3,5,7-triamino-1-azaadamantane (LXXXIV), obtained by reducing compound (XL)[27] with sodium nitrite in concentrated hydrobromic acid, results in the substitution of the amino-group by a bromine atom, as in the diazotisation of aminotriazaadamantane (LXVII), and in the formation of 3,5,7-tribromo-1-azaadamantane (LXXXV). Thus deamination accompanied by substitution of aminoazaadamantane with preferential formation of halogenoazaadamantanes is a common reaction for compounds of this class; however, it does not extend to 1-aminoadamantane, which is converted into adamantan-1-ol under similar conditions.




The diazaadamantanones (LXIII) are intermediates for the synthesis of various derivatives of diazaadamantane, particularly those with functional groups at the C(6) atom. The reactivity of the carbonyl group in these compounds is determined to a large extent by the number and character of the substituents at the bridgehead positions.[104] In the presence of only one substituent or two substituents such as the methyl group, diazaadamantanones (LXIII) are reduced to 1,3-diazaadamantan-6-ols (LXXXVI, R = H, R′ = $CH_3$ or R = R′ = $CH_3$) even on treatment with sodium tetrahydroborate,[104] whereas the synthesis of the diazaadamantanols (LXXXVI, R = R′ = $C_6H_5$, $C_6H_5CH_2$, $C_6H_5S$ or R = $C_6H_5$, R′ = $C_6H_5S$, 4-$CH_3C_6H_5S$) from the corresponding ketones (LXIII) requires reduction with lithium tetrahydroaluminate.[58-60,68,104]

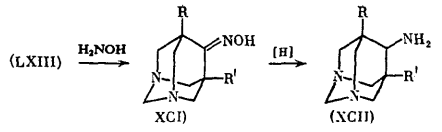


Various arylthiodiazaadamantanones (LXIII, R and/or R′ = $C_6H_5S$) have been obtained with the aim of their subsequent conversion into diazaadamantane derivatives without substituents at the bridgehead positions by eliminating sulphur, but the study of this reaction demonstrated their interesting and important feature: on heating with Raney nickel in alcohol, monoarylthioadamantanones (LXIII, R = $C_6H_5S$, R′ = $C_6H_5$, $COOCH_3$) smoothly eliminate sulphur with simultaneous reduction of the keto-group to an alcoholic group and are converted into monosubstituted diazaadamantanols (LXXXVI, R = H, R′ = $C_6H_5$, $COOCH_3$), whereas di(phenylthio)diazaadamantanone (LXIII, R = R′ = $C_6H_5S$) does not eliminate sulphur under these conditions and is merely reduced to di(phenylthio-diazaadamantanol (LXXXVI, R = R′ = $C_6H_5S$).[63]

Diazaadamantanones (LXIII) react with methylmagnesium iodide and organolithium compounds affording the corresponding tertiary alcohols (LXXXVII).[104,105]

Depending on the structure of the substituents R and R′, diazaadamantanones (LXIII) react in different ways with hydrazine: on heating with hydrazine hydrate, methyldiazaadamantanone (LXIII, R = $CH_3$, R′ = H) affords only the azine (LXXXVIII) as the stable product, while phenyl- and dimethyl-diazaadamantanones (LXIII, R = H, R′ = $C_6H_5$, $CH_3$ or R = R′ = $CH_3$) readily form the corresponding hydrazones (LXXXIX) whose fusion with alkali gives rise to the diazaadamantanes (XC).[104] Diazaadamantanones with two substituents such as the phenyl, phenylthio-, or *p*-tolylthio-group are reduced to the diazaadamantanes (XC, R = R′ = $C_6H_5$, $C_6H_5S$ or R = $C_6H_5$, R′ = $C_6H_5S$, $CH_3C_6H_4S$) by the Huang-Minlon method.[59,60,63,68,104]

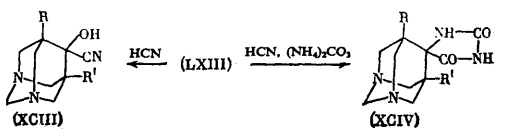
Monosubstituted diazaadamantanones and dimethyldiazaadamantanone react with hydroxylamine to form the oximes (XCI, R = H, R′ = $CH_3$, $C_6H_5$ or R = R′ = $CH_3$) in an aqueous medium,[104] whereas the oxime of diphenyldiazaadamantanone (XCI, R = R′ = $C_6H_5$) is formed only after prolonged heating with hydroxylamine in a pyridine-ethanol mixture in a yield of only 48%.[106]




R=H, R′=$CH_3$, $C_6H_5$; R=R′=$CH_3$, $C_6H_5$.

