RUSSIAN CHEMICAL REVIEWS
Uspekhi Khimii

October 1970

U.D.C. 547.518

Advances in the Chemistry of Adamantane

V.V.Sevost'yanova, M.M.Krayushkin, and A.G.Yurchenko

The review deals with the latest data on the chemistry of adamantane and its nearest homologues—noradamantane and homoadamantane. A systematic account is given of the methods for the preparation of adamantane derivatives. The reactivities of the bridgehead and bridge sites in the adamantane structure have been considered in detail.
The bibliography includes 192 references.

CONTENTS

I.	Introduction	817
II.	Synthesis of the adamantane structure	818
III.	Synthesis of nearest homologues of adamantane	820
IV.	Physicochemical properties of adamantane	821
V.	Chemical properties of adamantane	822
VI.	Quantitative study of the reactivity of adamantane	827
VII.	Applications	830

I. INTRODUCTION

In the last two decades there has been an increase of interest in the chemistry of skeletal compounds. Adamantane occupies a special place among them—it was the first hydrocarbon which proved to have a diamond-like structure and it has in fact served as a touchstone for the investigation of the chemical and physicochemical properties of substances of this type. In the 1960's several reviews on the chemistry of polyhedral compounds were published[1-6].

The number of reports on the chemistry of adamantane increases sharply each year. In the last 2-3 years interesting and fundamentally new methods for synthesising adamantane and its derivatives have been developed. There has been an increase of interest in adamantane derivatives as biologically active substances.

The aim of the present review is to give a general account of the latest data on the chemistry of adamantane(I) and its nearest homologues—noradamantane (II) and homoadamantane (III).



(I) (II) (III)

On the basis of quantitative physicochemical data for adamantane and their comparison with data for other carbocyclic compounds, an attempt is made to estimate quantitatively the characteristics of the chemical behaviour of adamantane and to determine its position in the series of other cyclic systems.

Heteroadamantanes are not considered in the review; as far as possible, the literature up to July 1969 is included.

II. SYNTHESIS OF THE ADAMANTANE STRUCTURE

1. Synthesis of Adamantane by the Isomerisation of Organic Compounds of Various Classes

The range of compounds capable of isomerisation to the adamantane structure has been extended so much that the term "adamantisation"[7] now appears quite natural and valid. While initially polycyclic perhydroaromatic hydrocarbons containing ten and more carbon atoms were subjected to adamantisation[8-11], nowadays a much wider range of compounds, including derivatives with different functional groups, has been investigated in this reaction. The isomerisation of cholesterol, cholestane, abietic acid, cedrene, caryophyllin, cyclohexane, squalene, squalane, and dodecane leads to the formation of a mixture of alkyladamantanes in 2–45% yield[12]. The reaction is carried out under pressure in the presence of aluminium halides at 110–130°C for 2–5 days. The solvents employed are cyclohexane and carbon disulphide or the reaction is carried out without a solvent. It is interesting to note that adamantane itself has not been detected in the isomerisation products—the main products were 1,3,5,7-tetramethyl-, 1,3,5-trimethyl-, and 1,3-dimethyl-adamantanes; 1-methyl- and 3-ethyl-1-methyl-adamantanes were isolated only in small amounts.

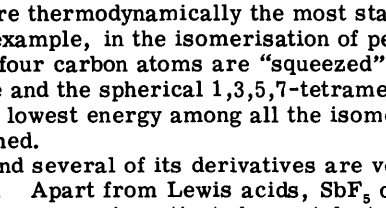
Possibly the above study will serve as the starting point of the search for industrial methods for the synthesis of polyalkyladamantanes. The isomerisation of cedrane[12,13] is already the best method for the synthesis of 7-ethyl-1,3,5-trimethyladamantane.

1,3-Dimethyladamantane is formed in the isomerisation of 1-ethyladamantane[14] and *endo*- and *exo*-2,2-dimethyltetrahydrodicyclopentadiene[15] in the presence of aluminium chloride.

An effective isomerisation catalyst proposed by Robinson[11] consists of a mixture of t-butyl bromide and aluminium bromide; the catalyst is employed in the form of a suspension in the hydrocarbon to be isomerised.

Schneider et al.[16] made a detailed study of the conversion of a mixture of isomeric C_{14} perhydroanthracenes and perhydrophenanthrenes into the adamantane system. The experimental data convincingly show that alkyladamantanes, particularly those substituted at the nodal sites (methyladamantanes), are stable final isomerisation products. Careful calculations by the authors of the enthalpies and entropies of the initial hydrocarbons and various products of their skeletal isomerisation showed that adamantane homologues are thermodynamically the most stable isomers. For example, in the isomerisation of perhydrophenanthrene four carbon atoms are "squeezed" out of the ring structure and the spherical 1,3,5,7-tetramethyladamantane, with the lowest energy among all the isomers investigated, is formed.

Twistane and several of its derivatives are very easily adamantised[7]. Apart from Lewis acids, SbF_5 or an SbF_5/SO_2 mixture were investigated as catalysts; the reaction was carried out at −80°C for 30 min:

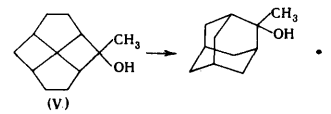


(IVa, b)

where R = R′ = H in (IVa) and R = H and R′ = OH in (IVb).

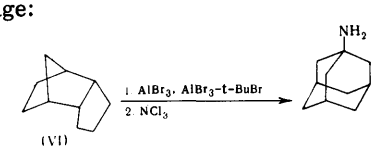
The transition from the twistane structure to the adamantane structure, which includes the "untwisting" of one methylene bridge, takes place via the initial formation of a cation. Experiments with deuterated compounds showed that the removal of hydrogen takes place during the rearrangement and the adamantyl cation formed is stable in relation to hydrogen exchange.

2-Methyl-2-adamantanol was obtained under the same conditions in the isomerisation of 2-methyl-2-twistanol (V):



(V)

The recently developed method for the synthesis of 1-aminoadamantane from tricyclo[5,2,1,$0^{2,6}$]decane (VI)[17,18] undoubtedly merits attention. The isomerisation and amination with nitrogen trichloride may be carried out in a single stage:



(VI)

The above reaction is interesting because it made it possible for the first time to introduce a functional group in the isomerisation process and to obtain a high yield of 1-aminoadamantane (amantidine), which is now in the stage of comprehensive clinical tests.

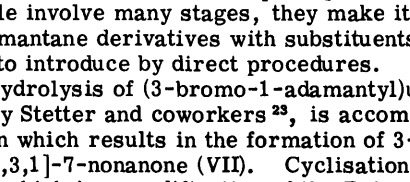
Thus the isomerisation conditions developed at the present time permit the synthesis with fairly high yields of adamantane, its homologues, and certain functional derivatives from a wide range of organic compounds.

All these studies are of undoubted theoretical interest also in another connection; they throw light on the origin of skeletal and in particular adamantane compounds in petroleum[4,19]. A number of studies have been made on the development of methods for the isolation of adamantane and its homologues from petroleum[20-22].

2. Synthesis of the Adamantane Nucleus from Bicyclic Systems.

The greatest number of studies have been made on the synthesis of adamantane derivatives from compounds containing the bicyclo[3,3,1,]nonane system. Although the methods for the synthesis of bicyclo[3,3,1]nonane derivatives as a rule involve many stages, they make it possible to obtain adamantane derivatives with substituents which are difficult to introduce by direct procedures.

Alkaline hydrolysis of (3-bromo-1-adamantyl)urethane, carried out by Stetter and coworkers[23], is accompanied by fragmentation which results in the formation of 3-methylenebicyclo[3,3,1]-7-nonanone (VII). Cyclisation of this compound[24], which is a modification of the Prins reaction, takes place in an acid medium with the initial formation of the 3-hydroxy-1-adamantylcarbonium ion, capable of further addition with formation of compound (VIII):

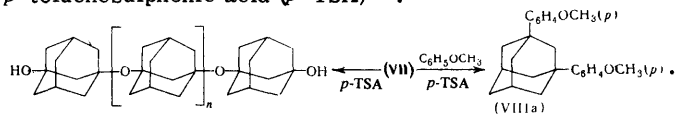


(VII) (VIII)

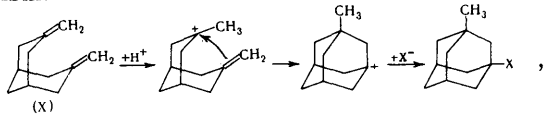
where X = OH, OC_2H_5, SC_2H_5, Cl, $NHCOCH_3$, NH_2, or N⟨ ⟩.

Compound (VII) undergoes ring closure to adamantane not only in an acid medium but also in the reaction with ammonia and amines (piperidine). The authors suggest that in this case the reaction initially involves the carbonyl group and that on heating a carbonium ion is formed, which subsequently undergoes further ring closure to adamantane [24].

When (VII) is heated with anisole, (VIIIa) is readily formed and heating of (VII) in a solvent (benzene, chlorobenzene, or carbon tetrachloride) leads to the formation of the polyester (IX); both reactions are catalysed by *p*-toluenesulphonic acid (*p*-TSA) [24]:

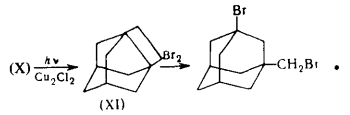


3,7-Dimethylenebicyclo[3,3,1]nonane (X), which undergoes ring closure to adamantane derivatives under the action of electrophilic reagents [25,26], is formed from (VII) by the Wittig reaction. The conversion of (X) into adamantane derivatives undoubtedly involves an ionic mechanism:

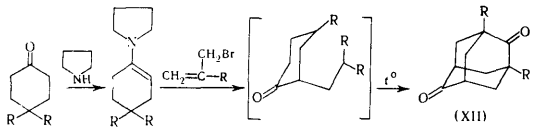


where X = Cl, Br, I, OH, OCH_3, $NHCOCH_3$, or p-$C_6H_4OCH_3$.

Photoinitiation of the cyclisation of (X) [27] leads to the formation of tetracyclo[4,3,1,$1^{4,8}$,$0^{1,4}$] undecane (XI), a highly strained compound, which on refluxing in bromine combines with one mole of the latter:

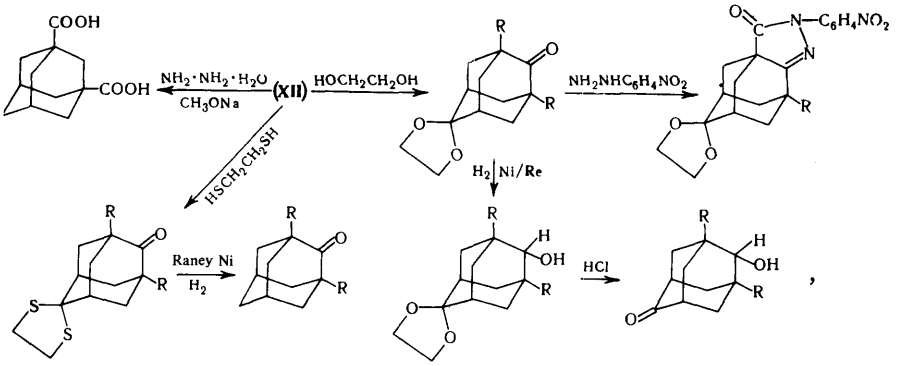


The recently developed method for the synthesis of the diethyl ester of 2,6-dioxa-adamantane-1,3-dicarboxylic acid (XII) is attractive because of the ready availability of the starting material, high yields at all stages, and the possibility of obtaining polysubstituted adamantanes [28,29]:



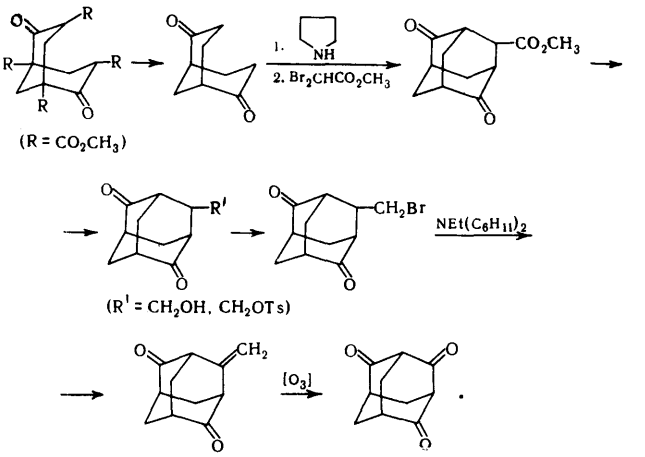
where R = $CO_2C_2H_5$.

