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Reactions of adamantanes in electrophilic media

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Contents

I.	Introduction	1001
II.	Substitution reactions in the adamantane series in electrophilic media	1001
III.	Halogenoadamantanes	1004
IV.	Synthesis of hydroxyadamantanes and their nitrates	1011
V.	Synthesis of adamantanecarboxylic acids	1013
VI.	Aminoadamantanes	1014
VII.	Aryladamantanes	1016

Abstract. Published data on the synthesis of adamantane derivatives bearing various functional groups (halogen, hydroxy, nitrato, amino, carboxy and others) are systematised and generalised. The bibliography includes 236 references.

I. Introduction

Synthesis, reactivity and application of adamantane derivatives have been considered in several monographs and reviews.[1–4] These compounds are used both in the synthesis of pharmaceuticals [5, 6] and for the preparation of novel polymers.[7, 8] It was found that introduction of an adamantyl fragment into medical compounds enhances their biological activities owing to the higher fat-solubility.[6, 9] Some adamantane derivatives exhibit antiviral activities, *e.g.*, 1-aminoadamantane and 1-ethylaminoadamantane hydrochlorides, which are the active principles of antiviral Mydantan and Remantadinum manufactured by the pharmaceutical plant in Olaine, Latvia.

Nucleophilic substitution reactions of hydrogen are most widely used in the synthesis of adamantane derivatives. Nevertheless, no special consideration of the reactions of adamantane and its derivatives in electrophilic media has been given before even in the most comprehensive monographs.[10, 11]

The present review systematises and generalises published data on the synthesis of functionally substituted adamantanes using reactions in electrophilic media.

II. Substitution reactions in the adamantane series in electrophilic media

Hydride transfer reactions in organic chemistry are most comprehensively revealed in monographs.[12, 13] In these reactions, aluminium halides, BF_3, sulfuric acid, carbenium ions, protonated quinones and azobenzenes and some other compounds are commonly used as acceptors of the hydride ion.

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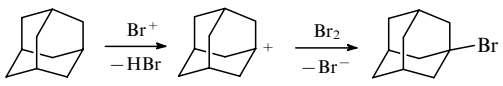
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The reactions of adamantane in electrophilic media should be considered as nucleophilic substitution at the saturated carbon atom.[10, 11] These reactions for adamantane and its derivatives can follow only the S_N1 mechanism, *i.e.*, *via* adamantyl cations, which then react with nucleophiles.[14–22] The reaction rates are mostly controlled by electronic factors, *viz.*, electron-donating properties of substituents, which serve as 'internal' nucleophiles thus delocalising the positive charge on the central carbon atom, electron-withdrawing properties of the substituents in the leaving groups, which decrease the basicity of these groups and electrophilic properties of a medium.

Only a few examples describing the nucleophilic substitution of hydrogen are known. These data mainly relate to the substitution of the hydride ion in polyhedranes (adamantane, proto- and homoadamantane, diamantane, bicyclo[3.3.1]nonane, *etc.*). The nucleophilic substitution of hydrogen in adamantane (**1**) has successfully been performed in electrophilic media (sulfuric acid, nitric acid, bromine), which, on the one hand, facilitated the hydride ion abstraction and, on the other hand, served as sources of nucleophilic species (HSO_4^-, ONO_2^- and Br^-).

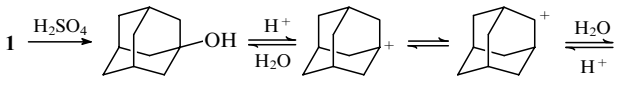
Thus the bromination of adamantane (**1**) in liquid bromine occurs selectively at the bridgehead carbon atom yielding only monobromoadamantane **2**.[14–16]

The reaction mechanism presumably involves the intermediate formation of the adamantyl cation **3**.[16]

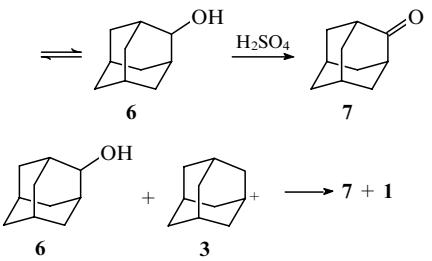


1 **3** **2**

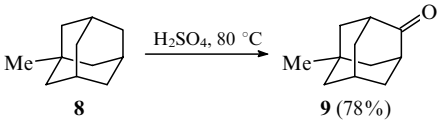
The reaction of adamantane (**1**) with sulfuric acid leads to adamantanone (**7**).[17–19] The reaction scheme includes the oxidation of **1** with 96% sulfuric acid to 1-hydroxyadamantane (**4**), the generation of the adamantyl cation **3** and the 1,2-hydrogen shift resulting in an equilibrium between 1-hydroxyadamantane (**4**) and 2-hydroxyadamantane (**6**) and the oxidation of 2-hydroxyadamantane (**6**) to adamantanone (**7**). The latter can also be formed, along with adamantane **1**, due to the intermolecular transfer of the hydride ion from 2-hydroxyadamantane (**6**) to the cation **3**.



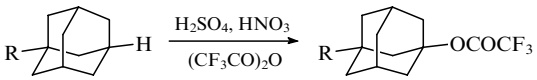
4 **3** **5**



The reaction of 1-methyladamantane (**8**) with 96% sulfuric acid at 80°C leads to a complex mixture of products in which 5-methyladamantan-2-one (**9**) is the major component.[19]

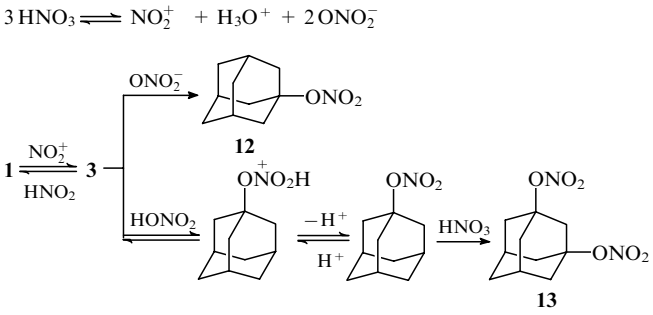


In systems containing a strong mineral acid (H_2SO_4, HNO_3) and trifluoroacetic anhydride, the role of the hydride ion acceptor is probably played by the cations HSO_3^+ or NO_2^+, which are generated *in situ* from the corresponding acids and weakly nucleophilic trifluoroacetic anhydride.[20] Thus the reactions of adamantane (**1**) and aryladamantanes **10a–e** in such systems yield the corresponding trifluoroacetoxy-substituted adamantanes **11a–e**.[20]



R = 4-$NO_2C_6H_4$ (**a**), 4-$MeSO_2C_6H_4$ (**b**), 3-NO_2-4-MeC_6H_3 (**c**), 4-BrC_6H_4 (**d**), 4-$MeO_2CC_6H_4$ (**e**).

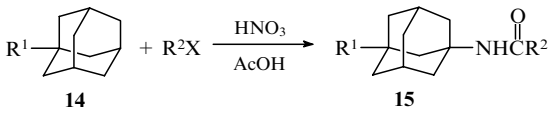
The reaction of adamantane (**1**) with concentrated nitric acid affords 1-adamantyl nitrate (**12**) and adamantane-1,3-diyl dinitrate (**13**).[21]



A mechanism of the formation of the nitrate **12** involving the stage of generation of the adamantyl cation **3** has been suggested[22,23] based on studies of the behaviour of adamantane (**1**) in nitric acid and its mixtures with acetic acid.

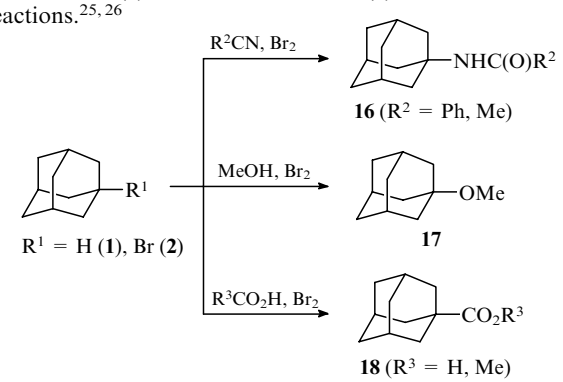
Exploration of the behaviour of adamantane (**1**) in electrophilic media made possible the development of the methods of synthesis of 1-bromoadamantane (**2**), 1-hydroxyadamantane (**4**) and nitrate **12**, which are convenient starting materials for the preparation of various functionally substituted adamantanes. It should be noted that the latter of these three compounds is the most readily available. The functionalisation of adamantane has been achieved using sulfuric and nitric acids[24] or bromine as electrophilic media.

The reactions of adamantane (**1**) and its derivatives **14** with nucleophiles such as urea, urethane or nitriles in concentrated nitric acid or in a mixture of HNO_3 and AcOH afford functionally substituted adamantanes **15**.[24]

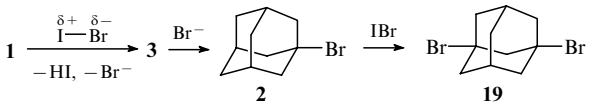


R^1 = H, Me, Et: X = NH_2CO; R^2 = NH_2, OEt;
X = CN, R^2 = $(CH_2)_2OMe$.

It has been shown[18,19] that functionalisation of adamantane and its derivatives can be performed in liquid bromine, which also functions as a Lewis acid. As an example, synthesis of compounds **16–18** using this method can be mentioned. By comparison with adamantane (**1**), bromoadamantane (**2**) reacts faster in these reactions.[25,26]

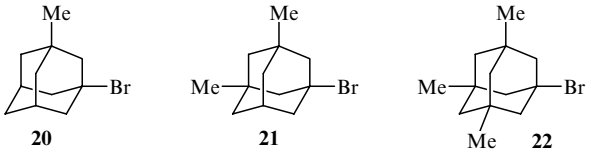


Yurchenko *et al.*[27,28] have shown that adamantane (**1**) reacts with iodine monobromide in CCl_4 to give a mixture of 1-bromoadamantane (**2**) and 1,3-dibromoadamantane (**19**).



The authors believe that a dipole $I^{\delta+}-Br^{\delta-}$ with a partial positive charge on the iodine atom is responsible for the hydride ion abstraction from the adamantane molecule. Adamantyl cation **3** thus formed then reacts with the bromide anion. The dibromide **19** is formed from the bromide **2** according to the same mechanism.

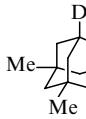
UV-Spectral studies[29] showed that 1-bromoadamantane (**2**), 1-bromo-3-methyladamantane (**20**), 1-bromo-3,5-dimethyladamantane (**21**) and 1-bromo-3,5,7-trimethyladamantane (**22**) form molecular complexes with bromine, which have linear structures. Presumably, complexes of the π,σ-type with charge transfer from the lone pair of the bromine atom in bromoadamantanes to the molecule of Br_2 are realised in these cases. As a result, the polarisation of the C–Br bond is increased.