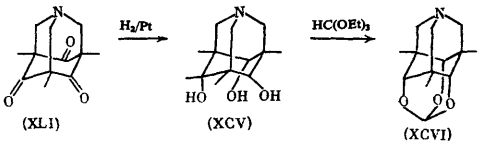
The oximes (XCI) are reduced to 6-amino-1,3-diazaadamantanes (XCII) by a nickel-aluminium alloy in an aqueous alkaline medium.[104]

The diazaadamantanones (LXIII) with two bulky substituents, such as the phenyl and phenylthio-groups, do not form cyanohydrins, whereas methyl- and dimethyl-diazaadamantanones are readily converted into the corresponding cyanohydrins (XCIII) on heating with acetone cyanohydrin. 1,3-Diazaadamantane-6-spiro-5′-hydantoins (XCIV) were obtained from the cyanohydrins by the Bucherer method.[107]

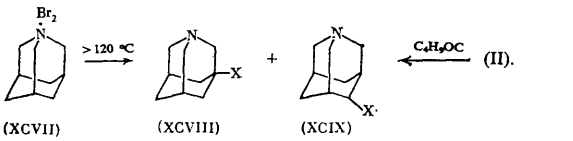



R=H, R′=$CH_3$; R=R′=$CH_3$.

The reactivity of the monoazaadamantanones (XLI) and (XLII) is still to be investigated, but so far it has been shown that the hydrogenation of trimethylazaadamantanetrione (XLI, R = R′ = $CH_3$) in the presence of a platinum catalyst results in the formation of trimethylazaadamantanetriol (XCV) with the axial disposition of all three hydroxy-groups relative to the cyclohexane ring, which has been confirmed by its conversion into the heterodiamantane (XCVI).[36]

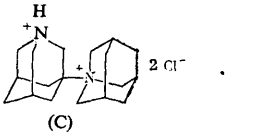



The most important intermediates in the synthesis of derivatives of adamantane (I) itself are halogenoadamantanes obtained by its halogenation.[7] The halogenation of 1-azaadamantane (II) has been investigated.[108,109] When bromine is added to a solution of azaadamantane (II) in carbon tetrachloride, complex (XCVII) is formed. When an attempt is made to obtain from it 3-bromo-1-azaadamantane (XCVIII, X = Br) via an ionic mechanism by adding aluminium chloride or bromide and bromine, it is possible to isolate only the complexes of azaadamantane with these salts. On the other hand, on heating complex (XCVII) to 120 °C, a mixture of 3- and 4-bromo-1-azaadamantanes (XCVIII, X = Br) and (XCIX, X = Br) is formed.




The absence of 2-bromo-1-azaadamantane from the radical bromination products probably indicates its instability.[108] 3-Chloro- and 4-chloro-1-azaadamantanes (XCVIII) and (XCIX) with X = Cl have been obtained by irradiating with UV light a mixture of azaadamantane and t-butyl hypochlorite.[108] Comparison of the ratios of the products of the radical halogenation of adamantane (I) and 1-azaadamantane (II) shows that the introduction of a nitrogen atom into the adamantane nucleus does not have a significant influence on the radical halogenation reaction.

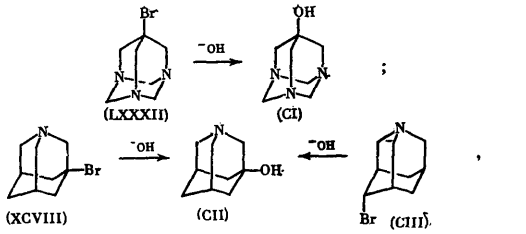
When a solution of azaadamantane (II) in carbon tetrachloride is irradiated with UV light or when it is treated with hydrogen peroxide, the salt (C) is formed and can be regarded formally as the product of the alkylation of azaadamantane with 3-chloro-1-azaadamantane.