Starting from compound (XII), the authors carried out the following series of reactions [29]:

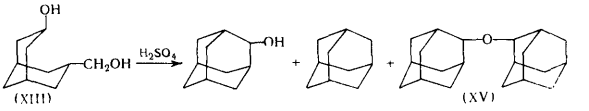


where R = $CO_2C_2H_5$.

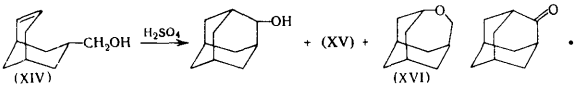
The methyl ester of 2,6-dioxoadamantane-4-carboxylic acid was obtained from Meerwein's ester and some of its reactions have been investigated [30]:



In contrast to the cyclisation of 3,7-disubstituted bicyclo[3,3,1]nonanes, which leads to the formation of 1,3-disubstituted adamantanes, the cyclisation of 3-hydroxymethylbicyclo[3,3,1]-7-nonanol (XIII) and 3-hydroxymethylbicyclo[3,3,1]non-2-ene (XIV) in the presence of sulphuric acid gives 2-monosubstituted adamantanes [31]. On treatment with 48% sulphuric acid in dioxan, a mixture of 2-hydroxyadamantane (39%), adamantane (17%), and 2-adamantyl ether (XV) (26%) is formed from (XIII):



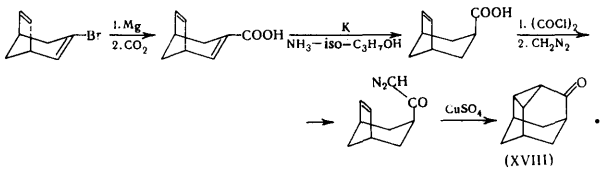
The cyclisation of (XIV) under the same conditions leads to the formation of 2-hydroxyadamantane (80%), small amounts of (XV), 2-oxatricyclo[4,3,1,$1^{4,8}$]undecane (XVI) and adamantanone:



The idea of the possible synthesis of adamantane derivatives by the ring closure in the 3- and 7-positions of bicyclo[3,3,1]nonane was already put forward in the first studies on the synthesis of the adamantane nucleus. The novel feature of the studies quoted above consists in the fact that the adamantane system is formed as a result of

intramolecular condensation; a methylene bridge is formed from the carbon atom already present in the bicyclo[3,3,1]nonane ring.

An interesting scheme for the synthesis of the adamantane structure was recently proposed by Baldwin and Foglesong[32]. They started with 3-bromobicyclo[3,2,1]-octa-2,6-diene (XVII), which was converted into 8,9-dehydro-2-adamantanone (XVIII) by the mechanism below:

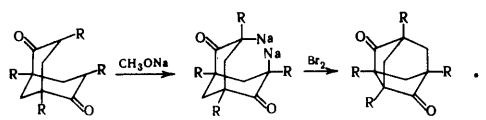


(XVIII)

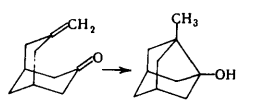
III. SYNTHESIS OF NEAREST HOMOLOGUES OF ADAMANTANE.

In this review we are considering only two nearest homologues of adamantane: tricyclo[3,3,1,$0^{3,7}$]nonane (noradamantane) and tricyclo[4^{3},1,$1^{3,8}$]undecane (homoadamantane).

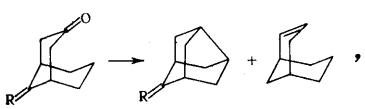
Meerwein was the first to obtain the noradamantane system by the cyclisation of the Meerwein ester[33]:



Many years later disubstituted noradamantane was obtained by the reduction of 3-methylenebicyclo[3,3,1]-7-nonanone with sodium in wet ether[34]:

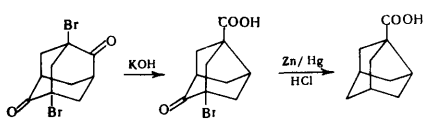


The noradamantane structure is formed on dry distillation of salts of the tosylhydrazone of bicyclo[3,3,1]-3-nonanone[35]:



where R = H_2 or $-OCH_2CH_2O-$. In both cases the transannular cyclisation of the bicyclo[3,3,1]nonane system to the noradamantane system takes place extremely readily.

A completely different approach to the synthesis of the noradamantane system was achieved by Vogt and Hoover, who started with 1,5-dibromoadamantane-2,6-dione (XIX), which was converted by the Favorskii reaction into substituted noradamantane[36]:

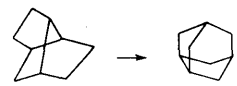


(XIX)

This method merits attention for two reasons: firstly, there is no doubt about the noradamantane structure obtained in this way and, secondly, the presence of three functional substituents permits the preparation of a wide variety of derivatives.

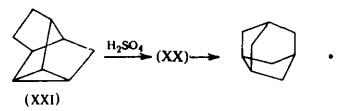
Noradamantane as well as adamantane may be obtained by the isomerisation of tri- and tetra-cyclic hydrocarbons in the presence of Lewis acids. Hitherto this isomerisation has been investigated only for a few isolated examples.

Brexane—tricyclo[4,3,0,$0^{3,7}$]nonane (XX)—isomerises very readily to noradamantane in the presence of aluminium bromide; the reaction is carried out for 30 min in carbon disulphide at 25°C, the yield of noradamantane being 75%[37]:



(XX)

Deltacyclane (XXI), which is a convenient starting material for the formation of the brexane skeleton, can isomerise to noradamantane under the action of 96% sulphuric acid[38]:

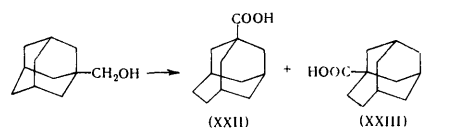


(XXI)

Depending on the method of treatment of the product, after isomerisation it is possible to obtain noradamantane with various substitutents in the 2-position.

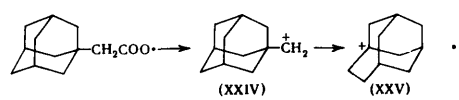
Noradamantane is a white crystalline substance melting at 203–204°C and readily subliming. Its chemical and physical properties have so far been little investigated.

The principal method for the preparation of homoadamantane derivatives involves the expansion of one of the rings in the adamantane nucleus. In 1959 Stetter and coworkers[39] obtained homoadamantane-3-carboxylic acid from 1-hydroxymethyladamantane by the Koch–Haaf reaction. A more detailed study of the properties of this compound[40,41] showed that the substance obtained by Stetter consisted of a mixture of 80% of homoadamantane-1-carboxylic acid (XXII) and 20% of homoadamantane-3-carboxylic acid (XXIII):



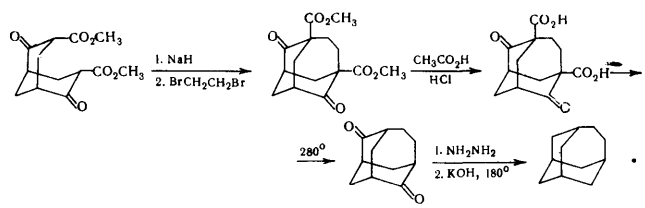
(XXII) (XXIII)

When the sodium salt of adamantane-1-acetic acid is electrolysed, the radical $AdCH_2COO^{\cdot}$, which is formed at the anode, loses carbon dioxide and is oxidised further to the cation (XXIV), which then rearranges to the 3-homoadamantyl cation (XXV)[42,43]:



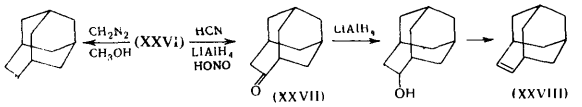
(XXIV) (XXV)

A specific synthesis of homoadamantane was achieved by Vogt[44] from bicyclo[3,3,1]nonane:

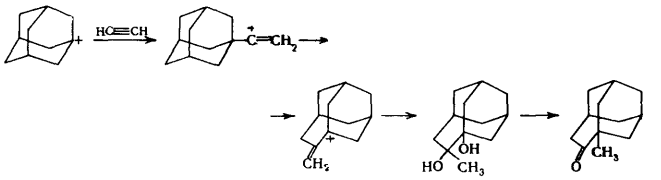


Promising methods for the synthesis of the homoadamantane system have been demonstrated[45,46]. In both

cases the authors started with the readily available adamantanone (XXVI):

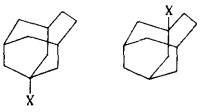


Subsequent reduction of 4-homoadamantanone (XXVII) leads to the formation of the corresponding alcohol, the dehydration of which gives 4,5-dehydrohomoadamantane (XXVIII). The formation of small amounts of homoadamantyl derivatives has been noted in the reaction of adamantane with acetylene[47]. The author suggested the following mechanism:



Other cases of the formation of the homoadamantane structure have also been observed but the reactions described are not unsuitable for preparative purposes[4].

The electrolysis of homoadamantanecarboxylic acids was investigated in the studies already mentioned[42,43]. Electrolysis of homoadamantane-1-carboxylic acid in methanol gives 1-methoxyhomoadamantane and homoadamantane-3-carboxylic acid is converted under the same conditions into 3-methoxyhomoadamantane. Two series of homoadamantane derivatives with substituents in the 1- or 3-position have been synthesised from the methoxy-derivatives[42]:



where X = OCH_3, Br, Cl, OH, $NHCOCH_3$, NH_2, COOH, $COOCH_3$, or CN.

The position of the substituents in the 1- and 3-bromo-derivatives of homoadamantane is confirmed also by a comparison of the relative rates of solvolysis. 1-Bromohomoadamantane is solvolysed only three times faster than 1-bromoadamantane, while 3-bromohomoadamantane is solvolysed 500 times faster[42].

IV. PHYSICOCHEMICAL PROPERTIES OF ADAMANTANE.

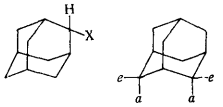
The principal physicochemical properties of adamantane have been very thoroughly described in the review mentioned above[3]. Subsequent studies dealt mainly with the revision and checking of results already published. Thus Nordman and Schmitkons[48] assert that at room temperature adamantane has a disordered face-centred cubic structure, probably belonging to the F_m3_m group rather than $F\bar{4}3m$ suggested previously. The same workers confirmed the occurrence of a phase transition at −65°C and determined the parameters of the low-temperature unit cell.

A phase transition to the tetragonal structure at 208.62°K was established by Resing[49] using the "spin echo" method. The phase behaviour of adamantane was also investigated at elevated temperatures and pressures[50].

It has been noted[3] that an experimental test of the lack of strain in adamantane is impossible without knowing the enthalpy of sublimation. Bratton and Szilard measured the vapour pressure of adamantane in the range 40–80°C and calculated the enthalpy of sublimation from the integral form of the Clausius–Clapeyron equation. It proved to be 14.0 kcal mole^{-1}. Subsequent calculations by the authors confirmed the conclusion that adamantane has a low strain energy[51]. The results of Bower et al.[54], who reported the formation of an adamantane radical-anion, were checked by Jones[52] and Gerson et al.[53], who showed that these data are erroneous. The signals in the ESR spectra assigned to the adamantane radical-anion are in fact due to contamination by benzene.

The NMR spectra of adamantane substituted at the bridgehead positions were already partly discussed in the review of Fort et al.[3] A detailed publication[55] showed that the NMR spectra yield much information about the structure of adamantane derivatives by virtue of the additivity of the chemical shifts of all the protons in the adamantane nucleus. The spectra of polysubstituted adamantanes may be calculated by the algebraic summation of the chemical shifts of the β-, γ-, and δ-protons of the corresponding monosubstituted adamantane derivatives in relation to unsubstituted adamantane. The relatively large difference between the chemical shifts, the absence of geminal spin–spin coupling, and the low vicinal coupling constant made the interpretation of the spectra easy. When the lines overlap, the use of benzene as a solvent makes it possible to elucidate all the structural detail. The effect of aromatic solvents on the NMR spectra of adamantane derivatives was studied in detail by Fort and Lindstrom[56], who postulated the presence of a 1:1 complex with the solvent in solutions of 1-halogenoadamantanes in benzene, which, however, is so unstable that it could not be detected by any method other than NMR spectroscopy.