It is supposed[30] that the increase in the polarity of the C–Br bond in bromoadamantanes is associated with localisation of the positive charge in the centre of the adamantane cage rather than on the carbon atom of the C–Br bond. This is possible owing to the overlap of the inwardly directed, hybridised orbitals of the bridgehead carbon atoms in adamantanes. Complexation facilitates nucleophilic reactions at the carbon atom of 1-bromoadamantane (**2**). It has also been shown[22] that the reactions that occur efficiently in liquid bromine, occur also in neutral solvents in the presence of molecular bromine, if its concentration is sufficient for the complexation.

The kinetics of the reactions of adamantane (**1**) and its derivatives and homologues with nitric acid in dichloromethane

Table 1. The rate constants for the reactions of adamantane derivatives with nitric acid in dichloromethane [a] (Ref. 31).

Compound	Temperature /°C	Concentration /mol litre^{-1}	$10^3 k_{eff}$ /s^{-1}
 (**1**)	0	0.025	15.0±0.8
 Me (**8**)	0	0.025	8.7±0.4
 Me (**23**)	0	0.025	4.6±0.2
 Me (**24**)	0	0.025	1.78±0.09
	0	0.05	1.98±0.09
	10	0.05	4.2±0.1
	20	0.05	8.0±0.4
	30	0.05	1.21±0.05
 Me (**25**)	20	0.05	1.81±0.1
 CH_2CO_2Me (**26**)	20	0.05	41±2
 CO_2Me (**27**)	20	0.025	3.9±0.4
 ONO_2 (**12**)	20	0.025	0.24±0.01
 $C(NO_2)_3$ (**28**)	20	0.025	0.041±0.002

[a] Initial concentration of HNO_3 was 4 mol litre^{-1}.

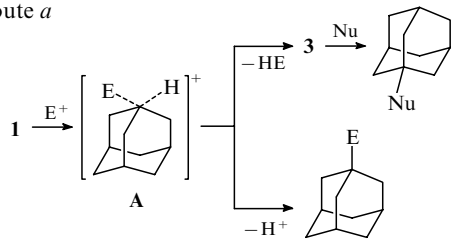
have been studied.[31] Sequential methylation of the bridgehead positions of adamantane results in monotonic decrease in reactivity (Table 1), which is typical of the reactions involving the intermediacy of carbocations. The logarithms of the rate constants (k_{eff}) for these reactions calculated taking into account the statistical factor correlate fairly well ($r = 0.993$) with the logarithms of the rate constants for the solvolysis of the corresponding bromides (in 80% aqueous ethanol at 75 °C),[32] which suggests that both types of reactions have similar mechanisms. Introduction of electron-withdrawing substituents into adamantane decreases the reactivities of its derivatives (Table 1). A correlation between the logarithms of the rate constants and the σ^* Taft constants is observed ($r = 0.99$, $\rho^* = -0.77$) for adamantanes substituted by the CH_2CO_2Me, CO_2Me, ONO_2 and $C(NO_2)_3$ groups. The sign of the reaction constant indicates that these substituents destabilise the positively charged intermediate species. The rather high absolute value of the ρ^* constant suggests that transition states in the reactions of adamantanes with nitric acid are highly polar.

The kinetic isotope effect for the reactions of 1,3,5-trimethyladamantane (**24**) and 7-deuterio-1,3,5-trimethyladamantane (**25**) is 4.4±0.3.[31] This suggests that the dissociation of the C–H bond at the tertiary carbon atom is the rate-determining step. It is worth mentioning that the kinetic isotope effect for the reactions of adamantane (**1**) with nitronium salts is 1.86 (Ref. 33) and that for the oxidation of isobutane with a mixture of H_2SO_4 and HNO_3 is 2 (Ref. 34).

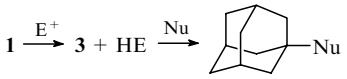
The activation energy and entropy for the reaction of 1,3,5-trimethyladamantane (**24**) are equal to 43±7 kJ mol^{-1} and 147±24 J mol^{-1} K^{-1}, respectively.

Judging from these data, it is reasonable to assume that the reaction of adamantane (**1**) with nitric acid involves the intermediate formation of the adamantyl cation **3**. The rate-determining step of this process is obviously the abstraction of the hydride ion from the tertiary carbon atom by an electrophile, which is most likely the nitronium ion. The adamantyl cation **3** thus formed is further stabilised by adding a nucleophile.[31] The reactions of saturated hydrocarbons with sulfuric or nitric acids or their mixtures are well known. The mechanism of activation of the C–H bonds in adamantane or, in the other words, the mechanism of the hydride ion transfer is discussed in Refs 35–37. In adamantane and its homologues, this activation can be realised by three routes.

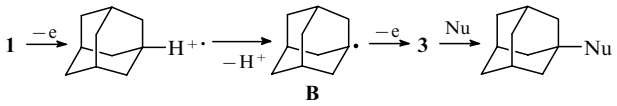
Route *a*



Route *b*



Route *c*

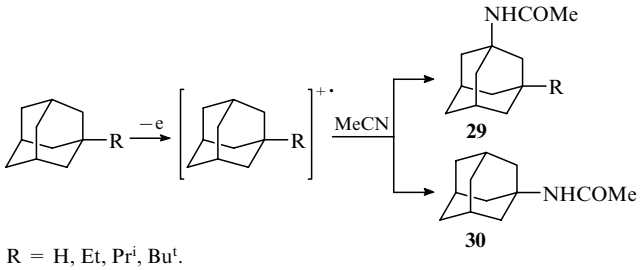


Of these three, no route can be ruled out from consideration, since each of them leads to the adamantyl cation **3**. Route *a* implies realisation of a transition state **A** with a five-coordinate carbon atom. Such a transition state is used [35] to describe hydride ion transfer in the reactions of alkanes with carbocations in sulfuric acid or with nitronium salts. The nitration of alkanes according to Olah,[38] *viz*., with nitronium salts in a mixture of dichloromethane and sulfolane at 25 °C in the dark in the absence of moisture, giving rise to a mixture of nitroalkanes and nucleophilic substitution products also invokes the realisation of the transition state with a five-coordinate carbon atom. However, the question whether the transition state **A** is converted into the final products by proton abstraction or by the elimination of HNO_2 and subsequent reaction of the cation **3** with a nucleophile still remains open.

The route *b* has already been considered in detail for the reactions of adamantane (**1**) in such electrophilic media as liquid bromine, sulfuric and nitric acids. In these cases, the initially formed adamantyl cation **3** reacts further with HSO_4^-, ONO_2^-, Br^- or other nucleophilic species. The reactivity of adamantane in these electrophilic media decreases in the following order: $H_2SO_4 > HNO_3 > Br_2$.

The reactions of adamantane (**1**) through a stage of single-electron transfer (route *c*) are also possible. However, this is considered in a limited number of publications (see, for example, Ref. 36).

The anodic oxidation of alkyladamantanes in dry acetonitrile yields 1-acetamido-3-alkyladamantane **29**, while the anodic fragmentation of the same compounds leads to 1-acetamidoadamantane (**30**). The ratio of the reaction products depends on the nature of the alkyl substituents.[36]



R = H, Et, Pr^i, Bu^t.

Later, the decomposition of 1,1′-azoadamantane (**31**) into adamantyl radical **B** involving the stage of the formation of $[AdN{=}NAd]^{+\bullet}$ (Ad is 1-adamantyl) (route *c*) was described.[37] Thus the reaction of 1,1′-azoadamantane (**31**) with thianthreniumyl perchlorate in acetonitrile affords 1-acetamidoadamantane (**30**) in 90% yield.

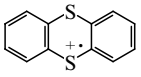
$$Th^{+\bullet} + \underset{\mathbf{31}}{AdN{=}NAd} \rightleftharpoons Th + [AdN{=}NAd]^{+\bullet}$$

$$[AdN{=}NAd]^{+\bullet} \longrightarrow \underset{\mathbf{B}}{Ad^{\bullet}} + \underset{\mathbf{3}}{Ad^{+}} + N_2$$

$$Th^{+\bullet} + Ad^{\bullet} \longrightarrow Th + Ad^{+}$$

$$Ad^{+} + MeCN \longrightarrow AdN{=}\overset{+}{C}Me$$

$$AdN{=}\overset{+}{C}Me \xrightarrow[-H^{+}]{H_2O} \underset{\mathbf{30}}{AdNHCOMe}$$

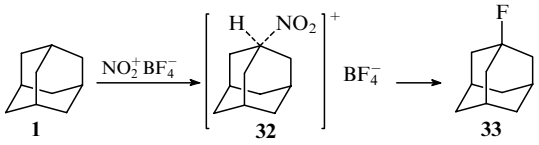
$Th^{+\bullet}$ =  ClO_4^-.

III. Halogenoadamantanes

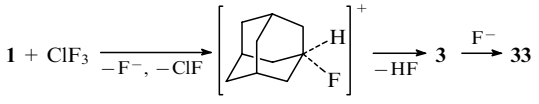
Halogenoadamantanes can be obtained from both adamantane itself and its derivatives bearing hydroxy, nitroxy and other nitrogen-containing functional groups or halogen atoms.

After the first reports[14,15] on the synthesis of halogenoadamantanes from adamantane (**1**), several publications appeared in the literature, describing methods of introduction of fluorine, chlorine, bromine and iodine atoms into the adamantane molecule, which involve the intermediate formation of the adamantyl cation **3**. Using these methods, four halogen atoms can be introduced in the bridgehead positions of adamantane.

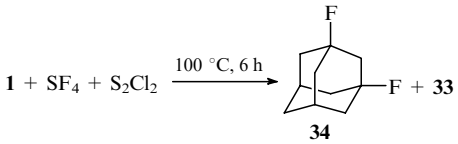
1-Fluoroadamantane (**33**) has been obtained by the reaction of adamantane (**1**) with a mixture of poly(hydrogen fluoride) and pyridine (30% Py, 70% HF).[39] The fluorination is carried out in the presence of nitronium tetrafluoroborate. The complex **32** with the five-coordinate carbon is assumed to be formed in the attack of the nitronium cation on adamantane, which then decomposes to give 1-fluoroadamantane (**33**).