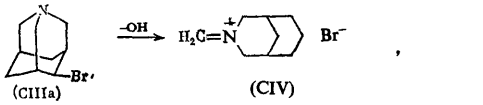

The same product is also formed in the photochemical chlorination of azaadamantane with trichloromethanesulphonyl chloride.[108] Here it was shown that 3-chloro-1-azaadamantane (XCVIII, X = Cl) does not participate in the formation of the salt (C), since irradiation of a mixture of compound (XCVIII, X = Cl) and azaadamantane (II) does not lead to the formation of the salt (C). On this basis, it has been suggested that the alkylating agent in the formation of compound (C) is the 1-azaadamantane radical-cation.[109]

The halogen atoms in 1-halogenoadamantanes, which are key intermediates in the chemistry of adamantane (I), are comparatively

readily substituted by nucleophiles. Kinetic studies have shown that the rate of hydrolysis of 3-bromo-1-aza- and 7-bromo-1,3,5-triaza-adamantanes (XCVIII, X = Br) and (LXXXII) is lower by several orders of magnitude than the rate of hydrolysis of their analogue—1-bromoadamantane.[108,110] The passivating influence of nitrogen atoms can be explained by their electron-accepting inductive effect and the impossibility, for geometrical reasons, of their anchimeric involvement, as in other β-halogenoamines. Hydrolysis of the halogenoazaadamantanes indicated leads to 1,3,5-adamantan-7-ol (CI) and 1-azaadamantan-3-ol (CII), which could not be obtained by other methods hitherto.[110]



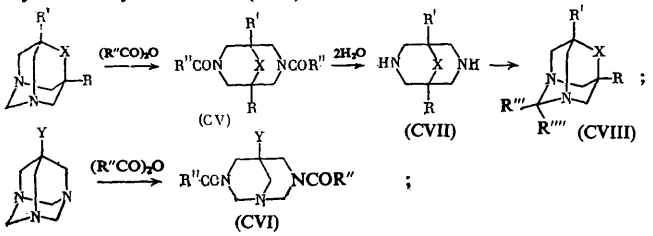
Hydrolysis of the isomeric 4-bromo-1-azaadamantanes (CIII) proceeds in different ways: the isomer (CIIIa) with the bromine atom in the axial position relative to the piperidine ring is unstable under hydrolysis conditions and is converted into the methylene-immonium cation (CIV), i.e.



where the isomer (CIIIb) with the equatorial orientation, obtained by treating 1-azaadamantan-4-ol (XII) with phosphorus pentabromide, hydrolyses to 3-hydroxy-1-azaadamantan (CII) and not to the 4-hydroxy-derivative.[16]

## 2. Reactions with elimination of aminal methylene groups

The di- and tri-azaadamantanes containing aminal methylene group split them off on treatment with various reagents. Diazaadamantanes react with carboxylic acid anhydrides and chlorides to form diacylbispidines (CV), while triazaadamantanes afford diacyltriazabicyclononanes (CVI).[63,64,67,68,71,112–116]



X = CO, CHOH, $CH_2$; Y = $NO_2$, NHOH, $NH_2$, NHCOR;
R, R′ = H, $C_6H_5S$, 4-$CH_3C_6H_4S$;
R″ = H, $CH_3$, $C_6H_5$, $C_2H_5O$, $ClCH_2$;
R‴ = H, R′′′′ = $CH_3$, $C_2H_5$, $C_3H_7$, $C_6H_5$, 4-$O_2NC_6H_4$, 4-$CH_3OC_6H_4$, α-$C_4H_3O$, 4-($ClCH_2CH_2$), $NC_6H_4$, $H(CHOH)_4$, $H(CHOH)_5$ or R‴R′′′′ = $(CH_2)_4$, $CH_2)_5$.