The symmetry of adamantane derivatives with the substituent in the 2-position is much lower than that of 1-derivatives and therefore analysis of the spectra of such compounds is much more complicated. The NMR spectra of 2-derivatives of adamantane consist of a series of poorly resolved lines which do not show appreciable vicinal splitting. Analysis of the spectra recorded at a 100 MHz using double resonance established that J_{vic} = 2.6 Hz and J_{gem} = 12 Hz for compounds (XXIX)–(XXXIII). The chemical shifts for the majority of protons have also been determined[57]:

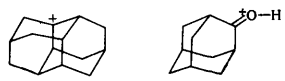


where X = Cl for (XXIX), X = Br for (XXX), X = I for (XXXI), X = OH for (XXXII), and X = NH_2 for (XXXIII).

2,4-Dihalogeno-derivatives of adamantane can exist in three stereoisomeric forms—2a, 2e; 2a, 4e; 2e, 4a. Analysis of the NMR spectra[58] of 2,4-dichloro-, 2,4-dibromo-, and 2,4-di-iodo-adamantanes established the configuration of these compounds and it was found that the chemical shifts of the protons of adamantane derivatives with substituents at the secondary carbon atoms are additive.

In individual NMR studies adamantane derivatives were also investigated among other compounds. Thus Olah and Lucas[59], who studied the behaviour of cycloalkanes in "magic" acid (a mixture of fluorosulphonic acid and antimony pentafluoride), found that, on dissolution in this mixture, adamantane loses a hydride ion and forms the

adamantyl cation. Trimethylenenorbornane is also converted under these conditions into the adamantyl cation with loss of a hydride ion. Diadamantane ("congressane") behaves analogously, losing a hydride ion from the tertiary position in the "belt" [(XXXIV)]. Adamantanone forms an oxonium species in "magic" acid[60]:

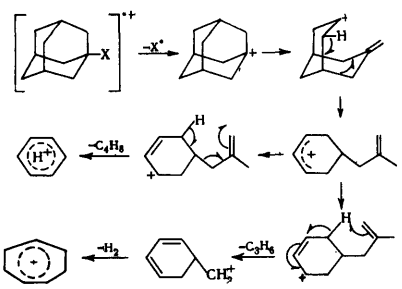


(XXXIV)
diamantane ("congressane")

Oleneva et al.[61] examined the infrared and Raman spectra of mono- and 1,3-di-substituted derivatives of adamantane. They noted that the absorption bands of the C–H and CH_2 groups are located in the regions characteristic of cyclohexane structures. The skeletal vibrations of the adamantane structure differ appreciably from those of the corresponding cyclohexane vibrations but they are not characteristic and probably cannot be used to identify the adamantane nucleus.

A combined approach to the study of alkyladamantanes has been demonstrated[62,63]. The authors characterise alkyladamantane on the basis of its infrared and Raman spectra and gas–liquid chromatography.

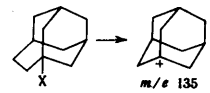
A detailed study of the behaviour of adamantane derivatives on electron impact has been made only for 1-substituted adamantanes[64]. Depending on their behaviour under electron impact, 1-derivatives of adamantane can be divided into two groups: compounds whose molecular ions split off the substituent in the form of a neutral fragment, while the remaining fragment $C_{10}H_{15}^+$ is further cleaved according to the mechanism



where X = Cl, Br, NO_2, CH_2OH, $COCH_3$, COOH, $COOCH_3$, C_6H_{11}, or $C_{10}H_{15}$, and compounds (X = OH, NH_2, $NHCOCH_3$, C_6H_5, or OCH_3) which split off olefin molecules, forming charged fragments where the substituent is retained. Adamantane itself gives a very intense peak due to the molecular ion which decomposes with elimination of olefins.

In contrast to adamantane, the molecular ion of homoadamantane[41] fragments into neutral radicals, forming thereby significant ionic species with odd masses. Like the 1-derivatives of adamantane, homoadamantane derivatives containing a substituent both in the 1-position and the 3-position can be divided into two groups differing in the nature of the mass spectra. The 1- and 3-derivatives of homoadamantane with Cl, Br, COOH, and $COOCH_3$ substituents give rise on electron impact to a molecular ion which splits off the substituent in the form of a neutral fragment and breaks down further with elimination of olefins.

Thermal rearrangement of the Wagner–Meerwein type to adamantane derivatives, leading to the formation of a fragment with $m/e = 135$ ($C_{10}H_{15}^+$) is characteristic of 3-substituted homoadamantanes of this group.



The presence or absence of the ion with $m/e = 135$ makes it possible to distinguish the 1- and 3-substituted homoadamantane derivatives.

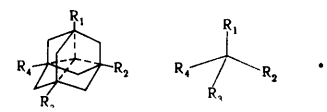
The molecular ions of 1- and 3-derivatives of homoadamantanes containing OH, OCH_3, NH_2, and $NHCOCH_3$ substituents split off neutral radicals and all the principal ions retain the substituent. The most intense peak in the mass spectra of compounds of this group is that corresponding to the $M - C_5H_{11}$ ion. The ratio of the intensity of this ion to that of the $M - C_4H_9$ ion in the case of the 1-substituted derivatives is 10:1 or above, while in the case of 3-substituted derivatives it is not more than 3:1, which makes it possible to distinguish these series of isomers.

In a study of the mass spectra of adamantane-1-acetic and homoadamantane-3-carboxylic acids deuterated in the carboxy-group, it was found that vigorous deuterium exchange with the nucleus takes place. Probably the 2-position of the adamantane or homoadamantane nucleus is capable of exchange.

Other spectroscopic methods were used to study adamantane derivatives to a much lesser extent. Chadwick et al.[65] calculated from the parameters of microwave spectra the carbon–halogen bond length in 1-halogenoadamantanes.

Certain properties of the ultraviolet and circular dichroism spectra have been investigated for β-substituted adamantanones[66].

Adamantane with four different substituents at the bridgehead carbon atoms may be regarded as a formal analogue of a compound with an asymmetric carbon atom:



The attempts to separate into optical isomers 3,5 and 3,5,7-substituted adamantane-1-carboxylic acids were unsuccessful[67]. By fractional crystallisation, Hamill and McKervey isolated an optically active dehydroabietylammonium salt of 5-bromo-3-methyladamantane-1-carboxylic acid[68]. The bromo-acid isolated from the salt proved to be optically inactive, but after conversion into 5-bromo-3-methyl-1-adamantylurethane and subsequent fragmentation, the optically active 1-methyl-3-methylenebicyclo[3,3,1]-7-nonanone ($[\alpha]_D^{23} = 10.4°$) was obtained.

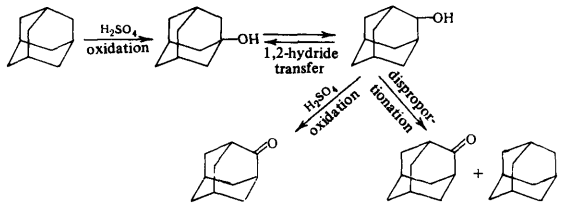
V. CHEMICAL PROPERTIES OF ADAMANTANE

During the last five years the chemistry of adamantane has developed very rapidly. The hydride transfer reactions, which permit the interchange of functional groups between bridgehead and bridge positions in the adamantane ring, must be regarded as the most important achievements in this field. Notable advances have been made in the synthesis of adamantane derivatives with substituents in the bridge positions. Finally, the increasing interest in the radical reactions of adamantane may be noted.

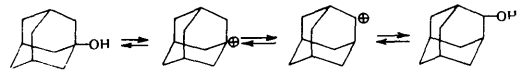
1. Hydride Transfer Reactions in the Adamantane Ring

These include in the first place oxidation of adamantane by sulphuric acid and the disproportionation of its hydroxy- and halogeno-derivatives.

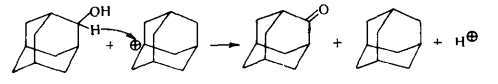
In 1967 Geluk and Schlatmann reported the direct oxidation of adamantane to adamantanone by sulphuric acid[69,70]. The mechanism of this multistage process is as follows:



They established that the individual stages in the conversion of adamantane into adamantanone are: (a) oxidation of adamantane to 1-adamantanol; (b) 1,2-hydride transfer leading to the equilibrium

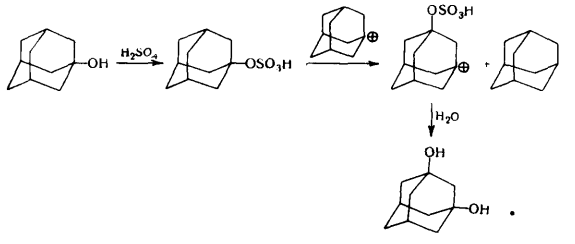


(c) intermolecular hydride transfer in which the adamantyl cation functions as a hydride ion acceptor:

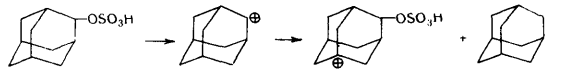


Adamantanone is formed also in the oxidation of 2-adamantanol by nitric acid.

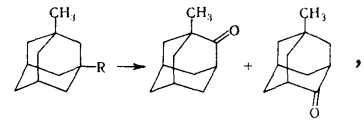
The composition of the products formed in the reaction of 1-hydroxy- or 2-hydroxy-adamantane with sulphuric acid depends to a considerable degree on the concentration of sulphuric acid, temperature, and duration of reaction. The 1,2-hydride transfer mentioned above [process (b)] takes place readily in 96% acid, while in 70% acid 1,3-hydride transfer takes place[71]:



Here too the acceptor is the adamantyl cation and the donor the sulphate ester of 1-adamantanol formed in sulphuric acid. In 70% sulphuric acid 2-adamantanol is similarly converted into an equimolar mixture of adamantane and 1,4-dihydroxyadamantane:

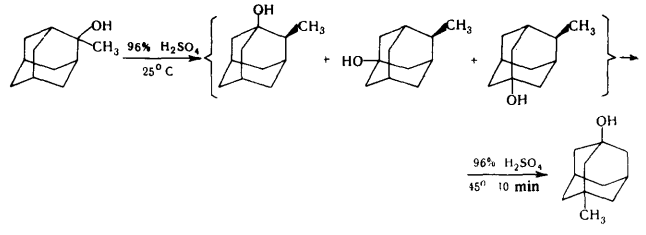


The structure of 1,4-dihydroxyadamantane obtained in the form of a mixture of two stereoisomers was rigorously demonstrated by the authors and on its basis a series of 1,4-disubstituted adamantanes were obtained. 1-Methyladamantane, 3-bromo-1-methyladamantane, and 3-hydroxy-1-methyladamantane as well as unsubstituted adamantane are oxidised by sulphuric acid to a mixture of isomeric 1-methyladamantanones[72]:

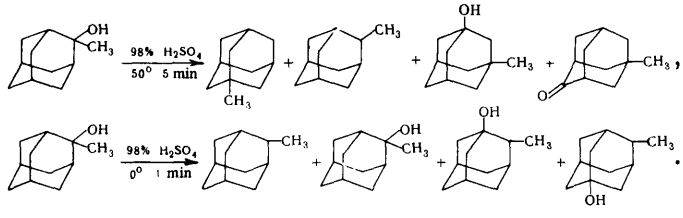


where R = Br, H, or OH.

The behaviour of 2-hydroxy-2-methyladamantane in sulphuric acid is fairly complex, which is probably the reason for a somewhat contradictory nature of the available literature data on its reaction products. At room temperature 2-hydroxy-2-methyladamantane[73] is immediately isomerised in 96% sulphuric acid to a mixture of 3 isomeric hydroxymethyladamantanes, the hydroxy-group being located at a bridgehead carbon atom. At 45°C the methyl group is also located at a tertiary carbon atom, as shown in the mechanism below:



The isomerisation of 2-hydroxy-2-methyladamantane in concentrated sulphuric acid at 0° and 50°C is likewise accompanied by intermolecular hydride transfers[73]:



The authors believe that the 2-methyl-2-adamantyl cation formed initially rapidly isomerises to a mixture of all other tertiary cations.