1-Fluoroadamantane (**33**) can also be prepared by the reaction of adamantane (**1**) with xenon fluoride[40] or with ClF_3.[41] In the latter case, 1,3-difluoro- and 1,3,5-trifluoro-adamantanes were formed together with the 1-fluoroadamantane (**33**). The reaction presumably involves the intermediacy of a complex with five-coordinate carbon and the adamantyl cation.[41]



Sulfur tetrafluoride reacts with adamantane in the presence of sulfur monochloride to give a mixture of 1-fluoro- (**33**) and 1,3-difluoro-adamantanes (**34**).[42]

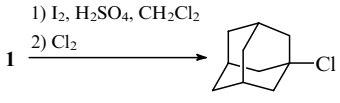


The fluorination of 1,3-dimethyladamantane (**23**) over CoF_3 affords a mixture of perfluorotrimethylbicyclo[3.3.1]nonane and perfluoro-1,3-dimethyladamantane (5%–10%).[43] The fluorination of 1,3-difluoro-5,7-dimethyladamantane, prepared by the reaction of 1,3-dihydroxy-5,7-dimethyladamantane with SF_4 (125 °C, 4 h), over CoF_3 also leads to a mixture of perfluorinated derivatives.[43]

1-Fluoro- (**33**), 1,3-difluoro- (**34**), 1,3,5-trifluoro- and 1,3,5,7-tetrafluoro-adamantanes have been obtained by the action of sulfur tetrafluoride on adamantane (**1**).[44]

Much more attention is paid to the problem of the adamantane chlorination. Molecular chlorine, organic and mineral acid chlorides, $AlCl_3$, $FeCl_3$ and others are used as chlorinating agents.

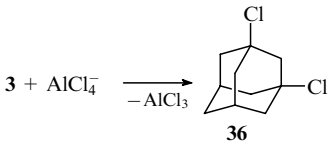
1-Chloroadamantane (**35**) can be obtained either by the treatment of adamantane (**1**) with a mixture of iodine and sulfuric acid in dichloromethane followed by passing of molecular chlorine through the reaction mixture[45] or by the reaction of adamantane (**1**) with molecular chlorine adsorbed on SiO_2.[46]



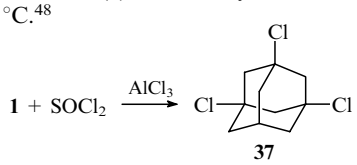
Acyl chlorides RCOCl (R = Me, Pr^n, Pr^i, Ph, cyclohexyl) in the presence of $AlCl_3$ are also rather efficient chlorinating agents. Thus the reaction of adamantane (**1**) with acetyl chloride yields 1,3-dichloroadamantane (**36**).[47]

$$MeCOCl + AlCl_3 \rightleftharpoons MeCO^{+}AlCl_4^{-}$$

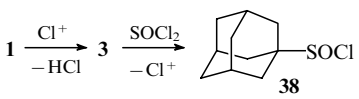
$$\mathbf{1} + MeCO^{+} \rightleftharpoons \mathbf{3} + MeCHO$$



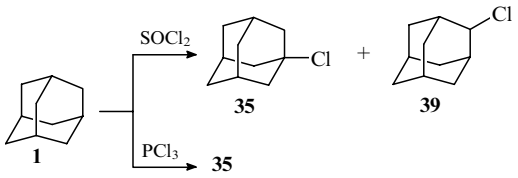
1,3,5-Trichloroadamantane (**37**) is obtained by the reaction of adamantane (**1**) with thionyl chloride in the presence of $AlCl_3$ at 75 °C.[48]



In this reaction, adamantane sulfinyl chloride (**38**) is formed as the minor product probably due to the nucleophilic attack by the lone electron pair of the sulfur atom of thionyl chloride on the carbenium ion **3**.



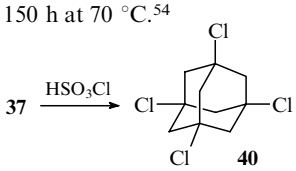
Adamantane (**1**) reacts with sulfuryl chloride in sulfolane at 60 °C to give 1-chloro- (**35**) and 2-chloro-adamantanes (**39**) in 97.5% and 2.5% yield, respectively.[49] 1-Chloroadamantane (**35**) is also obtained by the reaction of adamantane with phosphorus trichloride in trifluoroacetic acid.[50]



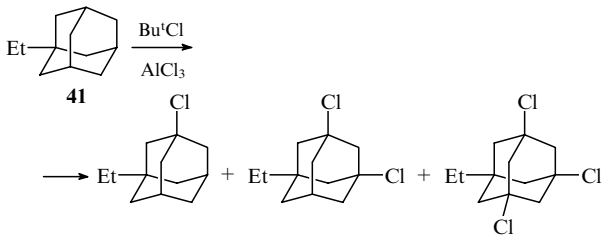
Unlike pure fluorosulfonic acid, which reacts with adamantane (**1**) to give 1-hydroxyadamantane (**4**),[51] chlorosulfonic acid halogenates adamantane at −5 °C [the ratio of reactants 1 : (8–10)] providing 1-chloroadamantane (**35**) in 60% yield.[52]

Synthesis of 1-chloro-, 1,3-dichloro- and 1,3,5-trichloroadamantanes by the reaction of adamantane (**1**) with chlorosulfonic acid has been described.[53] When the reaction mixture is kept below 5 °C for less than 1 h, 1-chloroadamantane (**35**) is formed in 18.7% yield. 1,3-Dichloroadamantane (**36**) is obtained in 80.7% yield after 50–60 h, and 1,3,5-trichloroadamantane (**37**) is obtained in 70% yield after 140–240 h of the reaction. Either 1-chloro-3,5-dimethyl- or 1,3-dichloro-5,7-dimethyladamantane is formed in the chlorination of 1,3-dimethyladamantane (**23**) depending on the reaction conditions. 1,3,5-Trimethyladamantane (**24**) gives 1-chloro-3,5,7-trimethyladamantane.

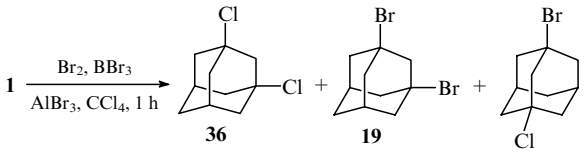
1,3,5,7-Tetrachloroadamantane (**40**) has been obtained by heating 1,3,5-trichloroadamantane (**37**) with chlorosulfonic acid for 150 h at 70 °C.[54]



Chlorination of adamantane (**1**) and its homologues can be accomplished with alkyl halides in the presence of Lewis acids. Thus the treatment of 1-ethyladamantane (**41**) with a mixture of *tert*-butyl bromide or *tert*-butyl chloride and $AlCl_3$ affords 1-chloro-3-ethyl-, 1,3-dichloro-5-ethyl- and 1,3,5-trichloro-7-ethyl-adamantanes.[55]



A mixture of 1,3-dichloro- (**36**), 1,3-dibromo- (**19**) and 1-bromo-3-chloro-adamantanes was obtained by refluxing adamantane (**1**) in CCl_4 in the presence of boron tribromide and aluminium bromide.[56]



A mixture of 1-chloro- (**35**) and 1,3-dichloro-adamantanes (**36**) was formed in the reaction of adamantane (**1**) with CCl_4 in the presence of $AlCl_3$ at 20 °C.[57]

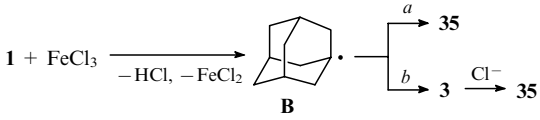
1,3,5,7-Tetrachloroadamantane (**40**) was prepared in 55% yield by refluxing adamantane (**1**) with $AlCl_3$ in CCl_4.[58]

The reaction of adamantane (**1**) with $AlCl_3$ in CCl_4 for 4 h at 20 °C affords 1,3-dichloroadamantane (**41**) in 49% yield.[59]

The effects of solvents and Lewis acids on the chlorination of adamantane (**1**) have been studied in detail.[59, 60] The yields and the ratio of 1-chloro- (**35**) and 2-chloro-adamantanes (**39**) obtained in these reactions in the presence of $FeCl_3$ or $SbCl_5$ are listed in Table 2. The yields of 1-chloroadamantane (**35**) are higher when $SbCl_5$ is used as a catalyst. The ratio of the isomers is influenced by the nature of the solvent and the Lewis acid.

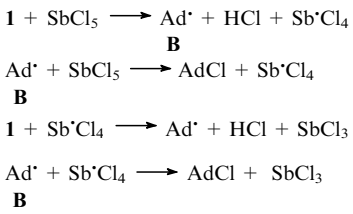
The mechanisms of the halogenation reactions of adamantane considered above are probably not purely ionic, since 2-chloroadamantane (**39**) can be formed exclusively by the free-radical mechanism.

Two different mechanisms can be suggested for the reactions in the presence of $FeCl_3$: the route *a* involving direct reaction of the radical **B** with $FeCl_3$ and providing 1-chloroadamantane (**35**) and the route *b* implying the intermediacy of the cation **3**.



(*a*) $FeCl_3$ ($-FeCl_2$); (*b*) $FeCl_3$ ($-FeCl_2$, $-Cl^-$).

The reaction of adamantane (**1**) with $SbCl_5$ can also be described by a scheme including a stage of the adamantyl radical **B** formation.



The chlorination of adamantane (**1**) in the presence of $AlCl_3$ and $AgSbF_6$ has been studied by Olah *et al.*[61] A mixture of 1-chloro- (**35**) and 2-chloro-adamantanes (**39**) (in 63.2% and 2.9% yields, respectively) is formed when the ratio of the reactants $Cl_2 : AlCl_3 : AdH$ is 1 : 0.1 : 1 (21 h, 25 °C). If the ratio

Table 2. Chlorination of adamantane (**1**) in the presence of $FeCl_3$ and $SbCl_5$.[59, 60]

Solvent	Temperature /°C	$FeCl_3$			$SbCl_3$		
		Time /h	Total yield of **35** and **39** (%)	Ratio of **35** and **39**	Time /h	Total yield of **35** and **39** (%)	Ratio of **35** and **39**
CCl_4	78	6.5	4	11 : 1	3	7–9	(11–15) : 1
		54	64–72	(12–15) : 1	4	14–20	(13–15) : 1
		–	–	–	36	66–79	(11–16) : 1
CH_2Cl_2	40	7	2	20 : 1	0.5	24	31 : 1
		10	4	28 : 1	1	40–42	(35–39) : 1
		–	–	–	3	68–79	(36–42) : 1
CH_2Cl_2, CCl_4	48	2.5	3	42 : 1	2	52	22 : 1
		4.5	3–6	(27–42) : 1	5	75	21 : 1
		7	8–9	(23–30) : 1	6.5	76	22 : 1

$Cl_2 : AgSbF_6 : AdH$ is 5 : 1 : 10 (21 h, −15.5 °C), the yields of 1-chloro- (**35**) and 2-chloro-adamantanes (**39**) are 62.4% and 1.2%, respectively. In addition, 1-hydroxyadamantane (**4**) is formed in 36.3% yield. On the other hand, the ratio of 1-chloroadamantane (**35**) to 2-chloroadamantane (**39**) in photochemical chlorination was 1 : (0.6–2.1).[62]

It is known that triphenylmethyl cation is an effective acceptor of the hydride ion (*i.e.*, this serves as a 'soft' organic acid in terms of the HSAB principle). Using this cation, it is possible to generate carbenium ions from hydrocarbons and functionalise them by the reactions with appropriate nucleophiles. Triphenylmethyl cation can be used in such reactions as a catalyst. In this case, triphenylmethane derivatives serve as the sources of nucleophiles which react with the newly formed carbenium ions and also regenerate the triphenylmethyl cations.

$$RH + Ph_3C^+X^- \rightleftharpoons R^+X^- + Ph_3CH,$$

$$R^+X^- + Ph_3CY \rightleftharpoons RY + Ph_3C^+X^-$$

X^- is a weakly nucleophilic anion.