*NN*-Diformylbispidines (CV, R″ = H) can be obtained by the reaction of diazaadamantanes with chloroform in an alkaline medium.[65,114]

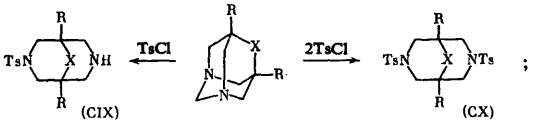
Arylthio- and diarylthio-diacetylbispidines (CV, R and/or R′ = $C_6H_5S$, 4-$CH_3C_6H_4S$) readily eliminate sulphur on treatment with Raney nickel, being converted into diacetylbispidines (CV, R and/or R′ = H) with one or two bridgehead positions free from substituents.[12,63,67,68]

The bispidines (CVII) without substituents at the nitrogen atoms can be obtained by the hydrolysis of diacetylbispidines (CV). They condense with various aldehydes and ketones to diazaadamantane derivatives (CVIII) with substituents at the aminal carbon atom.[63,64,68,71,115]

Under hydrolysis conditions, the bispidinones (CVII, X = CO) can be converted into the corresponding diazaadamantanones (LXIII).[63]

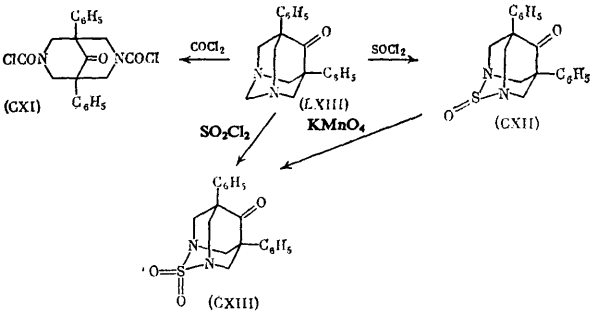
The hydroxyamino- and amino-derivatives (CVI, Y = NHOH, $NH_2$) can be obtained by hydrogenating nitrodiacetyltriazabicyclononane (CVI, Y = $NO_2$).[84,85]

Treatment of diazaadamantanes with toluene-*p*-sulphonyl chloride can yield *N*-tosylbispidines (CIX) or *NN*′-ditosylbispidines (CX).[63,109]

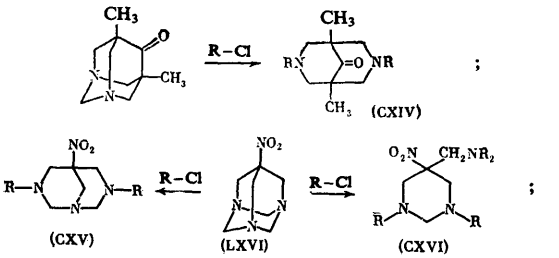


X = CO, $CH_2$; R = H, $C_6H_5$.

The attempt to replace the aminal methylene group in diphenyldiazaadamantane (LXIII, R = R′ = $C_6H_5$) by treating it with phosgene led to the formation of only the bispidine derivative (CXI), whereas treatment with thionyl or sulphuryl chloride in pyridine affords the 2-oxide (CXII) of the 2,2-dioxide (CXIII) of 5,7-diphenyl-1,3-diaza-2-thiaadamantan-6-one; the former can be oxidised to the latter with potassium permanganate.

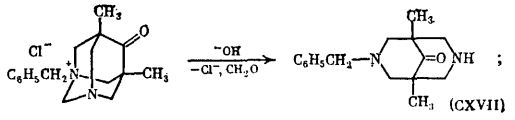


The interaction of di- and tri-azaadamantanes with benzyl, allyl, and propargyl chlorides, α-chloroketones, and chloroacetic acid esters can also be accompanied by the elimination of the aminal methylene groups; triazaadamantanes can then split off both one and two methylene groups, affording the corresponding derivatives of bispidine (CXIV), triazabicyclononane (CXV), and hexahydropyrimidine (CXVI).[118,119]

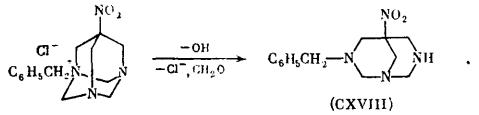


R = $C_6H_5CH_2$, $CH_2$=$CHCH_2$, HC≡$CCH_2$, $C_6H_5COCH_2$, $C_2H_5OOCCH_2$.