Patent data have also been published on the ready isomerisation of 2-hydroxyadamantane derivatives to the corresponding 1-hydroxyadamantanes[74]. 2-Hydroxyadamantane disproportionates under the influence of phosphoric and perchloric acids or Lewis acids[70].

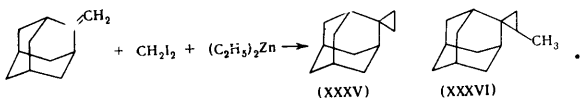
The rate of isomerisation of 2-hydroxy-2-methyladamantane is apparently sharply reduced when the temperature is decreased, since the only product of the isomerisation of 2-hydroxy-2-methyltwistane in an SbF_5/SO_2 mixture at −78°C is 2-hydroxy-2-methyladamantane[7].

2. Reactions Involving the Bridge Positions in the Nucleus.

Starting with adamantanone, which is now readily available, the following derivatives have been obtained by standard methods: 2-hydroxy-, 2-chloro-, 2-bromo, 2-carboxy-, 2-amino-, 2-cyclopentyl-, and 2-methyleneadamantanes[75,76].

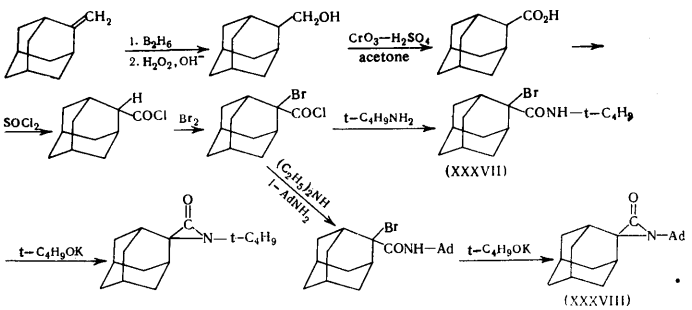
Methyleneadamantane also serves as a starting material for the synthesis of adamantanes substituted in the 2-position.

Like other olefins, methyleneadamantane reacts with methylene iodide and diethylzinc, forming spiro[adamantane-2,1′-cyclopropane] (XXXV) [77]; under the same conditions, 2-methylspiro[adamantane-2,1′-cyclopropane] (XXXVI) is formed from ethylideneadamantane:



(XXXV) (XXXVI)

The α-lactams (XXXVII) and (XXXVIII) can also be obtained from methyleneadamantane by the following mechanism [78]†:

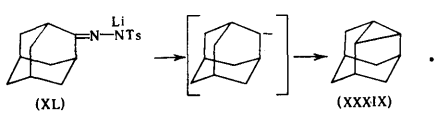


(XXXVII)

(XXXVIII)

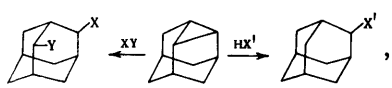
The lactams (XXXVII) and (XXXVIII) thus obtained are quite stable despite containing β-hydrogen atoms, since the latter are located at the bridgehead positions and the isomerisation of lactams with ring opening is blocked.

A fundamentally new method for the synthesis of adamantanes with substituents in bridge positions was developed starting from 2,4-dehydroadamantane (XXXIX) obtained by the pyrolysis of the dry lithium salt of the *p*-tosylhydrazone of adamantone (XL) at 130–140°C [79]:



(XL) (XXXIX)

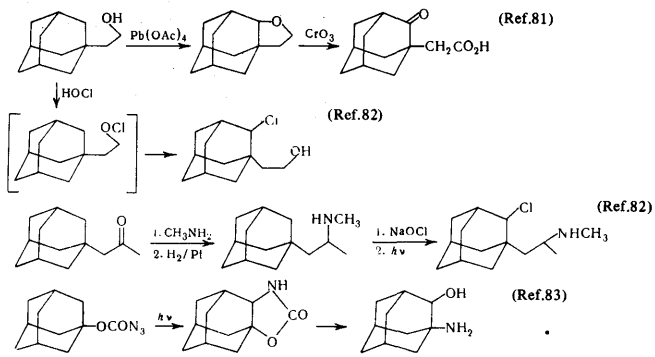
Compound (XXXIX), which is a readily available hydrocarbon with m.p. 202.5–203.5°C, is a very convenient starting material for the synthesis of 2-monosubstituted and 2,4-disubstituted adamantane derivatives [80]:



where X = Cl, H, Br, I, OH, =O, or $NHCOCH_3$, Y = Cl, Br, I, C_6H_5, OH, or H, and X′ = $OCOCH_3$, OCH_3, C_6H_5, $(o+p)$-$C_6H_4CH_3$, or $(o+p)$-$C_6H_4OCH_3$.

Reactions with the opening of the three-membered ring proceed under mild conditions and lead to the synthesis of the final products in high yields. A series of new 2-monosubstituted and 2,4-disubstituted adamantanes have been obtained by this reaction.

A general method for the preparation of 1,2-disubstituted adamantane derivatives is intramolecular cyclisation with participation of the vicinal carbon atoms of the adamantane nucleus with subsequent ring opening and the formation of 1,2-derivatives [81–83]:

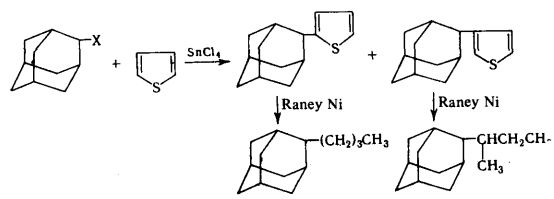


(Ref.81) (Ref.82) (Ref.82) (Ref.83)

The intramolecular ring closure to give 1-substituted adamantanes has so far been very little investigated; the use of photolysis in the ring closure stage appears to be promising.

The Koch synthesis of carboxylic acids from 2-hydroxyadamantane yields a mixture of adamantane-1-carboxylic and adamantane-2-carboxylic acids, the greatest yield of the latter being obtained when the ratio 2-hydroxyadamantane : H_2SO_4 = 1 : 1500. A series of adamantane derivatives substituted in the 2-position has been obtained from adamantane-2-carboxylic acid [84].

Hock and coworkers developed an interesting method for the introduction of butyl and isobutyl groups into the adamantane nucleus [85]. This method consists in the alkylation of halogenoadamantanes with thiophen and subsequent hydrogenolysis of the resulting compounds. 2-Halogenoadamantanes are less readily alkylated than 1-halogeno-derivatives, but the final products can nevertheless be obtained in a yield of about 40%:



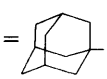
where X = Cl or Br.

2-Butyladamantane was also obtained in a high yield by the reaction of adamantanone with butyl-lithium [86].

In an overall assessment of this section on the chemistry of adamantane, the striking progress in this new field is noteworthy. It is sufficient to recall that only a few years ago even the synthesis of adamantanone was an extremely laborious process. It is to be expected that in the near future the study of the reactivity of polyhedranes at the bridgehead and bridge positions will lead to many applications of this unusual type of compounds in the solution of important synthetic and applied problems.

3. Free-radical Reactions

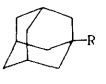
The first chemists who began a comparative study of the stability of skeletal radicals were Applequist and Kaplan [86]. A convenient reaction for such study is decarbonylation of aldehydes. The authors investigated the ease of the loss of carbon monoxide by the acyl radicals

† Here and henceforth Ad = 

ṘCO, where R is subject to different degrees of limitation of skeletal coplanarity:

$$\begin{array}{l} \dot{R}CO \xrightarrow{k_1} R\cdot + CO \\ CCl_4 \downarrow k_2 \quad\quad \downarrow \\ RCOCl \quad\quad RH, RCl \end{array} .$$

The stability of the radicals is estimated in terms of the ratio k_1/k_2, since the rate of capture of the RĊO radicals by the solvent (carbon tetrachloride) is less sensitive to the nature of R (i.e. k_2 is almost constant). Data for the relative stabilities of the radicals investigated‡ and the relative rates of solvolysis of the corresponding bromides§ are presented below:

		$(CH_3)_3CR$			
Relative stability of radicals k_1/k_2	R=CHO	1.00	2.5	1.2	0.007
Relative rate of solvolysis	R=Br	1.00	10^{-3}	10^{-6}	10^{-14}

Although these data do demonstrate a real difference between the stabilities of the t-butyl and 1-adamantyl radicals, when account was taken of the energies of the dissociation of the corresponding hydrocarbons into radicals, the authors concluded that the 1-adamantyl radical is more stable approximately to the extent of [only] 1 kcal than the t-butyl and 1-bicyclo[2,2,2]octyl radicals. The significant difference between the relative stabilities of the free radicals and carbonium ions is noteworthy. Probably steric factors play a greater role in ionic reactions than in radical reactions.

On the other hand, Chick and Ong[87] believe that the 1-adamantyl radical is less stable than the t-butyl radical, but unfortunately they do not quote quantitative data.

Free-radical substitution in adamantane was investigated in detail by Oda and coworkers[88-90]. They studied the fundamental problem of the relative reactivities of the 1- and 2-positions in radical reactions. While the 1-position is subject to steric limitations (the 1-adamantyl radical cannot be planar), the 2-position can give rise to a normal secondary free radical (sp^2-hybridisation is possible). Experiments on the radical halogenisation of adamantane[88,89] led the authors to the following conclusions:

1. In radical reactions the 1-adamantyl radical is formed more readily than the 2-adamantyl radical.
2. The bridgehead adamantyl radical is less stable than the bridge radical; the selectivity in this reaction (the ratio of the reactivities in the 1- and 2-positions) is 4.

The different selectivities of the adamantyl radicals are also shown in the Hünsdiecker reaction[88]: in chlorine-containing solvents (carbon tetrachloride) the 1-adamantyl radical abstracts chlorine preferentially from the solvent molecule relative to the 2-adamantyl radical.

In the radical chlorocarbonylation of adamantane[90] the 1- and 2-isomers are formed in proportions of 55:45. Among other advantages, this reaction provides a convenient method for the preparation of adamantane-2-carboxylic acid or its ester:

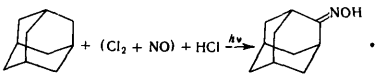
$$Ad + (COCl)_2 \xrightarrow{(C_6H_5COO)_2} \underset{55\%}{AdCOCl\ (1)} + \underset{45\%}{AdCOCl\ \ (2)} .$$

‡ The decarbonylation reactions were carried out at 135°C in carbon tetrachloride using di-t-butyl peroxide as an initiator.

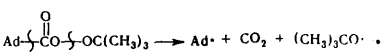
§ The solvolysis was carried out in 80% ethanol at 25°C.

In a recent paper Gleicher et al.[91] described the effect of atomic bromine (generated photochemically from *N*-bromosuccinimide) on adamantane and some of its 1-substituted derivatives; the reactions were carried out in carbon tetrachloride at 40°C. In each case a complex mixture of products is formed since both bridgehead and bridge positions are substituted by chlorine (from carbon tetrachloride) and bromine.

An interesting observation was made when deuterated adamantane was subjected to direct photochemical hydroximation with a mixture of chlorine and nitric oxide[92]. This reaction, which in all probability has a radical mechanism[93], does not involve the bridgehead positions in adamantane:



Peroxides of the adamantane series constitute a new little investigated class of compounds and therefore it is appropriate to mention here a study of the kinetics of the decomposition of the t-butylperoxy-ester of adamantane-1-carboxylic acid, which takes place via the intermediate formation of the adamantyl radical according to the mechanism[94]



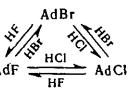
4. Reactions Involving the Bridgehead Positions

A large number of studies on the reactivity of adamantanes in the bridgehead positions have been made. The present review quotes all the investigations in this field, but only the most interesting and original of these are considered in detail.

Again much attention is devoted to the problem of the halogenation of adamantane. In the presence of aluminium chloride adamantane is readily chlorinated by agents such as acetyl chloride, propyl and isopropyl chlorides[95], and thionyl chloride[96]. The replacement of substituents in certain adamantane derivatives by bromine takes place readily on refluxing with anhydrous bromine[97]:

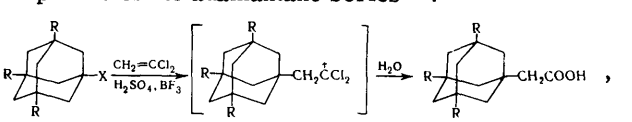
$$Ad - X \xrightarrow{Br_2} AdBr ,$$

where X = H, F, Cl, or OH. The reaction does not occur when X = CN, CO_2H, CH_3, or p-$NO_2C_6H_4$. The interchange of halogens of the bridgehead positions of adamantane is also possible using hydrogen halides[98]:



A number of studies have been made on the bromination catalysts[99,100]. The bromination of the side chain in adamantanes does not present difficulties; bromine in this position exhibits its normal mobility[100].