This type of functionalisation has been studied for various hydrocarbons, including adamantane.[63]

$$AdH + Ph_3CY \rightleftharpoons AdY + Ph_3CH$$

Y = OH, Cl, OMe, $O(CH_2)_2OAc$.

The reaction was carried out in a mixture of CH_2Cl_2 and $MeNO_2$ at 70 °C using $Ph_3COSO_2CF_3$ (0.05 mol per mol of AdH) as a precursor of triphenylmethyl cation. The results obtained are listed in Table 3.

Table 3. Functionalisation of adamantane (**1**) by triphenylmethane derivatives.[63]

Y	Ratio Ph_3CY : : AdH	Time /h	Yields (%) [a]			
			AdY	Ph_3CH	AdOH (**4**)	AdH (**1**)
OH	1 : 1	14	59(57)	80		40
Cl	1 : 1	9	78(40)		0	10
OMe	1.25 : 1	2.5	31(20)	87	12	20
$AcO(CH_2)_2O$	1.25 : 1	3.5	50(40) [b]	71	15	10

[a] Determined by GLC, the isolated yields are given in parentheses; [b] after deacylation.

As can be seen from the Table 3, such functional groups as Cl and OH are readily introduced into adamantane and these exchange reactions can find synthetic application. The yields of the ethers are substantially lower, probably because of competitive disproportionation of trityl ethers.

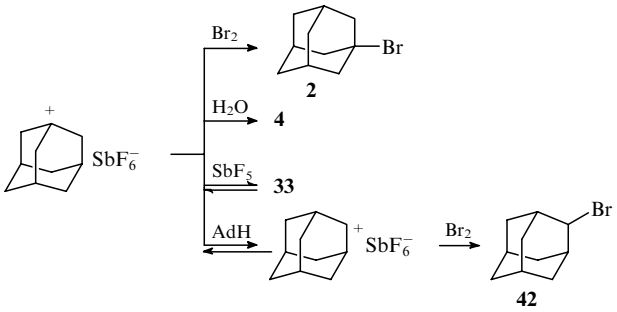
Several studies have been devoted to the preparation of bromoadamantanes. As has been mentioned above, 1-bromoadamantane (**2**) was synthesised in 78% yield by the reaction of adamantane (**1**) with bromine in the presence of $AlCl_3$.[15]

The synthesis of the bromide **2** by the oxidative bromination of adamantane (**1**) with the stoichiometric amount of bromine or an alkali metal bromide in trifluoroacetic acid in the presence of nitrogen-containing oxidants such as alkali nitrates or nitrites or NO_2 has been proposed as an alternative. This affords 1-bromoadamantane (**2**) in quantitative yield.[64]

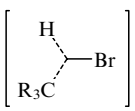
Anhydrous $AgSbF_6$ in CH_2Cl_2 catalyses the bromination of adamantane. At −45.5 °C, 1-bromoadamantane (**2**) is obtained in 54.1% yield.[65] A strongly polarised complex of Br_2 with $AgSbF_6$ is supposed to be the brominating species in this reaction.[65]

$$Br_2 + AgSbF_6 \rightleftharpoons \overset{\delta+}{Br}—\overset{\delta-}{Br} \longrightarrow Ag^+SbF_6^-.$$

1-Hydroxy- (**4**), 2-bromo- (**42**) and 1-fluoro-adamantanes (**33**) are also formed in this reaction.



A two-electron three-centre transition state of the carbenium type is believed [65] to be realised in this reaction.



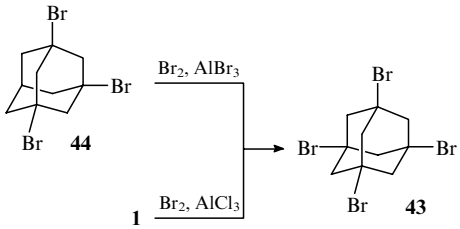
Synthesis of 1,3-dibromoadamantane (**19**) by the reaction of adamantane (**1**) with bromine in the presence of $AlBr_3$ (78% yield) or in the absence of a catalyst in autoclave at 150 °C for 22 h (12.4% yield) has been described.[15, 66–70]

A detailed study [66] of the reaction of adamantane (**1**) with bromine in the presence of a mixture of $AlBr_3$ and BBr_3 has been performed. It was shown that the composition of the reaction products depends on the ratio of the catalysts used. Later, 1,3-dibromoadamantane (**19**) was obtained in 97% yield by the bromination of adamantane (**1**) in the presence of Fe and small amount of water.[68]

The reaction of adamantane (**1**) with bromine in the presence of Fe in Freon-113 (1,1,2-trichloro-1,2,2-trifluoroethane) or in hexafluorobenzene affords dibromide **19** in 97.3% yield and of 99% purity.[69] A complex mixture of products comprising 1,3,5-trichloro- (**37**, 27.3%), 1-bromo-3,5-dichloro- (16.6%), 1,3-dibromo-5-chloro- (27.4%), 1,3,5-tribromo- (12.0%), 1-bromo-3,5,7-trichloro- (10.8%) and 1,3-dibromo-5,7-dichloro-adamantanes (5%) were obtained in the presence of $AlCl_3$.[69]

The treatment of adamantane (**1**) with bromine at 100 °C under 27.2 atm also yields 1,3-dibromoadamantane.[70]

1,3,5,7-Tetrabromoadamantane (**43**) has been obtained in 75% yield by heating 1,3,5-tribromoadamantane (**44**) with bromine and $AlBr_3$ in an autoclave at 150 °C for 2 h.[16]



Synthesis of 1,3,5,7-tetrabromoadamantane (**43**) by bromination of adamantane (**1**) has also been performed under relatively mild reaction conditions (an equimolar amount of $AlCl_3$, 30 min at 20 °C and then 3 h at 60 °C).[71]

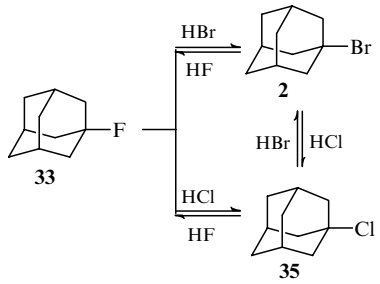
1,3,5-Tribromoadamantane (**44**) has been synthesised [72] from adamantane (**1**) under the conditions used earlier [15] for the preparation of 1,3-dibromoadamantane (**19**).

1,3-Dibromo- (**19**) and 1,3,5,7-tetrabromo-adamantanes (**43**) have been prepared from salts of the corresponding acids by the Hunsdiecker reaction.[73, 74]

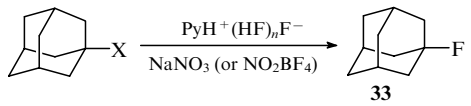
Interestingly, 1,3,5,7-tetrabromoadamantane (**43**) has also been synthesised by the reaction of 2-chloroadamantane (**39**) with bromine in the presence of the equivalent amount of $AlBr_3$.[75] No product containing the chlorine and bromine atoms together in the same molecule was detected in this reaction.

The methods for direct iodination of adamantane (**1**) are unknown. Iodoadamantanes can be obtained by a substitutive iodination of chloroadamantanes or hydroxyadamantanes. These methods are considered below.

Halogenated adamantanes can also be synthesised from adamantanes bearing other functional groups. A possibility for halogen exchange in halogenoadamantanes upon their treatment with appropriate hydrogen halides has been demonstrated.[76, 77]

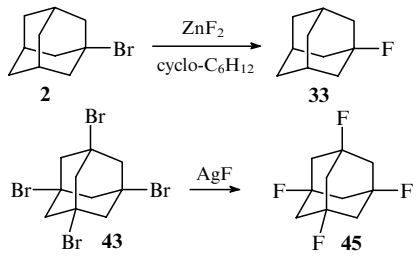


1-Fluoroadamantane (**33**) has been obtained by the treatment of 1-chloro-, 1-bromo- or 1-iodoadamantane with a mixture of poly(hydrogen fluoride) and pyridine in the presence of nitronium tetrafluoroborate or sodium nitrate.[78]

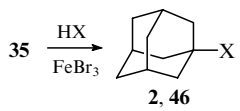


X = Cl, Br, I.

1-Fluoro- (**33**), 1,3-difluoro- (**34**) and 1,3,5,7-tetrafluoroadamantanes (**45**) have also been synthesised by the reactions of the corresponding bromides **2** and **43** with ZnF_2 or AgF.[79]



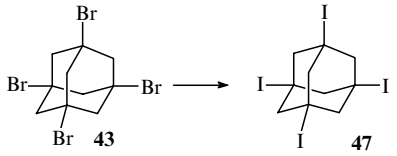
1-Bromo- (**2**) and 1-iodo-adamantanes (**46**) have been obtained by the reaction of 1-chloroadamantane (**35**) with gaseous HBr or HI in CCl_4 or CH_2Cl_2 in the presence of $FeBr_3$.[80] The latter was prepared *in situ* from $Fe(CO)_5$ and Br_2.



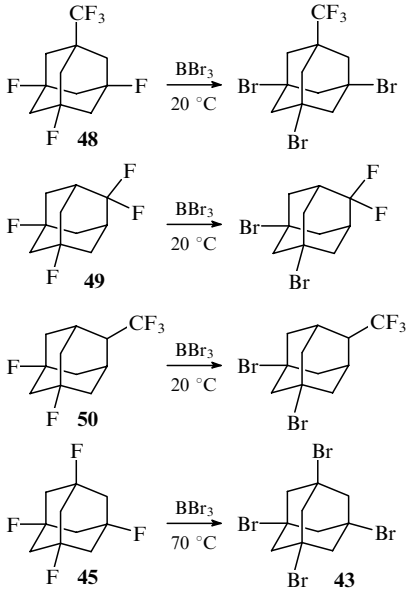
X = Br (**2**), I (**46**).

A similar procedure has been proposed[81] to exchange the bridgehead halogen atoms in bromoadamantanes. The method is based on the generation *in situ* of an aluminium halide catalyst by the reaction of an excess of aluminium with bromine in a halogenated solvent. The results obtained are summarised in Table 4. In CH_2I_2, exchange of bromine by iodine in 1-bromoadamantane occurs at room temperature in several minutes and is accompanied by the formation of adamantane (30%). Using this method, 1,3,5,7-tetraiodoadamantane was obtained in 83% yield.