These reactions can be explained by the fact that, in the quaternary salts formed from di- and tri-azaadamantanes, the bond between the aminal methylene group and the quaternary nitrogen atom is weakened, which has been demonstrated by the X-ray diffraction analysis of the methiodide of diphenyldiazaadamantanone (LXIII, R = R′ = $C_6H_5$).[120] On treatment with bases, the aminal methylene group therefore splits off, affording the bispidine and triazabicyclononane derivatives (CXVII) and (CXVIII).[118,119]

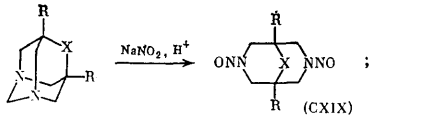


(CXVII)



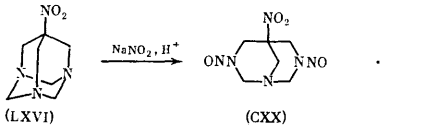
(CXVIII)

Treatment of di- and tri-azaadamantanes with nitrous acid leads to the formation of the dinitroso-derivatives of bispidine (CXIX) and triazabicyclononane (CXX).[63,121,122]



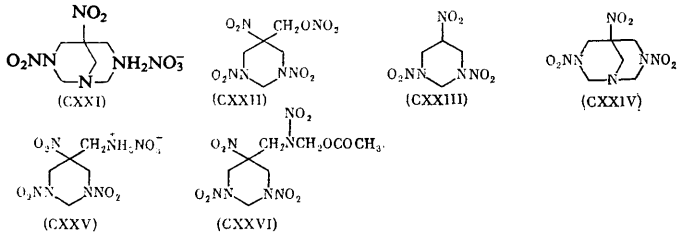
(CXIX)

R=H, $C_6H_5$; X=CO, $CH_2$.



(LXVI) (CXX)

Nitration of nitrotriazaadamantane (LXVI) [123] resembles the nitration of hexamethylenetetramine[124,125] and leads to the following products (depending on the conditions):

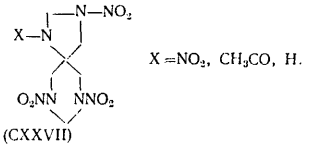


(CXXI) (CXXII) (CXXIII) (CXXIV)

(CXXV) (CXXVI)

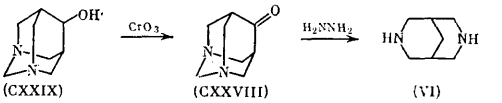
The bicyclic product (CXXI) is formed in the nitration of compound (LXVI) with fuming nitric acid at −40 °C, whereas on raising the temperature to −10 °C more far-reaching decomposition of the triazaadamantane skeleton takes place with formation of the monocyclic product (CXXII). This product is stable on heating in alcohols, but, on boiling in water, it is converted into 1,3,5-trinitrohexahydropyrimidine (CXXIII). Nitration with a mixture of concentrated nitric and sulphuric acids results in the formation of 3,5,7-trinitro-1,3,7-triazabicyclo[3.3.1]nonane (CXXIV). Nitration of compound (LXVI) with a mixture of concentrated nitric acid and ammonium nitrate gives rise to the product (CXXV), while nitration with a mixture of fuming nitric acid, acetic anhydride, and acetic acid at the usual temperature affords the product (CXXVI).

When aminotriazaadamantane (LXVII) is nitrated with fuming nitric acid, the tetraazabicyclic products (CXXVII) are formed.



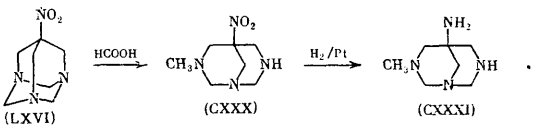
(CXXVII)

Under severe conditions, the aminal methylene groups can be split off also on treatment with hydrazine. Thus when an attempt was made to reduce 1,3-diazaadamantan-6-one (CXXVIII), [obtained by oxidising diazaadamantanol (CXXIX) with chromium trioxide[126]] by the Huang–Minlon method, bispidine (VI) was synthesised instead of diazaadamantane (III).[127]



(CXXIX) (CXXVIII) (VI)

The opening of one of the rings of nitrotriazaadamantane (LXVI) with the simultaneous reduction of the methylene group to the methyl group occurs when it is heated with formic acid under the conditions of the Leuckart reaction. The 3-methyl-5-nitro-1,3,7-triazabicyclo[3.3.1]nonane (CXXX) was hydrogenated to the amine (CXXXI) in the presence of a platinum catalyst.[23]