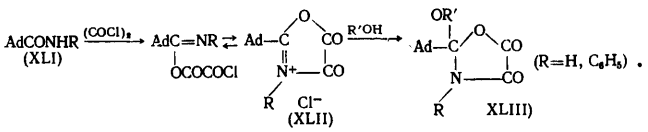
Bott extended his previously developed method for the synthesis of carboxylic acids using 1,1-dichloroethylene[101] to compounds of the adamantane series[102]:



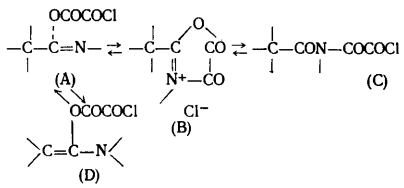
where X = Br, OH, or OAc and R = H or CH_3. Mono- and di-carboxylic acids can be obtained by this reaction in

high yields. When 1,1,2-trichloroethylene is introduced into this reaction, the same series of acids is formed with the chlorine atom in the α-position[103].

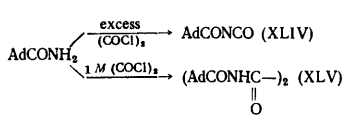
While the reactions of adamantylacetic acid involving the carbonyl group take place in the usual way and lead to a series of derivatives[104], the reactions of adamantane-1-carboxamides with oxalyl chloride have a mechanism different from that which usually obtains[105]. The reaction of adamantane-1-carboxamide (XLI) with oxalyl chloride at 0°C results in the intermediate formation of the unstable oxazoline-4,5-dione (XLII), which on treatment with protic solvents gives rise to substances with the general formula (XLIII):



The previously described reactions of carboxamides with oxalyl chloride lead to the formation of open-chain compounds (of types C or D):

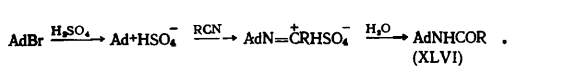


The reaction of adamantane-1-carboxamide with oxalyl chloride in various molar proportions at a temperature above 20°C leads to the formation of adamantane-1-carbonyl isocyanate (XLIV) and *NN*-bis(adamantane-1-carbonyl) oxamide (XLV):



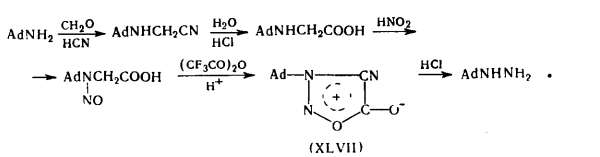
1-Aminoadamantane and its derivatives formed using the amino-group continue to attract the attention of chemists and biochemists as physiologically active substances. This concentration on the chemistry of 1-aminoadamantane proved very fruitful not only from the standpoint of medical chemistry but is also extremely interesting in its synthetic aspect. There are very many relevant examples and some of them will be considered.

For instance, the application of the Ritter reaction to 1-bromoadamantane and its subsequent development gave high yields of various *N*-(1-adamantyl)amides (XLVI) [106]:

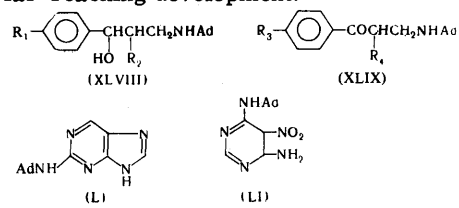


The alkylation of aliphatic and aromatic amines with 1-bromoadamantane has been investigated[107,108]; the reaction takes place under severe conditions.

1-Hydrazinoadamantane cannot be obtained directly but only via the intermediate formation of the sydnone (XLVII) [109]:



The synthesis of 1-(3-aryl-3-hydroxypropylamino)adamantanes (XLIX) [110], 1-(3-aryl-3-hydroxypropylamino)adamantanes (XLVIII) [110], and adamantyl derivatives of aminopurines (L), aminopyrimidines (LI) [111], *p*-aminobenzamide, and *p*-aminobenzenesulphonamide[112] also required far-reaching development:

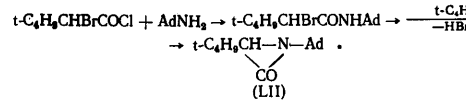


This applies equally to the synthesis of adamantane compounds containing in the side chains, diethylamine, piperidine, morpholine, and pyrrolidine residues[113].

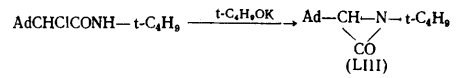
For biochemists, the reactions of aminoadamantanes in the organism are of primary interest; the microbiological oxidation of some of these compounds has been studied[114].

The synthesis, and chemical and physical properties of α-lactams of the adamantane series are of considerable interest. This is due to the fact that the α-lactams are the only class of three-membered heterocycles with a carbonyl group; a disadvantage of these reactive compounds is their low thermal stability, which of course hinders the study of their properties.

1-(1-Adamantyl)-3-t-butylaziridinone (LII), synthesised by the mechanism presented below, proved to be very stable[115,116], which made possible a detailed study of the chemical properties and spectroscopic characteristics of compounds of this class:

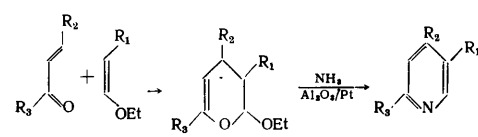


The α-lactam (LIII) was obtained by the same mechanism[117]:



The behaviour of 1-aminoadamantane in the Dem'yanov reaction has been investigated[118]. Numerous derivatives have been synthesised from aldehydes and ketones of the adamantane series. Aldehydes derived from adamantane have been obtained by the oxidation of the corresponding alcohols with lead tetra-acetate[119], by the reaction of organomagnesium derivatives of bromoalkyladamantanes with orthoformic ester[120], and also by other methods[117,121].

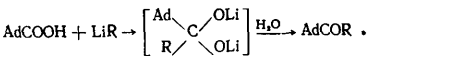
Unsaturated aldehydes are formed as a result of crotonic condensation[120] or by the condensation of acetals with ethyl vinyl ether via 1,1,3-triethoxyalkanes[122]. The acetals of adamantane aldehydes are converted into 1-adamantyl vinyl ethers when pyrolysed on magnesium phosphate[122]. Glutaric aldehydes of the adamantane series[123] and adamantylpyridines[124] have been obtained from unsaturated aldehydes or vinyl ethers via the corresponding pyrans:



where R_1 = H, Ad, or CH_2Ad, R_2 = H or CH_2Ad, and R_3 = H or Ad.

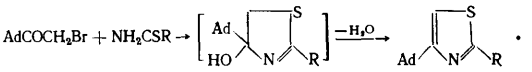
Aldehydes of the adamantane series form cyanohydrins which are hydrolysed to α-hydroxyacids, undergo the crotonic condensation, and are very readily oxidised (unusually so for aliphatic aldehydes) to the corresponding carboxylic acids on standing in air[120].

A convenient method for the synthesis of adamantyl ketones consists in the reaction of adamantane-1-carboxylic acid with alkyl-lithium[125]:

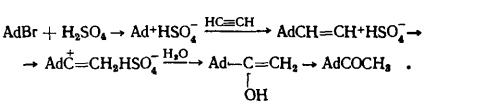


where R = CH_3, C_2H_5, or iso-C_3H_7.

Adamantyl methyl ketone enters into the Reformatskii reaction with bromosuccinic ester and the Mannich reaction with formaldehyde and dimethylamine[126]. The introduction of bromine into the α-position relative to the carbonyl group is possible by direct bromination or by the decomposition of the diazoketone obtained from the chloride of adamantanecarboxylic acid and diazomethane. The bromoketone can condense with acid thioamides to form thiazoles[127]:



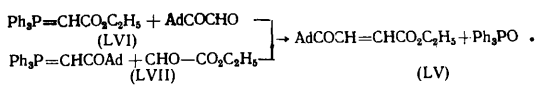
The interest in derivatives of adamantane with multiple bonds, which is the most recent and little investigated group of substances of this type, can be readily understood. Sasaki et al.[128] reported the formation of a vinyl cation and its rearrangement on addition of the adamantyl cation to acetylene. The reaction proceeds as follows:



1-Vinyladamantane was obtained by the thermal cleavage of β-(1-adamantyl)ethyl-S-methylxanthate (LIV) in the Chugaev reaction[129]:



The ethyl ester of β-(1-adamantoyl)acrylic acid (LV) may be synthesised either from 1-adamantylglyoxal and ethoxycarbonylmethylenetriphenylphosphorane (LVI) or from ethyl glyoxalate and (1-adamantoylmethylene)triphenylphosphorane (LVII)[130]:



Unfortunately the literature information about polyadamantanes is very scanty. It is noteworthy that the polyadamantane obtained by the Wurtz condensation of 3,3-dibromo-1,1-diadamantane is crystalline to the extent of more than 80%[131].

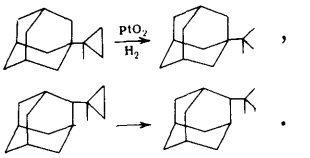
Alkylation of benzene with bromoadamantanes takes place readily[132,133] and, depending on the conditions, yields either adamantane containing several phenyl groups[134] or benzene containing up to three adamantyl residues[135]. These compounds are interesting because they comprise the adamantane nucleus with a tendency towards nucleophilic substitution reactions and the benzene ring which undergoes the characteristic electrophilic substitution reactions. Experiments have shown[132,133] that both nuclei exhibit their characteristic reactivities.

Alkylation of adamantane with olefins takes place readily in the presence of aluminium halides[136]. Under the same conditions 1-adamantylacetaldehyde is formed from 1-hydroxyadamantane[47].

It is very remarkable that the reaction of oestrone with adamantol did not yield an alkylation product; in this case adamantol reacted as a dehydrated agent and $\Delta^{9(11)}$-oestrone was isolated[137].

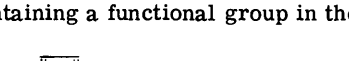
Organometallic derivatives of adamantane in which the metal is directly linked to the nucleus for a long time remained a "blank spot" in the chemistry of substances of this class. In 1965 Landsbury and Sidler[138] described for the first time the preparation of lithioadamantane by the action of t-butyl-lithium on iodoadamantane[138]. Bromoadamantane and alkyl-substituted adamantanes containing bromine in the side chain form Grignard reagents[139]. The synthesis of 1-(3-aryl-3-hydroxypropylamino)ada- bromo-derivatives of adamantane and zinc leading to the formation of 3,7-dimethylenebicyclo[3,3,1]nonane and 1,3,5,7-tetramethylenecyclo-octane.

Among new trends, one may include the study of the catalytic reactions and the pyrolysis of adamantane compounds. Hydrogenolysis of adamantanes containing the cyclopropane ring in the side chain takes place under mild conditions and yields compounds with a t-butyl substituent[140]:



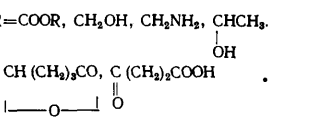
Pyrolysis of adamantane and its catalytic reactions in the presence of aluminosilicate or aluminium–chromium catalysts were investigated by Kazanskii and coworkers[141,142]; it was shown that the composition of the products in the catalytic reaction and pyrolysis is similar (mainly monocyclic aromatic hydrocarbons).

The catalytic desulphuration of adamantane derivatives of type (LVIII) is a convenient method for the synthesis of adamantanes containing a functional group in the side chain[143]:



(LVIII)

where



The oxidation of adamantane and its homologues takes place smoothly when chromium oxide in an acid medium is employed as an oxidising agent. Then, depending on the amount of oxidant employed, mono- or di-hydroxyderivatives of adamantane are formed[144].

A number of studies[145-151] illustrate the usual course of the reaction in the adamantane side chain.