1,3,5,7-Tetraiodoadamantane (**47**) is formed from 1,3,5,7-bromoadamantane (**43**) in 75% yield.[82]



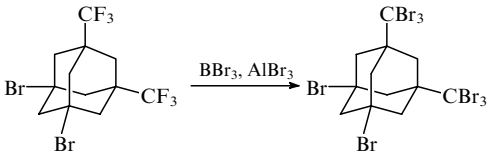
The replacement of the fluorine atoms in 1,3,5-trifluoro-7-trifluoromethyl- (**48**), 2,2,5,7-tetrafluoro- (**49**), 2-trifluoromethyl-5,7-difluoro- (**50**) and 1,3,5,7-tetrafluoroadamantane (**45**) by the bromine atoms under the action of BBr_3 has been studied.[83] The exothermic reactions of compounds **48**, **49** and **50** with BBr_3 begin at room temperature, whereas the exchange of the fluorine atoms in 1,3,5,7-tetrafluoroadamantane (**45**) by the bromine atoms requires heating.



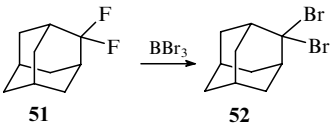
Only the bridgehead fluorine atoms were found to be exchangeable. The trifluoromethyl groups are completely inert towards the action of neat BBr_3. However, the addition of a catalytic amount of $AlBr_3$ allows the exchange of the fluorine atoms in the trifluoromethyl groups by bromine. The reactions were carried out with a great excess of BBr_3, which serves simultaneously as a reagent and as a solvent.[84]

Table 4. Reaction conditions and yields of halogenoadamantanes.[81]

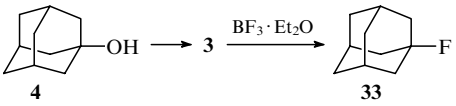
Substrate	Solvent	Temperature /°C	Time /min	Product	Yield (%)
1-Bromoadamantane (**2**)	CH_2I_2	20	0.5	1-Iodoadamantane (**46**)	47
	$CHCl_3$	65	1.5	1-Chloroadamantane (**35**)	89
1,3,5,7-Tetrabromoadamantane (**43**)	CH_2I_2	80	15	1,3,5,7-Tetraiodoadamantane (**47**)	83
	$CHCl_3$	20	1200	1,3,5,7-Tetrachloroadamantane (**40**)	88



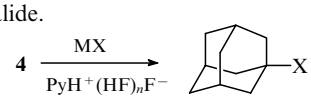
As reported by Cuddy *et al.*,[85] 2,2-dibromoadamantane (**52**) isomerises in the presence of $AlBr_3$. However, this dibromide can be obtained by the reaction of 2,2-difluoroadamantane (**51**) with BBr_3. No isomerisation of the reaction product was also observed in the reaction of 2,2,5,7-tetrafluoroadamantane with BBr_3.[86]



1-Hydroxyadamantane (**4**) or its nitrate **12** are widely used as starting compounds in the synthesis of halogenoadamantanes. Thus 1-fluoroadamantane (**33**) was obtained by the reaction of 1-hydroxyadamantane (**4**) with boron trifluoride diethyl etherate.[87–89]

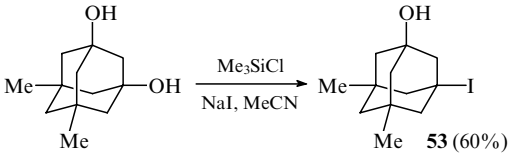


By analogy with the halogen substitution, pyridinium poly(hydrogen fluoride) was employed for the replacement of the adamantane hydroxy group by the fluorine atom.[90,91] 1-Fluoro- and 2-fluoro-adamantanes are formed from the corresponding alcohols in virtually quantitative yields. For the preparation of adamantanes with other halogen atoms, this reagent is used in combination with the appropriate metal or ammonium halide.



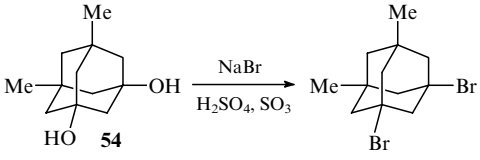
M = Na, K, NH_4; X = Cl, Br, I.

A convenient procedure for the replacement of the hydroxy group by iodine is the use of a the mixture of Me_3SiCl and NaI.[92] For example, 1-iodo- (**46**, yield 80%) and 1-hydroxy-3-iodo-5,7-dimethyl-adamantanes (**53**) have been prepared by this procedure. In the latter case, only one hydroxy group can be substituted even with an excess of the halogenating reagent.

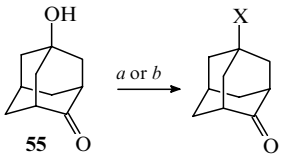


The replacement of the hydroxy group in compound **4** by a halogen can be performed by the reactions with halogens, alkali metal halides or hydrohalic acids in sulfuric acid. Thus 1-bromoadamantane derivatives have been obtained by the reactions of 1-hydroxyadamantane (**4**) and its derivatives with bromine in sulfuric acid.[93,94]

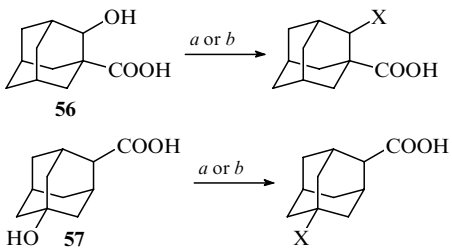
1,3-Dibromo-5,7-dimethyladamantane has been prepared by the reaction of 1,3-dihydroxy-5,7-dimethyladamantane (**54**) with bromine in oleum.[95–97]



The hydroxy groups in the hydroxy ketone **55** and hydroxy carboxylic acids **56** and **57** have successfully been replaced by halogens.[98–101]



(*a*) HBr, X = Br (83%); (*b*) $SOCl_2$, X = Cl (90%).



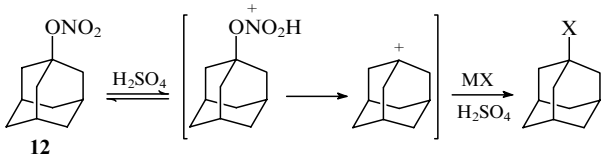
(*a*) PBr_5, X = Br; (*b*) KI, H_3PO_4; X = I.

The replacement of the hydroxy group in 2-hydroxyadamantane-1-carboxylic acid (**56**) by halogens presumably follows the S_N2 mechanism.

1,3-Diiodoadamantane has been obtained by the reaction of 1,3-dihydroxyadamantane with hydroiodic acid.[102]

Yet another method for the introduction of the halogen atoms into adamantanes is the reactions of adamantyl nitrates with hydrohalic acids or their salts in sulfuric acid.

Thus the nitrato groups in 1-adamantyl nitrate (**12**) and adamantane-1,3-diyl dinitrate (**13**) have successfully been replaced by the chlorine or bromine atoms using the reaction of these adamantanes with potassium (sodium) chloride or bromide in 98% sulfuric acid.[103]



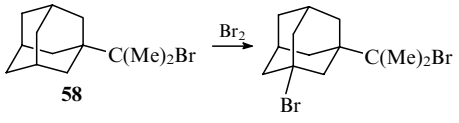
M = Na, K; X = Cl, Br.

1-Bromo-(**2**),[104] 1,3-dichloro- (**36**) and 1,3-dibromo-adamantanes (**19**)[105] were obtained in a similar manner.

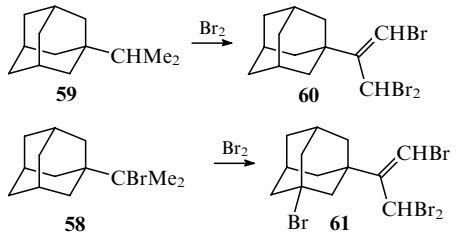
Under the action of halogenating agents on adamantanes bearing Alk, Ph, CO_2H, CF_3, $C(NO_2)_3$, NO_2, NH_2 and other groups either the adamantane hydrogen atom in the 3-position or the substituent is replaced depending on the nature of the substituent.

No problem arises in the bromination of 1-bromo-3-methyl-,[106] 1-methyl- (**8**),[107,108] 1-ethyl-,[109] 1-*tert*-butyl-,[110] 1,3-dimethyl- (**23**),[108] 1,3,5-trimethyl- (**24**)[111] and 1-ethyl-3-methyladamantanes with bromine.[106] The yields of the corresponding bromoadamantanes are almost quantitative.

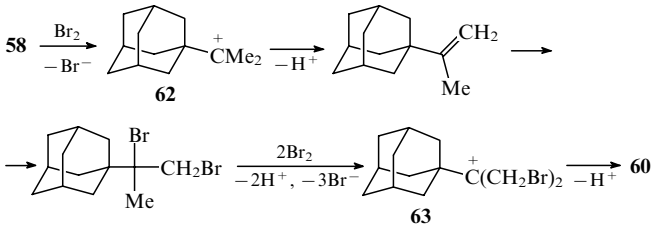
The bromination of 2-(1-adamantyl)-2-bromopropane (**58**) is worth a more detailed consideration, since the structure of the product obtained in this reaction has not initially been established. It was supposed that 2-(3-bromo-1-adamantyl)-2-bromopropane is formed in the bromination of compound **58** with bromine at 70–80 °C for 2 h.[112]



However, further studies [113, 114] have shown that it was the side chain that underwent bromination of 1-isopropyladamantane (**59**) yielding 2-(1-adamantyl)-1,3,3-tribromoprop-1-ene (**60**), and compound **58** is brominated to give tetrabromo-substituted derivative **61**.



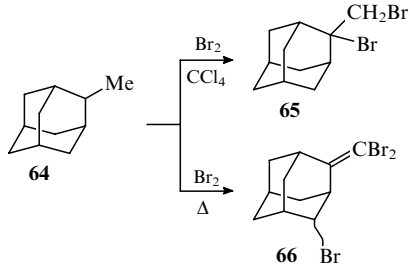
Analogous products were obtained in the bromination of 1-isopropyl-3,5,7-trimethyladamantane and 2-bromo-2-(3,5,7-trimethyl-1-adamantyl)propane.[113] A mechanism involving the intermediate formation of cations **62**, **63** and the tribromide **60** has been proposed [113] to account for the reaction of 2-(1-adamantanyl)-2-bromopropane (**58**) with bromine.



Judging from the ratio of the rate constants for solvolysis of 2-(1-adamantyl)-2-bromopropane (**58**) and 1-bromo-3-isopropyladamantane (10^4 : 1), an assumption was made [112] that the rates of bromination of the side chain and nucleus in 1-isopropyladamantane (**59**) should also differ by four orders of magnitude. However, since only the nucleus of 1-isopropyladamantane is brominated in the reaction, a complex reaction scheme including several rearrangements of carbenium ions was proposed to account for this contradiction.