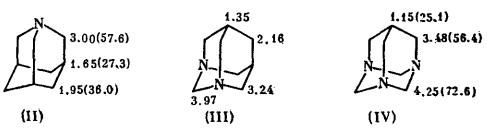


(LXVI) (CXXX) (CXXXI)

## IV. Physical and spectroscopic properties

The nitrogen atoms hardly affect the spherical shape (sphere diameter 6.71 Å) [7] of the adamantane nucleus, which represents the unit cell of the crystal lattice of diamond. Such molecular geometry determines many physical and spectroscopic characteristics of azaadamantanes.

By virtue of the high molecular symmetry, the NMR spectra of azaadamantanes are exceptionally simple and characteristic. The chemical shifts δ (in p.p.m.) of the protons measured in $CCl_4$ are listed below[8] (the $^{13}C$ chemical shifts are indicated in brackets[128]):



(II) (III) (IV)

The spectra of various azaadamantane derivatives have been published in a number of communications including Refs. 73, 74, 80, 112, and 129–131.

The protons at the bridgehead positions are manifested in all cases by broadened singlets in a higher field the greater the number of nitrogen atoms in the molecule.

The spectra of mono- and tri-azaadamantanes (II) and (IV) having the same molecular symmetry are similar and consist of singlets, due to the protons of the $NCH_2C$ groups, and of the AB-systems due to the remaining protons. On the basis of the splitting into doublets of the AB-systems, induced by the interaction

with the protons of the $NCH_2C$ groups, a definite orientation relative to the symmetry axes of the molecules can be assigned to the corresponding protons.

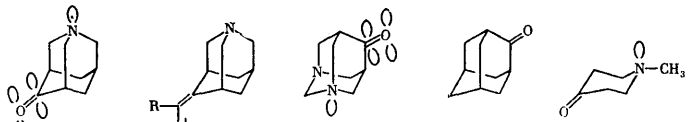
In the spectrum of diazaadamantane (III) the protons at the C(6) atoms and of the aminal methylene group are manifested by singlets, while the protons of the $NCH_2C$ groups are manifested by an AB-system.

It is noteworthy that, whereas the nitrogen atoms shield the protons at the bridgehead positions [$\delta$ = 1.87 p.p.m. for the methylidyne proton of adamantane (I)], the protons of the methylene groups in the β-positions are strongly deshielded [$\delta$ = 1.74 p.p.m. for the methylene protons of adamantane (I)].

The mass spectra of triazaadamantane (IV) and its derivatives contain intense peaks due to molecular ions, which decompose subsequently via two independent pathways depending on the character of the substituents. If the substituents of the C(7) atom are H, Cl, Br, and $NO_2$, then they are readily abstracted and the spectra of different derivatives differ little from one another. On the other hand, if the substituents are electron-donating groups such as the amino-group, they are not split off and persist in all the main ions of the mass spectrum. The molecular ions of halogenotriazaadamantanes can split off, apart from halogen atoms, also hydrogen halide molecules, although with a lower probability. The most intense ion in the mass spectra of triazaadamantanes is, as for hexamethylenetetramine, the $[C_2H_4N^+]$ ion.[132]

The mass spectra of diazaadamantanones (LXII) have been considered.[74] The decomposition of the molecular ions is accompanied by the breakdown of the adamantane nucleus with formation of the ions $[C_2H_4N]^+$, $[M-C_2H_4N]^+$, $[C_3H_2RCO]^+$, and $[M-C_2H_5N]^+$, the last one being as a rule the most intense.

The UV spectra of azaadamantanone (XI), diazaadamantanone (CXXVIII),[80,127,129] and substituted 6-methyleneazaadamantanes (CXXXII, R = R′ = H, CN; R = $COOC_2H_5$, R′ = H, CN) are of special interest.[131] The last compounds were obtained from the ketone (XI) via Wittig, Horner, or Knoevenagel reactions.[17]



(XI) (CXXXII) (CXXVIII) (CXXXIII) (CXXXIV)