VI. QUANTITATIVE STUDY OF THE REACTIVITY OF ADAMANTANE.

Much work has been done on the reactivity of adamantane. One of the promising studies in the field is the comparative investigation of the stability of the adamantyl

cation in a series of other polycyclic structures. Using the concept of the preferential planar configuration of the cations, Schleyer, Fort, and Gleicher proposed an elegant theory to account for the differences in the rates of solvolysis of the tertiary bromo-derivatives of adamantane, homoadamantane, bicyclo[2,2,2]octane, bicyclo[3,2,1]-nonane, bicyclo[2,2,1]heptane, bicyclo[2,1,1]hexane, and bicyclo[3,3,1]nonane and t-butyl bromide[3,6,152]. An undoubted achievement of their investigations is a satisfactory agreement between the experimental rate constants for the solvolysis of 1-chlorobicyclo[3,3,1]nonane and 1-bromobicyclo[3,3,1]nonane and the constants predicted by the theory[153,154].

Nucleophilic substitution reactions of bromine in 1-bromoadamantane take place exclusively by a unimolecular S_N1 mechanism. From this point of view, 1-bromoadamantane is exceptionally convenient for a detailed study of the structure of the transition state in unimolecular reactions. In this connection the problem of the involvement of the solvent in the activated complex is of interest. The studies in which the kinetics of the solvolysis of 1-bromoadamantane in aqueous ethanol and dimethyl sulphoxide were investigated[155,156] are probably the first stage of such investigations.

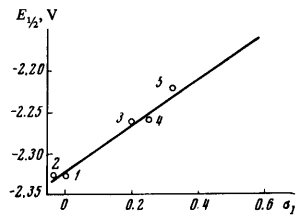


Figure 1. Variation of the half-wave potential $E_{1/2}$ with the σ_I constants of the substituents for 3-substituted 1-bromoadamantanes with the following substituents: 1) H; 2) CH_3; 3) CH_2COOCH_3; 4) OH; 5) $COOCH_3$.

The effect of substituents on the stability of the adamantyl and adamantylmethyl cations has been studied[157-159]. As was to be expected, the introduction of electronegative groups lowers the stability of the cation. It is remarkable that the presence of methyl groups at the bridgehead positions retards the solvolysis of bromoadamantane. Similar "anomalies" in the effect of the methyl group were also noted earlier[160]. Schleyer and coworkers suggest that in this case the anomaly is associated with some deformation of the cation in the transition state due to the presence of the methyl group. However, the problem remains open, because in other processes involving the formation of a cation the methyl groups exhibit electron-donating properties or have no effect[139].

The results obtained in the solvolysis of 3-substituted 1-bromoadamantanes were compared[157] with the σ^* constants and a fairly high correlation coefficient ($r = 0.996$) was obtained. In an analogous study[158] carried out using a large number of polar constituents, a correlation between the rate constants and the pK_a for the corresponding adamantanecarboxylic acid ($r = 0.986$) was obtained. The existence of such correlation is evidence that the substituents do not influence the geometrical structure of the adamantyl cation during its formation or their effect is negligibly small.

The mutual effects of the substituents in the adamantane nucleus are clearly shown in the hydrolysis of substituted acylamino-derivatives of adamantane. Depending on the nature of the substituent, the nitrogen–adamantane or the nitrogen–acyl group bond is cleaved[161,162]. In a number of studies a quantitative estimation of the influence of the substituents was undertaken. As usual, the first step was to investigate the ionisation constants of adamantanecarboxylic acids[163,165].

The correlation coefficient between the pK_a of 3-substituted adamantane-1-carboxylic acids and σ^* constants is 0.950–0.987 depending on whether account is taken of all the substituents or whether part of the points deviating to the greatest extent are rejected. The coefficient of sensitivity for this series $\rho^* = 0.263$. For bicyclo[2,2,2]-octane and *trans*-1,4-cyclohexane systems, these quantities are respectively 0.295 (in 50 wt.% ethanol) and 0.247. Such close values of ρ^* for systems where the substituents and the reaction centres are separated by different numbers of carbon atoms are evidence in favour of the hypothesis that the effect of substituents is transmitted mainly through space[160,166].

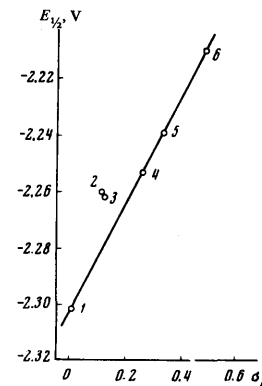


Figure 2. Variation of the half-wave potential $E_{1/2}$ with the σ_I constants of the substituents for 3-substituted 1-bromomethyladamantanes with the following substituents: 1) H; 2) C_6H_5; 3) CH_2COOCH_3; 4) OH; 5) $COOCH_3$; 6) Cl.

The effect of substituents on the reactivity has also been demonstrated by Leibzon et al.[167], who investigated the polarographic behaviour of derivatives of 1-bromoadamantane and 1-bromomethyladamantane. Bromine was reduced in 90% aqueous dimethylformamide at room temperature. Figs. 1 and 2 show the variation of the half-wave potentials $\epsilon_{1/2}$ with the σ_I constants of the substituents.

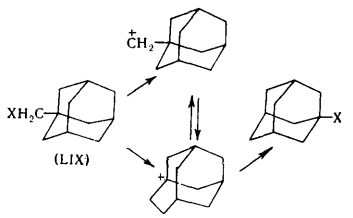
The sensitivities ρ_I of the reaction series for 1-bromomethyladamantanes and 1-bromoadamantanes were respectively 0.168–0.196 and 0.284–0.294. The correlation coefficient varied from 0.947 to 0.999. The low sensitivities of this reaction series are due to the considerable distance of the substituents from the reaction centre.

Using Palm's method[166], Leibson et al. estimated the contribution of the effect of substituents transmitted through space as 25% of the total effect. For the ionisation of adamantanecarboxylic acids, in which unit charge is produced, this quantity amounts to as much as 50% {57% for the bicyclo[2,2,2]octane system and 70% for the *trans*-1,4-cyclohexane system}.

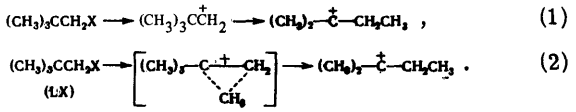
In an overall assessment of studies concerned with the quantitative estimation of the effect of substituents, a similarity between the behaviour of cyclohexane, bicyclooctane, and adamantane systems may be noted.

The exceptional properties of the adamantane structure—freedom from Baeyer and Pitzer strain—led to extensive application of adamantane derivatives as models for the solution of theoretical problems in organic chemistry.

Reactions with formation of 1-adamantylmethyl cations are known to involve a rearrangement of the adamantane structure to the homoadamantane structure, which is sterically more strained:



This finding has been used to elucidate the mechanism of the neopentyl rearrangement[168]. The problem of whether the neopentyl rearrangement takes place by the stepwise mechanism (1) or whether the ionisation process and the rearrangement occur simultaneously [mechanism (2)] is still controversial.



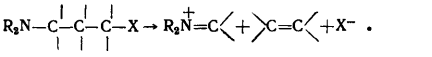
To solve this problem, some investigators suggest the use of a model compound of the neopentyl type, which, reacting by the ionic mechanism, would undergo rearrangement with greater difficulty than the neopentyl derivative. 1-Adamantylmethyltoluene sulphonate $AdCH_2OTS$ (LIX) has been suggested as a compound of this kind. It was postulated that the rates of solvolysis of neopentyltoluene sulphonate (LX) and of compound (LIX) should be similar if the rate-limiting step involves simple ionisation with formation of $Ad\overset{+}{C}H_2$ and $(CH_3)_3\overset{+}{C}CH_2$ respectively.

If, on the other hand, the rate-limiting step involves simultaneous ionisation and rearrangement, then neopentyltoluene sulphonate should be solvolysed faster (the migration of the methyl group takes place more readily than the rearrangement of the adamantane to the homoadamantane system, which is sterically more strained). It was found that the rate constants for the solvolysis of adamantylmethyltoluene sulphonate are actually somewhat higher than the corresponding rate constants for the neopentyl derivative (evidently owing to the inductive effect of the adamantane nucleus). According to the authors, these results are evidence in favour of the stepwise mechanism of the neopentyl rearrangement [mechanism (2)], in which ions (ion pairs) are formed in the first stage.

Grob and coworkers[169,170] investigated the mechanism of the fragmentation of γ-amino- and γ-alkyl-halogeno-derivatives using as an example the solvolysis of the amino- and alkyl derivatives of 1-bromoadamantane in 80% aqueous ethanol. They showed that the rate constants for the solvolysis of 3-amino-1-bromoadamantane and its *N*-methyl derivatives greatly exceed those for the corresponding 3-alkyl-1-bromoadamantanes. The activation entropy is lower in the first case than in the second. Moreover, whereas the sole products of the solvolysis of 3-alkyl-1-bromoadamantanes are their hydroxy-derivatives, in the case of the amino-compounds products indicating the fragmentation of the initial compounds were detected.

This led the authors to the conclusion that the solvolysis of alkyl-substituted 1-bromoadamantanes takes place by the usual unimolecular nucleophilic substitution mechanism.

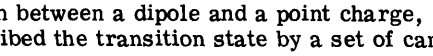
The data on the solvolysis of the amino-derivatives are evidence in favour of the synchronous fragmentation of γ-amino-substituted halides of the following type:



The authors attribute the reason for the synchronous occurrence of this type of five-centre reaction to the exceptionally favourable geometrical disposition of all the components of the structure.

Owens et al.[171] investigated the abstraction of hydrogen from 1-substituted adamantanes by the trichloromethyl radical. They noted that the reaction involves mainly bridgehead positions. The yield of side products does not exceed 10%. Treatment of the results using the Taft equation leads to $\rho^* = -0.40 \pm 0.04$ with a high correlation coefficient ($r = 0.980$).

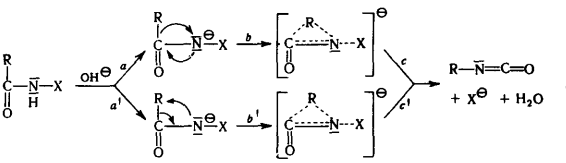
Using the Kirkwood–Westheimer equation describing the interaction between a dipole and a point charge, the authors described the transition state by a set of canonical structures:



and determined the amount of ionic character of the transition state as 10–12%.

An analogous approach to the determination of the transition state was employed by Gleicher et al.[91] They investigated the reaction of 1-substituted adamantanes with atomic bromine generated from *N*-bromosuccinimide. The sensitivity of this reaction $\rho^* = -0.59$, i.e. is somewhat greater than in the reaction with the trichloromethyl radical. The authors determined the "degree of ionic character" of this process as 17%.

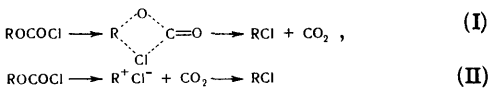
The pronounced electron-donating properties of the adamantane nucleus threw light on the hitherto not entirely clear mechanism of rearrangements at the nitrogen atom (the Hofmann, Curtius, and Lossen rearrangements)[172]. On the basis of the available experimental data, the mechanism of these rearrangements may be represented thus:



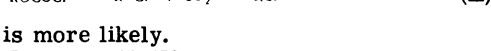
Strictly speaking, the experimental data do not allow a choice between pathways $a-c$ or $a'-c'$, although the majority of workers adopt the first without any stipulation. The above rearrangements take place readily and with high yield also in the adamantane series[161,172,173], although it is known that adamantane readily forms the 1-adamantyl

cation and the formation of the 1-adamantyl anion is not typical for this compound, i.e. the adamantyl group cannot migrate to the nitrogen atom with its electron pair. Therefore the mechanism of the rearrangement via the pathway $a'-b'-c'$ must be regarded as more likely.

Kevill and Weitl[174] attempted to revise the mechanism of the decomposition of alkyl formates using 1-adamantyl formate as an example. They assert that, of the two alternative mechanisms of the decomposition of alkyl formates



(I)



(II)

mechanism (II) is more likely.

Baldwin and Foglesong[175,176] adduced the results obtained in the solvolysis of 8,9-dehydro-2-adamantyl 3,5-dinitrobenzoate as a model compound to account for the unexpectedly high reactivity of cyclopropylmethyl derivatives. They concluded that in the transition state both structures give rise to a non-classical carbonium ion and in the case of adamantane the 2-, 8-, and 9-positions are approximately equivalent.

In conclusion we may note certain purely theoretical studies dealing with adamantane.