In fact, solvolysis of bromides and bromination involving the saturated carbon atom occur most likely by different mechanisms.[113] The rate-determining stage in the solvolysis is the formation of a carbenium ion, whereas the rate of the bromination is determined by a stage which precedes the ionisation, *e.g.*, the formation of a complex $R^+ - H^- - Br^+ - Br^-$. The energy of such a complex is lower if the adamantane nucleus rather than side chain takes part in the complex formation.

The reaction of 2-methyladamantane (**64**) with a 10% solution of bromine in CCl_4 leads to 2-bromo-2-bromomethyladamantane (**65**), while a mixture of *exo*- and *endo*-2-bromo-4-(dibromomethylidene)adamantanes (**66**) is formed upon refluxing 2-methyladamantane (**64**) with bromine for 4–5 h. A scheme of the formation of compound **66** has been proposed.[115]



A mixture of 1-bromo-2-methyl-, 1-bromo-4-methyl- and 1-bromo-3-methyl-adamantanes was formed upon treatment of 2-methyladamantane with bromine.[116]

Table 5. The rate constants for the solvolysis of alkylbromoadamantanes in 80% ethanol.

Compound	$10^5 k$ /s^{-1}	k_{rel}	$\Delta H^{\neq}$ /kcal mol^{-1}	$\Delta S^{\neq}$ /cal mol^{-1} deg^{-1}
1-Bromoadamantane (**2**)	8.76 (22.5)	1.00 (1.0)	23.1 (23.63)	−10.1 (−9.6) [a]
1-Bromo-3-methyladamantane (**20**)	6.05 (15.9)	0.69 (0.7)	23.6 (24.36)	−9.6 (−8.1) [a]
1-bromo-3-ethyladamantane	8.42 (22.5)	0.96 (1.0)	23.3 (24.5)	−9.4 (−7.0) [a]
1-Bromo-3-isopropyladamantane	11.9 (32.1)	1.36 (1.4)	24.5 (24.0)	−5.4 (−7.8) [a]
1-Bromo-3,5-dimethyladamantane (**21**)	4.12	0.47	24.5	−7.4
1-Bromo-3,5,7-trimethyladamantane (**22**)	(6.93)	0.31 (0.31)	–	–

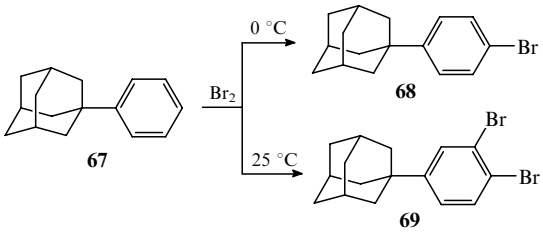
Note. According to the data in Ref. 117 (70 °C). Data from Ref. 109 (Et_3N, 75 °C) are given in parentheses.
[a] $\Delta S^{\neq}$ values at 60 °C.

The effect of the nature and number of alkyl substituents on the stability of the adamantyl cations can be evaluated by an analysis of the rate constants for the solvolysis of the corresponding alkylbromoadamantanes (Table 5).[117]

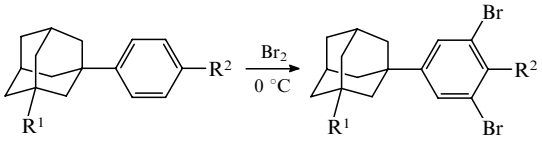
As expected, the more the number of methyl groups in 1-bromoadamantane, the lower the rate of solvolysis. However, this is increased in the series 3-methyl-, 3-ethyl- and 3-isopropyl-substituted 1-bromoadamantanes (6.05×10^{-5}, 8.42×10^{-5} and 11.9×10^{-5}, respectively).

Both the aromatic ring and the adamantane nucleus are expected to be susceptible in the bromination of aryladamantanes.

1-Phenyladamantane (**67**) reacts with bromine under reflux to give a mixture of products from which no individual compound was isolated;[118] however, 1-(4-bromophenyl)adamantane (**68**) was obtained at 0 °C, and 1-(3,4-dibromophenyl)adamantane (**69**) as the product of substitution of two hydrogen atoms in the aromatic ring was prepared at 25 °C.[119]

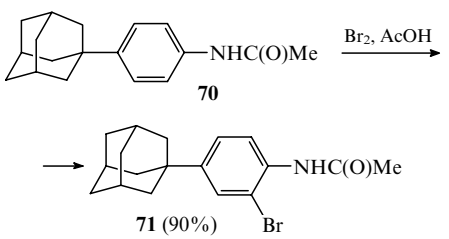


The introduction of the carboxy group into position 3 of the adamantane nucleus in 1-phenyladamantane does not affect the character of the phenyl ring substitution. On the other hand, if electron-donating substituents are present on the phenyl ring, the corresponding dibromides are formed even at 0 °C.[119]

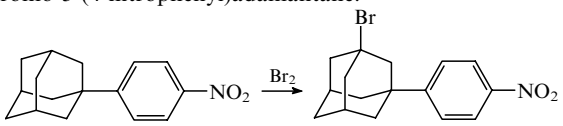


R^1 = H, CO_2H; R^2 = OMe, OH, Me.

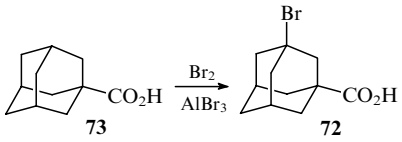
The bromination of 4-(1-adamantyl)acetanilide (**70**) with bromine in acetic acid leads to 4-(1-adamantyl)-2-bromoacetanilide (**71**).[120]



When the nucleophilicity of the aromatic ring is decreased due to the introduction of electron-withdrawing substituents, only the adamantane nucleus of aryladamantanes is brominated. Thus 1-(4-nitrophenyl)adamantane reacts with bromine to give 1-bromo-3-(4-nitrophenyl)adamantane.[110, 121]



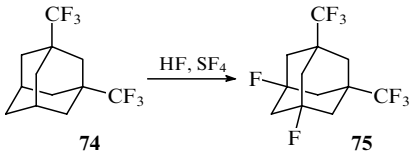
Adamantanes bearing electron-withdrawing groups such as CO_2H, COMe, $C(NO_2)_3$, CF_3, *etc*., are brominated only in the presence of catalysts. Thus 3-bromoadamantane-1-carboxylic acid (**72**) was obtained upon treatment of adamantane-1-carboxylic acid (**73**) with bromine in the presence of $AlBr_3$.[122]



The acid **73** can also be brominated in liquid bromine in the presence of water or acetic acid.[123] (3-Chloro-1-adamantyl)acetic acid was prepared by the reaction of (1-adamantyl)acetic acid with an alkali metal chloride in concentrated sulfuric acid.[124, 125] (3-Bromo-1-adamantyl)acetic acid is formed in 95% yield on treating (1-adamantyl)acetic acid with bromine at 20 °C for 18 h followed by refluxing the reaction mixture for 6 h. (3-Bromo-5-methyl-1-adamantyl)- and (3-bromo-5,7-dimethyl-1-adamantyl)-acetic acids were obtained under the same conditions.[126]

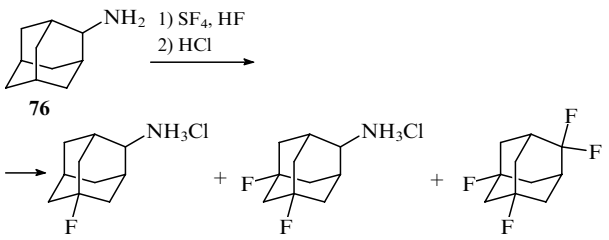
Adamantane-2-carboxylic acid is brominated with Br_2 in the presence of $AlBr_3$ to give 5,7-dibromoadamantane-2-carboxylic acid.[127]

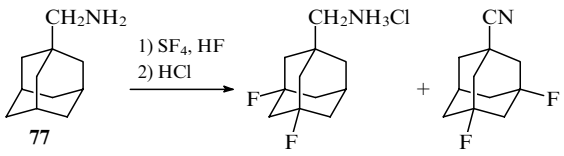
1,3-Bis(trifluoromethyl)adamantane (**74**) reacts with anhydrous hydrogen fluoride in the presence of SF_4 yielding 1,3-bis(trifluoromethyl)-5,7-difluoroadamantane (**75**).[128]



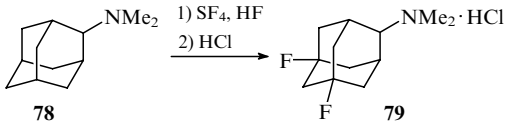
Halogenation of adamantanes bearing such functional groups as NO_2, NH_2, CH_2NH_2, NHCOMe, $NHCO_2Me$, *etc*., under the action of various halogenating agents has been studied in detail.

The fluorination of aminoadamantanes **76** and **77** with a mixture of liquid hydrogen fluoride and SF_4 affords several products.[129]

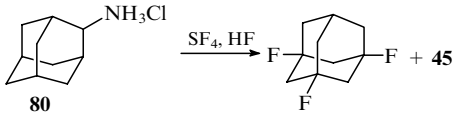




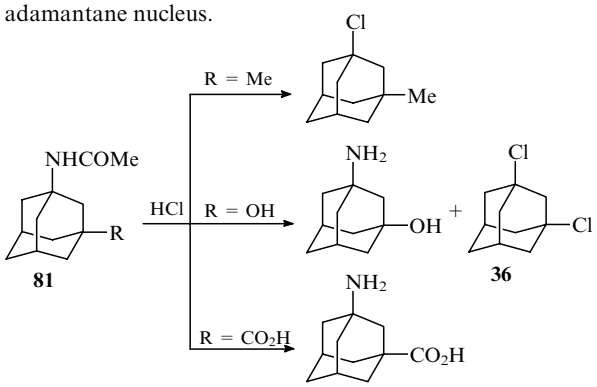
2-Dimethylaminoadamantane (**78**) reacts with HF and SF_4 much more selectively to give difluoride **79** in 99.3% yield.



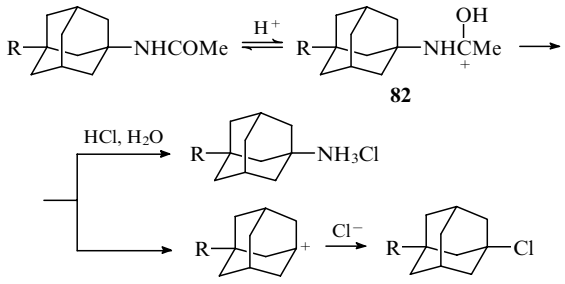
2-Aminoadamantane hydrochloride (**80**) is converted into 1,3,5-trifluoro- and 1,3,5,7-tetrafluoro-adamantanes (**45**) under the action of SF_4 in liquid hydrogen fluoride.[129] No reaction occurs in the absence of SF_4.