The point is that conditions under which the *n* electrons of the nitrogen atom can interact with the π-systems of the multiple bonds are largely maintained in these compounds: the orbitals of these electrons are almost parallel to one another and to the central bond along the σ-bonds separating them.[133–138] Such interaction, which has been called "σ-bonding interaction" or "σ-conjugation",[133] leads to the appearance in the near UV absorption spectrum of these compounds of intense bands which are not characteristic of the corresponding chromophores considered separately. Thus, whereas the spectrum of the adamantanone (CXXXIII) shows only a weak absorption with $\lambda_{max}$ = 290 nm ($\varepsilon \simeq 19$), due to the $n \rightarrow \pi^*$ transition in the keto-group, in the case of azaadamantanones (XI) and (CXXVIII), a strong absorption is observed with $\lambda_{max}$ = 243 nm ($\varepsilon$ = 1366) (in hexane) and 255 nm ($\varepsilon \simeq 1700$) (in dioxane) respectively. *N*-Methylpiperidinone (CXXXIV), which is related to compound (CXXXIII) as regards the distribution of the chromophores and whose lone electron pair occupies an axial position, does not absorb at all in the near UV.

The basicity of the azaadamantanes (II)–(IV) in water (see above) and in dimethyl sulphoxide has been determined by potentiometric titration.[8] The p*K* values in water at 22 °C for 1-azaadamantane (IV) (2.96) 4-methylene-1-azaadamantane (CXXXII, R = R′ = H) (4.16), and 1-azaadamantan-4-one (XI) (5.43) have been published.[13] On the other hand, the basicity of azaadamantane derivatives in the gas phase has been determined[135] by cyclotron magnetic resonance.

The lower basicity of methyleneazaadamantane and azaadamantanone compared with azaadamantane is not caused solely by the "σ-bonding interaction", since 1-methyl-4-piperidinone (CXXXIV) (p*K* = 6.01), in which σ-conjugation is impossible, is also less basic than *N*-methylpiperidine (p*K* = 3.92).[131]

## V. Conclusion

The development, especially in recent years, of simple and convenient methods of synthesis of azaadamantanes has made them entirely available for wide-scale research and practical applications.

There are as yet only a few published data concerning the practically useful properties and the possible applications of azaadamantanes. There are patent data[139] showing that the alkylaminotriazaadamantanes (LXX) and (LXXI) can be used as a solid rocket fuel, while their solutions in hydrocarbons can be used as a liquid rocket fuel. It has been suggested that the aminotriazaadamantane (LXVII) as well as the azomethines (LXIX) and ureas (LXXVII) obtained from it be used as stabilisers of various polymers against thermal light-induced ageing.[91,95,98,100,140] Diacetyltriazabicyclononanes (CVI) catalyse the formation of polyurethane resins and prevent the phase separation of liquid epoxy-resins in alcohol.[115] It has been suggested that certain triazaadamantane derivatives be used as modifying agents for rubbers.[141–145]

The thermal stability of azaadamantanes and their capacity for complex formation with various metal salts permit their application as additives to fuel-lubricating materials, as corrosion inhibitors, as high-temperature oil thickening agents, and as emulsifying agents and also for the regeneration of ion-exchange resins.[82]

Azaadamantanes can be used as catalysts in various processes,[8] for example, in the additional purification of a gas to remove sulphur.[146,147]

The use of azaadamantanes for the preparation of therapeutic drugs in medicine and veterinary science is particularly promising. It has been reported that diphenyldiazaadamantanol (LXXXVI, R = R′ = $C_6H_5$) and other diazaadamantanols exhibit a strychnine-like activity,[148] while diphenyldiazaadamantane (XC, R = R′ = $C_6H_5$) and some of its derivatives have a convulsant activity (Ref. 8, pp 348, 349). Derivatives of the trimethylazaadamantane (XLVII, X = COR) (R = alkyl, aryl, pyridyl, naphthyl, coumaryl, etc.) possess cardiovascular and antiarrhythmic activities.[149,150]

Experiments on mice have shown that the antiviral activity of 7-amino-1,3,5-triazaadamantane (LXVII) is close to that of the familiar preparation midantane.[151,152]

The available data concerning the practically useful properties of azaadamantanes and the specific chemical and physicochemical properties discovered in them lead to their differentiation as a separate new class of organic compounds of interest not only to chemists but also to representatives of other branches of science and engineering.

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