The high symmetry of adamantane, which greatly simplifies calculations, was used by Kitaigorodskii et al.[177], who attempted to calculate the Debye temperature θ for the face-centred cubic crystal of adamantane, having adopted intermolecular interaction as a basis. The values of θ obtained are quite reasonable, but it is so far difficult to test the results experimentally.

Quantum-chemical calculations on adamantane by the LCAO-MO method permit the calculation of the energies of the highest occupied molecular orbital (usually set equal to the ionisation potential with the sign reversed) and the charges at the carbon atom[178]. The latter proved to be −0.09 for the carbon atoms of the methylene (CH_2) groups and +0.18 for the methylidyne (C−H) groups. It is so far difficult to decide whether such calculations have any practical value, particularly since the differences between the reactivities at the bridgehead and bridge positions in adamantanes are quite definitely caused by the geometry of the transition state.

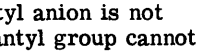
Maksic and Klasinc[179] employed the maximum overlap method proposed by Murrell[180] to calculate the degree of hybridisation of the carbon atoms in adamantane. They found that the hybridisation is somewhat different from sp^3 hybridisation, which they believe to be consistent with the slight deviations of the valence angles from the tetrahedral values.

VII. APPLICATIONS¶

Adamantane derivatives have found the widest application as physiologically active substances.

1-Aminoadamantane (amantidine) is an effective prophylactic agent against diseases due to viruses of groups A, A′, and A-2. Amantidine does not act directly on the virus but prevents its penetration into the cell[181–183]. For the same reason amantidine prevents the development of sarcoma centres on a nucleated culture[184]. Amantidine is relatively non-toxic (λD_{50} = 700 mg kg^{-1}), but can have a side effect on the functioning of kidneys[185].

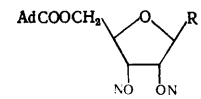
A number of adamantane derivatives of the type 1-R-Ad, where R = NH_2, NHEt, $NHCONH_2$, NCO, NCS,



the contraction of the smooth muscle initiated by 5-hydroxytryptamine[186].

Esters of adamantane-1-carboxylic acid readily dissolve in lipids and are resistant to hydrolysis owing to steric hindrance. This makes possible specific changes in the properties of testosterone[187].

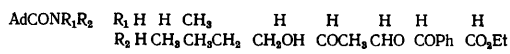
The esters of adamantanecarboxylic acid and certain nucleosides with the general structure where R = 6-azauracil, 6-mercaptopurine,



adenine, or hypoxanthine, exhibit antineoplastic activity[188].

$(CH_3)_3AdCON(^{14}CH_3)_2$ has been used to investigate the rate of oxidative *N*-demethylation[189].

Substituted amides of adamantane carboxylic acid,



may serve as sedatives[190].

The introduction of the adamantyl residue into 2-hydroxynaphthoquinone yields antimalarial preparations[191]. Polychloro- and polyfluoro-derivatives of adamantanecarboxylic acid exhibit insecticidal activity[192].

¶ This section was compiled by G. I. Danilenko.

REFERENCES

1. H. Stetter, Angew. Chem., 66, 217 (1954).
2. H. Stetter, Angew. Chem., 74, 361 (1962).
3. R. Fort, P. Schleyer, et al., Chem. Rev., 64, 277 (1964).
4. S. Landa, Neftekhimiya, 7, 476 (1967).
5. B. M. Mikhailov and L. F. Povarov, Zhur. Vses. Khim. Obshch. im. Mendeleeva, 12, 77 (1967).
6. R. Fort and P. Schleyer, "Advances in Alicyclic Chemistry", Academic Press, New York, London, 1966.
7. H. Whitlock and M. Siefken, J. Amer. Chem. Soc., 90, 4929 (1968).
8. A. Schneider, R. Warren, and E. Janoski, J. Amer. Chem. Soc., 86, 5365 (1964).
9. Dutch P. 300 223 (10th Sept., 1965); Chem. Abs., 64, 6528 (1966).
10. H. Cupery, US P. 3 274 274 (20th Sept., 1966); Chem. Abs., 66, 37 512 (1967).
11. M. Robinson and H. Tarratt, Tetrahedron Letters, 5 (1968).
12. M. Nomura, P. Schleyer, and A. Arz, J. Amer. Chem. Soc., 89, 3657 (1967).
13. P. Schleyer, G. Gleicher, and C. Cupas, J. Org. Chem., 31, 2014 (1966).
14. S. Hála and S. Landa, Coll. Czech. Chem. Comm., 29, 1319 (1964).
15. D. Cash and P. Wilder, Tetrahedron Letters, 6445 (1967).
16. A. Schneider, R. Warren, and E. Janoski, J. Org. Chem., 31, 1617 (1966).
17. P. Kovacic and S. Chaudhary, Tetrahedron, 23, 3563 (1967).

18. P. Kovacic and P. Poskos, Tetrahedron Letters, 5833 (1968).
19. S. Hala, M. Kuras, and S. Landa, Neftekhimiya, 6, 3 (1966).
20. S. Hala, S. Landa, Erdöl und Kohle, 19, 727 (1966).
21. E. I. Bagrii, E. I. Amosova, and P. I. Sanin, Neftekhimiya, 6, 665 (1966).
22. R. Warren, A. Schneider, and E. Janoski, Appl. Spectroscopy, 22, 115 (1968).
23. H. Stetter and P. Tacke, Ber., 96, 694 (1963).
24. H. Stetter, J. Gärtner, and P. Tacke, Ber., 98, 3888 (1965).
25. H. Stetter, J. Gärtner, and P. Tacke, Angew. Chem., 77, 171 (1965).
26. H. Stetter and J. Gärtner, Ber., 99, 925 (1966).
27. A. G. Yurchenko, A. T. Voroshchenko, and F. N. Stepanov, Zhur. Org. Khim., 6, 189 (1970).
28. H. Stetter and H. Thomas, Angew. Chem., 79, 529 (1967).
29. H. Stetter and H. Thomas, Ber., 101, 1115 (1968).
30. H. Stetter and H. Thomas, Ber., 99, 920 (1966).
31. A. Udding, H. Wynberg, and J. Strating, Tetrahedron Letters, 5719 (1968).
32. J. Baldwin and W. Foglesong, Tetrahedron Letters, 4089 (1966).
33. H. Meerwein, F. Kiel, G. Klösgen, and E. Schoch, J. Prakt. Chem., 104, 161 (1922).
34. M. Eakin, J. Martin, and W. Parker, Chem. Comm., 206 (1965).
35. M. Vegar and R. Wells, Tetrahedron Letters, 2565 (1969).
36. B. Vogt and J. Hoover, Tetrahedron Letters, 2841 (1967).
37. P. Schleyer and E. Wiskott, Tetrahedron Letters, 2845 (1967).
38. A. Nickon, G. Pandit, and R. Williams, Tetrahedron Letters, 2851 (1967).
39. H. Stetter, M. Schwarz, and A. Hirschhorn, Ber., 92, 1629 (1959).
40. F. N. Stepanov and S. S. Guts, Izv. Akad. Nauk SSSR, Ser. Khim., 430 (1970).
41. A. G. Yurchenko, F. N. Stepanov, B. M. Zolotariov, S. S. Isaeva, V. I. Kadentsev, and O. S. Chizhov, Org. Mass. Spectr., (in the Press).
42. F. N. Stepanov and S. S. Guts, Zhur. Org. Khim., 4, 1933 (1968).
43. F. N. Stepanov, V. F. Baklan, and S. S. Guts, "Sintez Prirodnykh Soedinenii, Ikh Analogov i Fragmentov" (The Synthesis of Natural Compounds and Their Analogues and Fragments) (Zhur. Obshch. Khim.), 1965, p. 95.
44. B. Vogt, Tetrahedron Letters, 1579 (1968).
45. P. Schleyer, E. Funke, and S. Liggero, J. Amer. Chem. Soc., 91, 3965 (1969).
46. J. Norlander, F. Ying-Hsiuchi Wu, S. Jindal, and J. Hamilton, J. Amer. Chem. Soc., 91, 3963 (1969).
47. K. Bott, Tetrahedron Letters, 1741 (1969).
48. C. Nordman and D. Schmitkons, Acta Cryst., 18, 764 (1965).
49. H. Resing, J. Chem. Phys., 43, 1828 (1965).
50. C. Pistorius and H. Snyman, Z. Phys. Chem., 43, 278 (1964).
51. W. Bratton and I. Szilard, J. Org. Chem., 32, 2019 (1967).
52. M. Jones, J. Amer. Chem. Soc., 88, 174 (1966).
53. F. Gerson, E. Heilbronner, and J. Heinzer, Tetrahedron Letters, 2095 (1966).
54. K. Bower, G. Holfi, and F. Greene, J. Amer. Chem. Soc., 85, 3707 (1963).
55. R. Fort and P. Schleyer, J. Org. Chem., 30, 789 (1965).
56. R. Fort and T. Lindstrom, Tetrahedron, 23, 3227 (1967).
57. F. Deursen and P. Korver, Tetrahedron Letters, 3923 (1967).
58. F. Deursen and A. Udding, Rec. Trav. Chim., 87, 1243 (1968).
59. G. Olah and J. Lucas, J. Amer. Chem. Soc., 90, 933 (1968).
60. G. Olah and M. Calin, J. Amer. Chem. Soc., 90, 938 (1968).
61. G. I. Oleneva, M. N. Krayushkin, V. V. Sevost'yanova, A. G. Yurchenko, G. I. Danilenko, N. O. Cherskaya, and S. S. Novikov, Manuscript deposited at the All-Union Institute of Scientific and Technical Information (VINITI) (No. 1023-69 Dep. from 15th September. 1969).
62. R. Warren, A. Schneider, and R. Moore, Appl. Spectroscopy, 22, 59 (1968).
63. R. Warren, A. Schneider, and E. Janoski, Appl. Spectroscopy, 22, 115 (1968).
64. Z. Dolejšek, S. Hála, V. Hanuš, and S. Landa, Coll. Czech. Chem. Comm., 31, 435 (1966).
65. D. Chadwick, A. Legon, and D. Millen, J. Chem. Soc., (A), 1116 (1968).
66. G. Snatzke and G. Eckhardt, Tetrahedron, 24, 4543 (1968).
67. F. N. Stepanov and V. F. Baklan, Zhur. Org. Khim., 2, 1635 (1966).
68. H. Hamill and M. McKervey, Chem. Comm., 864 (1969).
69. H. Geluk and J. Schlatmann, Chem. Comm., 426 (1967).
70. H. Geluk and J. Schlatmann, Tetrahedron, 24, 5361 (1968).
71. H. Geluk and J. Schlatmann, Tetrahedron, 24, 5369 (1968).
72. H. Geluk and J. Schlatmann, Rec. Trav. Chim., 88, 13 (1969).
73. M. McKervey, J. Alford, J. McGarrity, and E. Rea, Tetrahedron Letters, 5165 (1968).
74. Dutch P. 6511851 (11th March, 1966); Chem. Abs., 65, 3768 (1966).
75. S. Landa, J. Burkhard, and J. Vais, Z. Chem., 7, 388 (1967).
76. S. Landa, J. Vais, and J. Burkhard, Coll. Czech. Chem. Comm., 32, 570 (1967).
77. J. Vais, J. Burkhard, and S. Landa, Z. Chem., 8, 303 (1968).
78. E. Talaty and A. Dupuy, Chem. Comm., 790 (1968).
79. A. Udding, J. Strating, and H. Wynberg, Chem. Comm., 657 (1966).
80. A. Udding, J. Strating, and H. Wynberg, Tetrahedron Letters, 1345 (1968).
81. M. A. McKervery, Chem. Ind. (London), 1791 (1967).
82. C. W. Lunn, W. Podmore, and S. Szinai, J. Chem. Soc. (London), 1657 (1968).
83. W. Curran and R. Angier, Chem. Comm., 563 (1967).
84. J. Burkhard, J. Vais, and S. Landa, Z. Chem., 9, 29 (1969).
85. W. Hock, J. Strating, and H. Wynberg, Rec. Trav. chim., 85, 1045 (1966).
86. D. Applequist and L. Kaplan, J. Amer. Chem. Soc., 87, 2194 (1965).
87. W. Chick and S. Ong, Chem. Comm., 216 (1969).
88. I. Tabushi, J. Hamuro, and R. Oda, J. Amer. Chem. Soc., 89, 7127 (1967).