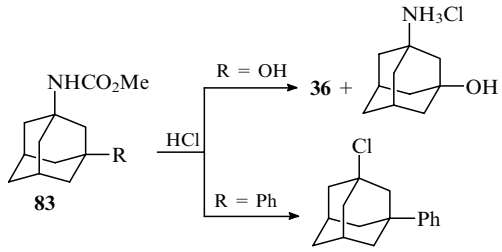
The reactions of 1-acetamidoadamantanes **81** with HCl have been studied.[130] The replacement of the acetamido group or/and its hydrolysis can occur depending on the nature of substituents in the adamantane nucleus.



A mechanism of this reaction was proposed. After protonation of the carbonyl group, two different reaction pathways are possible: (1) elimination of acetamide from an intermediate **82** affords the adamantyl cation, which is then attacked by the chloride anion yielding chloroadamantane; (2) hydrolysis of the acetamidoadamantane gives rise to aminoadamantane hydrochloride.



The reactions of urethanes **83** with hydrochloric acid can occur as the replacement of the methoxycarbonylamino group by chlorine.[130]



Treatment of 1-nitroadamantane with bromine in the presence of an equimolar amount of $AlBr_3$ was shown [131] to afford 1,3-dibromoadamantane (**19**) in 26% – 30% yield.

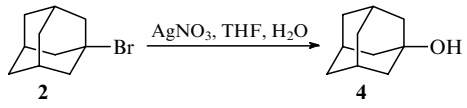
A method for the preparation of phosphorus-containing adamantanes by the reactions of hydroxy- and nitroxy-substituted adamantanes with phosphorus trichloride or acid chlorides of tervalent phosphorus has been developed.[132–134]

From the data presented above one can conclude that the introduction of the halogen atoms into adamantanes can be performed by various halogenating agents, *viz*., halogens, hydrogen halides, thionyl chloride, chlorosulfonic acid, alkali metal halides in sulfuric acid, a mixture of nitronium tetrafluorobrate with pyridinium poly(hydrogen fluoride), *etc*. The choice of the reagent is dictated by the nature of leaving group. The $NO_2BF_4 - PyH^+(HF)_nF^-$ system is the most versatile reagent, which can be employed for the replacement of the hydrogen and halogen atoms and hydroxy groups in adamantanes by fluorine atoms. From the practical standpoint, the most convenient method for the introduction of a halogen into adamantanes consists in the treatment of hydroxy- and nitroxy-adamantanes with hydrohalic acids or their salts in concentrated sulfuric acid.

IV. Synthesis of hydroxyadamantanes and their nitrates

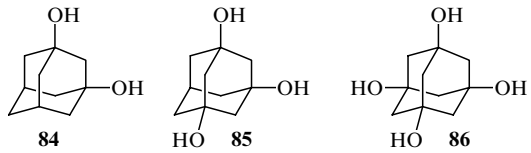
Adamantane (**1**) and 1-bromoadamantane (**2**) are most widely used as starting compounds in the synthesis of hydroxyadamantanes and their nitrates.

Preparation of adamantan-1-ol (**4**) by the hydrolysis of 1-bromoadamantane (**2**) was described for the first time by Landa *et al*.[14] This compound was also obtained by the reaction of 1-bromoadamantane (**2**) with silver nitrate in aqueous THF.[15]



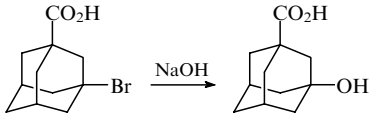
The reactions of 1-bromoadamantane (**2**) with silver nitrate in different solvents (benzene, phenol, dichloromethane, diethyl ether) was studied; it was shown that 1-adamantyl nitrate is formed in quantitative yield if the reaction is carried out in ether.[135]

Since the increase in the number of bromine atoms in adamantanes makes them more resistant to hydrolysis, 1,3-dihydroxy- (**84**), 1,3,5-trihydroxy- (**85**) and 1,3,5,7-tetrahydroxyadamantanes (**86**, 84% yield) were obtained by the reaction of the corresponding bromides with Ag_2SO_4 in concentrated sulfuric acid.[136, 137]



Hydrolysis of 1,3-dibromoadamantane (**19**) in an autoclave at 190 – 200 °C in alkaline, neutral and acidic media affords 1,3-dihydroxyadamantane (**84**) in quantitative yield.[138] When the reaction is carried out at lower temperature, 1-bromo-3-hydroxyadamantane could be isolated.1-Hydroxy-3-methyladamantane was obtained from 1-bromo-3-methyladamantane (**20**).[109]

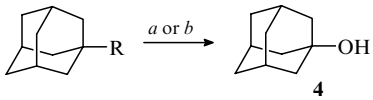
3-Bromoadamantane-1-carboxylic acid (**72**) undergoes the replacement of the bromine atom by the hydroxy group in 3 M aqueous alkali.[122]



The rate constants for the hydrolysis of 1-bromoadamantane (**2**), 3-bromoadamantane-1-carboxylic acid (**72**) and 1,3-dibromoadamantane (**19**) (100 °C, 74% aqueous dioxane) were found [118] to be equal to 7.98×10^{-4}, 1.3×10^{-5} and 2.4×10^{-6} s^{-1}, respectively.

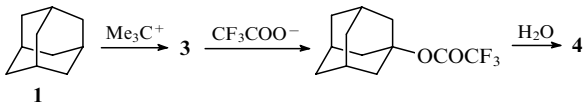
Hydroxyadamantanes were also prepared by the reactions of adamantane and its derivatives with sulfuric, nitric, fluorosulfonic and trifluoroacetic acids.

Treatment of adamantane (**1**) with a mixture of Br_2 and nitric acid affords 1-hydroxyadamantane (**4**).[139] This compound was also obtained by the action of 69% nitric acid on 1-bromoadamantane (**2**).[140]



(*a*) HNO_3, Br_2, R = H; (*b*) HNO_3, R = Br.

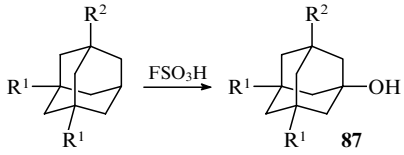
A one-step method for the preparation of adamantan-1-ol (**4**) from adamantane (**1**) by the reaction with a mixture of trifluoroacetic acid and Bu^{t}OH (55 °C, 12 h, the ratio AdH : Bu^{t}OH : CF_3CO_2H is 1 : 2.5 : 17) in dichloromethane was proposed.[141, 142] A reaction scheme including the intermediate formation of the adamantyl cation **3** was suggested.



The use of the system trifluoroacetic acid – 56% nitric acid made possible the preparation of 1-aryl-3-hydroxyadamantanes by the replacement of hydrogen in aryladamantanes. In the case of reactive aryl substituents, the oxidation is accompanied by the nitration of the aromatic ring.[20] The reaction conditions and the yields of the corresponding alcohols are listed in Table 6.

Treatment of adamantane with 100% nitric acid affords 1-hydroxyadamantan-4-one in 77% yield.[98]

Hydroxyadamantanes **87** were obtained by the reactions of adamantane (**1**) and its homologues with fluorosulfonic acid.[51]



$R^1 = R^2 = H$; R^1 = Me, $R^2 = H$; $R^1 = R^2$ = Me.

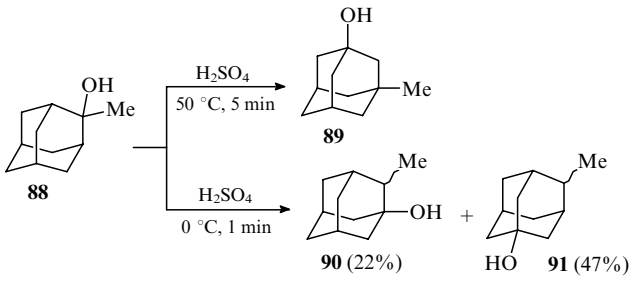
1-Hydroxyadamantane (**4**) is a reaction product of adamantane (**1**) with the system bis(trimethylsilyl) peroxide – trifluoromethanesulfonic acid.[143]

Adamantanes with the hydroxy group at the bridgehead carbon atom can be obtained by the isomerisation of 2-alkyl-2-hydroxyadamantanes on treating them with concentrated sulfuric acid. Thus 2-hydroxy-2-methyladamantane (**88**) is converted into tertiary alcohols **89** – **91** (a mixture of *Z*- and *E*-isomers) under the action of 96% H_2SO_4.[144] The composition of the reaction products depends on the temperature and time of the reactions.

Table 6. Synthesis of hydroxyadamantanes.[20]

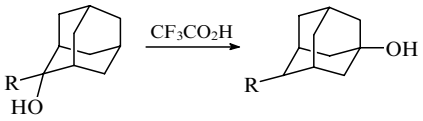
Substrate [a]	t /h	Products	Yield (%)
AdC_6H_4Me-4 (2.4 : 1)	2	HO-C_6H_3Me-4-NO_2-3	20
		C_6H_3Me-4-NO_2-3	62
$AdC_6H_3Me_2$-3,4 (3.6 : 1)	3	HO-$C_6H_2Me_2$-3,4-NO_2-5	26
$AdC_6H_4NO_2$-4 (2.4 : 1)	2	HO-$C_6H_4NO_2$-4	60
AdC_6H_4Br-4 (1.2 : 1)	2	HO-C_6H_4Br-4	32
AdC_6H_3Me-4-NO_2-3 (3.6 : 1)	3	HO-C_6H_3Me-4-NO_2-3	58
$AdC_6H_4CO_2H$-4 (1.2 : 1)	2	HO-$C_6H_4CO_2H$-4	11

[a] The ratio HNO_3 : substrate is given in parentheses.



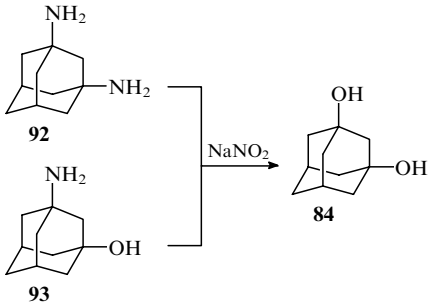
At 25 °C, 2-hydroxy-2-methyladamantane (**88**) gives a mixture of alcohols **90** and **91**, while at 45 °C (10 min), 1-hydroxy-3-methyladamantane (**89**) is the major reaction product.[19]

In trifluoroacetic acid, 2-hydroxy-2-R-adamantanes isomerise into *Z*- and *E*-isomers of 1-hydroxy-4-R-adamantanes.[145]



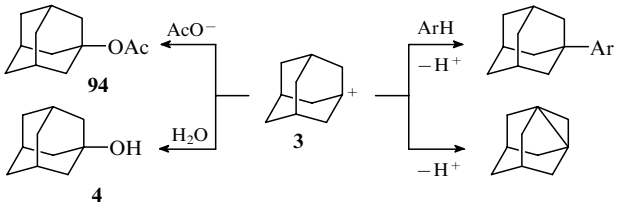
Thus the isomerisation of 2-hydroxy-2-methyladamantane (**88**) leads to a 1 : 1 mixture of *Z*- and *E*-isomers of 1-hydroxy-4-methyladamantane in 90% overall yield.