89. I. Tabushi, J. Hamuro, and R. Oda, J. Chem. Soc. Japan, 89, 789 (1968).
90. I. Tabushi, J. Hamuro, and R. Oda, J. Org. Chem., 33, 2108 (1968).
91. G. Gleicher, J. Jackson, P. Owens, and J. Unruh, Tetrahedron Letters, 833 (1969).
92. E. Müller and U. Trense, Tetrahedron Letters, 4979 (1967).
93. E. Müller and G. Fieder, Ber., 98, 3493, 3501 (1965).
94. G. A. Razuvaev, L. S. Boguslavskaya, V. S. Etlis, and G. V. Brovkina, Dokl. Akad. Nauk SSSR, 183, 1346 (1968).
95. I. Tabushi, J. Hamuro, and R. Oda, J. Chem. Soc. Japan, 89, 794 (1968).
96. H. Stetter, M. Krause, and W. D. Last, Angew. Chem., 80, 970 (1968).
97. M. Peterson and G. Wahl, Chem. Comm., 1552 (1968).
98. F. N. Stepanov and Yu. I. Srebrodol'skii, Zhur. Org. Khim., 2, 1633 (1966).
99. E. Talaty, A. Cancienne, and A. Dupuy, J. Chem. Soc. (C), 1902 (1968).
100. F. N. Stepanov, V. F. Baklan, and S. D. Isaev, Zhur. Org. Khim., 1, 280 (1965).
101. K. Bott, Angew. Chem., 77, 967 (1965).
102. K. Bott, Ber., 101, 564 (1968).
103. K. Bott, Angew. Chem., 79, 943 (1967).
104. T. Sasaki, S. Eguchi, and T. Toru, Bull. Chem. Soc. (Japan), 41, 238 (1968).
105. T. Sasaki, S. Eguchi, and T. Toru, Tetrahedron, 25, 2909 (1969).
106. T. Sasaki, S. Eguchi, and T. Toru, Bull. Chem. Soc. Japan, 41, 236 (1968).
107. F. N. Stepanov and Z. E. Stolyarov, Zhur. Org. Khim., 5, 537 (1969).
108. E. Krumkalns and W. Pfeifer, J. Medicin. Pharmaceut. Chem., 11, 1103 (1968).
109. H. Daeniker, Helv. Chim. Acta, 50, 2008 (1967).
110. C. Podesva and C. Solomon, J. Medicin. Pharmaceut. Chem., 11, 634 (1968).
111. V. M. Cherkasov, G. S. Tret'yakova, L. K. Kurilenko, V. N. Zavatskii, Ukrain. Khim. Zhur., 33, 1316 (1967).
112. S. Zakrzewski, A. Bloch, and C. Nichol, J. Medicin. Pharmaceut. Chem., 11, 885 (1968).
113. D. Kontonassios, C. Sandris, G. Tsatsas, S. Casadio, B. Lumachi, and C. Turba, J. Medicin. Pharmaceut. Chem., 12, 170 (1969).
114. M. Herr, R. Johnson, H. Murray, L. Reineke, and G. Fonken, J. Org. Chem., 33, 3201 (1968).
115. I. Lengyel and D. Uliss, Chem. Comm., 1621 (1968).
116. E. Talaty and A. Dupuy, J. Medicin. Pharmaceut. Chem., 12, 195A (1969).
117. K. Bott, Tetrahedron Letters, 3323 (1968).
118. B. A. Kazanskii, E. A. Shokova, and S. I. Knopova, Izv. Akad. Nauk SSSR, Ser. Khim., 2645 (1968).
119. H. Stetter and E. Ranscher, Ber., 93, 1161 (1960).
120. F. N. Stepanov and N. L. Dovgan', Zhur. Org. Khim., Report 29 (in Press).
121. F. N. Stepanov and N. L. Dovgan', Zhur. Org. Khim., 4, 277 (1968).
122. F. N. Stepanov and N. L. Dovgan', Zhur. Org. Khim., Report 22 (in Press).
123. F. N. Stepanov and N. L. Dovgan', Zhur. Org. Khim., Report 30 (in Press).
124. F. N. Stepanov, N. L. Dovgan', and A. G. Yurchenko, Zhur. Org. Khim., Report 31 (in Press).
125. S. Landa, J. Burkhard, and J. Vais, Neftekhimiya, 8, 323 (1968).
126. F. N. Stepanov and R. A. Myrsina, Zhur. Org. Khim., 2, 644 (1966).
127. F. N. Stepanov and S. D. Isaev, Zhur. Org. Khim., Report 26 (in Press).
128. T. Sasaki, S. Eguchi, and T. Toru, Chem. Comm., 780 (1968).
129. F. N. Stepanov and Z. E. Stolyarov, Zhur. Org. Khim., 5, 91 (1969).
130. M. Kuchař, Coll. Czech. Chem. Comm., 33, 880 (1968).
131. H. Reinhardt, J. Polymer Sci., B, 2, 567 (1964).
132. H. Stetter, J. Weber, and C. Wulf, Chem. Ber., 97, 3488 (1964).
133. F. N. Stepanov, E. I. Dikolenko, and G. I. Danilenko, Zhur. Org. Khim., 2, 640 (1966).
134. H. Stetter and M. Krause, Tetrahedron Letters, 1841 (1967).
135. W. Rundel, Ber., 99, 2707 (1966).
136. B. A. Kazanskii, E. A. Shokova, and T. V. Korosteleva, Izv. Akad. Nauk SSSR, Ser. Khim., 2161 (1968).
137. W. Lunn and E. Farkas, Tetrahedron, 24, 6773 (1968).
138. P. Landsbury and J. Sidler, Chem. Comm., 373 (1965).
139. V. D. Sukhoverkhov, Candidate's Thesis, Kiev, 1969.
140. C. Woodworth, V. Buss, and P. Schleyer, Chem. Comm., 569 (1968).
141. B. A. Kazanskii, E. A. Shokova, and T. V. Korosteleva, Izv. Akad. Nauk SSSR, Ser. Khim., 2642 (1968).
142. B. A. Kazanskii, E. A. Shokova, and T. V. Korosteleva, Izv. Akad. Nauk SSSR, Ser. Khim., 2640 (1968).
143. W. Hock, H. Wynberg, and I. Strating, Rec. trav. chim., 85, 1054 (1966).
144. S. Landa, J. Vais, and J. Burkhard, Z. Chem., 7, 233 (1967).
145. W. Haas, E. Krumkalns, and K. Gerzon, J. Amer. Chem. Soc., 88, 1988 (1966).
146. F. N. Stepanov and G. I. Danilenko, Zhur. Org. Khim., 3, 533 (1967).
147. F. N. Stepanov and R. A. Myrsina, Zhur. Org. Khim., 3, 530 (1967).
148. R. Scartazzin and K. Mislow, Tetrahedron Letters, 2719 (1967).
149. US P. 3 203 970 (31st August, 1965); Chem. Abs., 64, 615 (1966).
150. Dutch P. 292 605 (26th July, 1965); Chem. Abs., 64, 4969 (1966).
151. H. Stetter and M. Krause, Annalen Chem., 717, 60 (1968).
152. G. Gleicher and P. Schleyer, J. Amer. Chem. Soc., 89, 582 (1967).
153. W. Dauben and C. Poulter, J. Org. Chem., 33, 1237 (1968).
154. P. Schleyer, D. Isele, and R. Bingham, J. Org. Chem., 33, 1239 (1968).
155. I. Delhoste, G. Gomez, and G. Lamaty, Compt. rend., C266, 1468 (1968).
156. I. Delhoste, G. Gomez, and G. Lamaty, Compt. rend., C266, 1508 (1968).
157. P. Schleyer and C. Woodworth, J. Amer. Chem. Soc., 90, 6529 (1968).
158. M. M. Krayushkin, V. V. Sevost'yanova, and G. I. Danilenko, Izv. Akad. Nauk SSSR, Ser. Khim., 2844 (1969).
159. G. I. Danilenko, M. M. Krayushkin, and V. V. Sevost'yanova, Izv. Akad. Nauk SSSR, Ser. Khim., 444 (1970).

160. F. Baker, R. Parish, and L. Stock, J. Amer. Chem. Soc., 89, 5677 (1967).
161. F. N. Stepanov and Yu. I. Srebrodol'skii, "Sintez Prirodnykh Soedinenii, Ikh Analogov i Fragmentov" (The Synthesis of Natural Compounds and Their Analogues and Fragments) (Zhur. Org. Khim.), 1965, p. 97.
162. F. N. Stepanov and Yu. I. Srebrodol'skii, Zhur. Org. Khim., 2, 1612 (1966).
163. H. Stetter and J. Mayer, Ber., 95, 667 (1962).
164. G. Snatzke and D. Marquarding, Ber., 100, 1710 (1967).
165. M. N. Krayushkin, V. V. Sevost'yanova, G. I. Danilenko, and S. S. Novikov, Izv. Akad. Nauk SSSR, Ser. Khim. (in Press).
166. V. Palm, "Osnovy Kolichestvennoi Teorii Organicheskikh Reaktsii" (Fundamentals of a Quantitative Theory of Organic Reactions), Izd. Khimiya, Leningrad, 1967.
167. V. N. Leibzon, S. G. Mairanovskii, M. M. Krayushkin, V. V. Sevost'yanova, G. I. Danilenko, and S. S. Novikov, Izv. Akad. Nauk SSSR, Ser. Khim. (in Press).
168. J. Nordlander, S. Jindal, P. Schleyer, R. Fort, J. Harper, and R. Nicholas, J. Amer. Chem. Soc., 88, 4475 (1966).
169. C. Grob and W. Schwarz, Helv. Chim. Acta, 47, 1870 (1964).
170. C. Grob, W. Schwarz, and H. Fischer, Helv. Chim. Acta, 47, 1385 (1964).
171. P. Owens, G. Gleicher, and L. Smith, J. Amer. Chem. Soc., 90, 4122 (1968).
172. Z. E. Stolyarov, Candidate's Thesis, Kiev, 1968.
173. H. Stetter and K. Wulf, Ber., 96, 2302 (1962).
174. D. Kevill and F. Weitl, J. Amer. Chem. Soc., 90, 6416 (1968).
175. J. Baldwin and W. Foglesong, J. Amer. Chem. Soc., 90, 4303 (1968).
176. J. Baldwin and W. Foglesong, J. Amer. Chem. Soc., 89, 6372 (1967).
177. A. I. Kitaigorodskii, B. D. Koreshkov, and A. G. Kul'kin, Fiz. Tverd. Tela, 7, 643 (1965).
178. M. Newton, F. Boer, and W. Lipscomb, J. Amer. Chem. Soc., 88, 2367 (1966).
179. Z. Maksic and L. Klasinc, Croat. Chem. Acta, 40, 101 (1968).
180. J. Murrell, J. Chem. Phys., 32, 767 (1960).
181. R. Grunert, J. McGahen, and W. Davies, Virology, 26, 262 (1965).
182. W. Davies, R. Grunert, R. Haff, J. McGahen, E. Neumayer, M. Paulshock, J. Watts, T. Wood, E. Hermann, and C. Hoffmann, Science, 144, 862 (1964).
183. J. Bryans, W. Zeut, R. Grunert, and D. Bonghton, Nature, 212, 1542 (1967).
184. Q. Wallbank, R. Matter, and N. Klinikowski, Science, 152, 1760 (1966).
185. U. Lessler, Arzneimittel-Forsch., 18, 221 (1968).
186. W. Wesemann and F. Zilliken, J. Pharm. Pharmacol., 19, 203 (1967).
187. R. Rapala, R. Craay, and K. Gerzon, J. Medicin. Pharmaceut. Chem., 8, 580 (1965).
188. K. Gerzon and Don Kan, J. Medicin. Pharmaceut. Chem., 10, 189 (1967).
189. H. Sullivan, R. Billings, and R. McMahon, J. Medicin. Pharmaceut. Chem., 11, 250 (1968).
190. K. Gerzon, D. Tobias, and R. Holmes, J. Medicin. Pharmaceut. Chem., 10, 603 (1967).
191. L. Fieser, M. Nazer, et al., J. Medicin. Pharmaceut. Chem., 10, 517 (1967).
192. M. Paulshock, US P. 3 218 355 (16th November, 1965); Chem. Abs., 64, 3381 (1966).

Zelinskii Institute of Organic Chemistry, USSR Academy of Sciences, Moscow