The well-known method for the preparation of alcohols such as deamination of amines is also used in the synthesis of hydroxyadamantanes.[146–151] Thus the deamination of 1,3-diaminoadamantane (**92**) and 1-amino-3-hydroxyadamantane (**93**) by the action of $NaNO_2$ in acetic acid was shown to result in the formation of 1,3-dihydroxyadamantane **84**.[146]



Besides the expected 1-hydroxyadamantane (**4**), adamantane (**1**) was identified as the reaction product in the deamination of 1-aminoadamantane (**80**).[149]

The deamination of 1-aminoadamantane (**80**), including that in the presence of benzene and anisole, has been studied in detail.[150] It was expected that the adamantyl cation **3** would alkylate the arenes, react with external nucleophiles or rearrange.

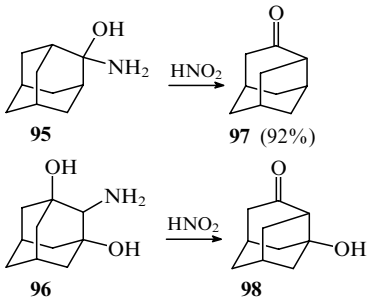


However, no aryladamantane was found among the reaction products when the deamination was carried out in the presence of benzene or anisole (Table 7).[148]

Table 7. Deamination of 1-aminoadamantane (**80**).[148]

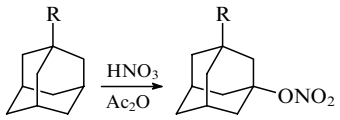
Reagent	Reaction conditions		Yield (%)	
	Solvent	T /°C	**4**	**94**
$NaNO_2$	AcOH, H_2O	85	97.0±1.0	3.0±1.0
$NaNO_2$	HCl, H_2O	85	100	
n-$C_5H_{11}ONO$	AcOH, PhH	refluxing	40.0±0.5	59.0±0.5
n-$C_5H_{11}ONO$	AcOH, PhOMe	the same	100	

The deamination of 2-amino-2-hydroxy- (**95**) and 2-amino-1,3-dihydroxy-adamantanes (**96**) is accompanied by a carbon skeleton rearrangement leading to the formation of tricyclic ketones **97** and **98**.[151]



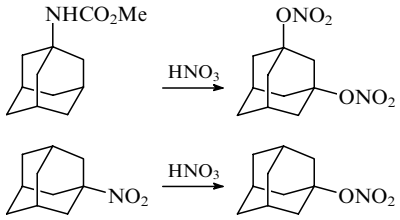
Hydroxyadamantanes are also synthesised from the corresponding nitrates, which, as was mentioned above, are prepared by the treatment of adamantanes with nitric acid.[21] Later, the reactions of substituted adamantanes with nitric acid in acetic anhydride was studied.[152] In these reactions, 1-chloro- (**35**) and 1-bromo-adamantanes (**2**) produce nitrate **12** due to the replacement of the halogens. As regards adamantane-1-carboxylic acid

(**73**), 1-(trinitromethyl)adamantane (**28**) and the nitrate **12**, they undergo the replacement of the hydrogen atom in the 3-position.



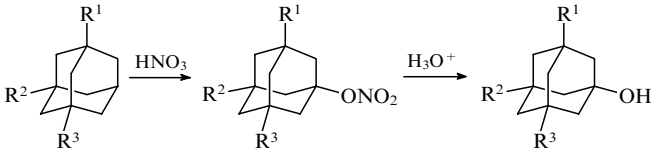
R = CO_2H, $C(NO_3)_3$, ONO_2.

Adamantanes with nitrogen-containing functional groups like $NHCO_2Me$ and NO_2 react with nitric acid through the replacement of these groups by the nitrato group.



Upon treatment with a mixture of nitric acid and acetic anhydride, urethanes give nitrourethanes and 1-aminoadamantane (**80**) gives 1-nitroxy-3-nitroadamantane.[152]

A method for the preparation of alkyladamantanols by the hydrolysis of the corresponding nitrates in 25% – 30% nitric acid has been described.[153]



R^1 = Me: $R^2 = R^3$ = H; R^2 = Me, R^3 = H; $R^2 = R^3$ = Me;
R^1 = Et, $R^2 = R^3$ = H.

The preparation of hydroxyadamantanes from their nitrates is the most convenient method, taking into account its simplicity and availability of the starting materials. Using this method, 1-hydroxyadamantane (**4**), 1,3-dihydroxyadamantane (**84**), 3-hydroxyadamantane-1-carboxylic acid and many other compounds have been synthesised.

Later, this method was extended to 2-substituted adamantanes.[154 – 156]

V. Synthesis of adamantanecarboxylic acids

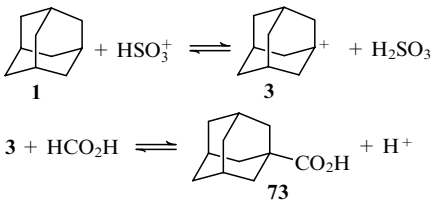
The Koch – Haaf reaction is widely used in the synthesis of carboxylic acids of the adamantane series. Adamantane (**1**), 1-bromoadamantane (**2**), 1-hydroxyadamantane (**4**) and its nitrate **12** are used as starting compounds.

Adamantane-1-carboxylic acid (**73**) was obtained by the reaction of 1-bromo- (**2**) or 1-hydroxyadamantane (**4**) with formic acid in sulfuric acid[15, 157] or of adamantane (**1**) with formic and sulfuric acids in the presence of *tert*-butyl alcohol.[158, 159]

As was shown by Langhals *et al.*,[160] the maximum yield (84%) of adamantane-1-carboxylic acid (**73**) was achieved when the ratio AdOH (**4**) : HCOOH : H_2SO_4 was 1 : 1 : 24. The yield is decreased in a deficiency of formic acid.

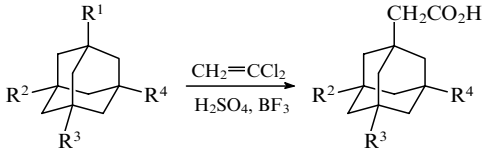
Adamantane-1-carboxylic acid (**73**) was also obtained from adamantane (**1**) in 20% oleum.[161, 162] The reaction is assumed[161] to involve the intermediate formation of the adamantyl cation **3**.

$$SO_3 + H_2SO_4 \rightleftharpoons HSO_3^+ + HSO_4^-$$



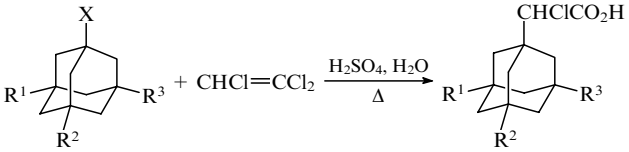
To synthesise adamantanecarboxylic acids from adamantane, the latter is made to react with CO in sulfuric acid or in oleum (autoclave, 90 – 160 °C).[163, 164] This provides a mixture of adamantane-1-carboxylic acid (**73**) and adamantane-1,3-dicarboxylic acid in the ratio of 1 : 6.

(1-Adamantyl)acetic acid is synthesised from 1-bromo- (**2**) or 1-hydroxy-adamantanes (**4**) and dichloroethylene in 80% – 100% H_2SO_4 in the presence of BF_3 at 0 – 15 °C.[165] The preparation of adamantylacetic acids from functionally substituted adamantanes and adamantane homologues has also been described.[166]



R^1 = Br, OH, OAc; R^2, R^3, R^4 = H, Me.

The reactions of adamantane and its derivatives with trichloroethylene in the presence of 90% sulfuric acid yield the corresponding α-chloroacetic acids.[167]

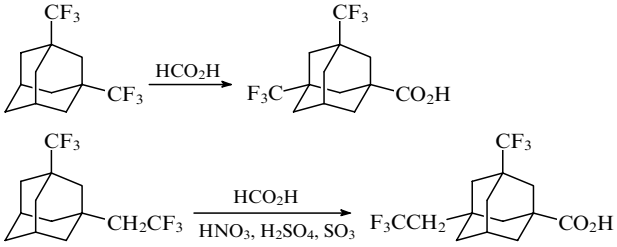


X = H, Br, OAc; R^1, R^2 = H, Me; R^3 = H, Br, CH_2CO_2H.

3-Alkyladamantane-1-carboxylic acids are obtained from alkyladamantanes in sulfuric acid in the presence of *tert*-butyl alcohol and 95% formic acid.

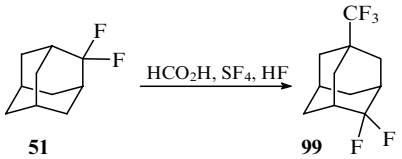
Using this approach, 3-methyl-, 3,5-dimethyl- and 3,5,7-trimethyl-adamantane-1-carboxylic acids have been synthesised in 72%, 49.8% and 38.5% yields, respectively.[111] Also, the synthesis of 3-methyl-,[106] 3-methyl-5-ethyl- and 3-bromomethyl-adamantane-1-carboxylic acids[107] as well as of 3-carboxymethyl-1-adamantyl-, 3-carboxymethyl-5-methyl-1-adamantyl- and 3-carboxymethyl-5,7-dimethyl-1-adamantyl-acetic acids[126] has been described. Adamantane-2-carboxylic acid was synthesised from 2-hydroxyadamantane (**6**).[168, 169]

Adamantanecarboxylic acids bearing the trifluoromethyl groups were also prepared by the Koch reaction.[170]

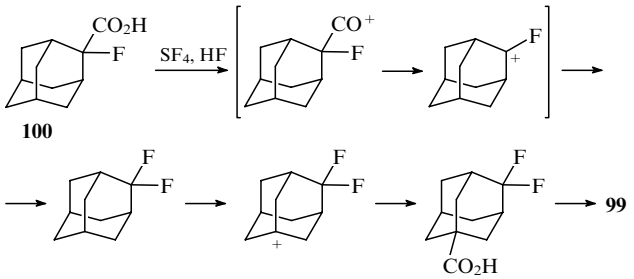


The reactivities of the trifluoromethyl- and trifluoroethyl-substituted adamantanes were shown[171] to be lower than those of non-fluorinated adamantanes due to the more difficult hydride ion abstraction from the former with the generation of the corresponding carbenium cations. Therefore, the preparation of 3-fluoromethyladamantane-1-carboxylic acid from 1-trifluoromethyladamantane required that the reaction of the latter with CO was carried out in a mixture of nitric and sulfuric acids.[171]

Treatment of adamantane (**1**) or 2,2-difluoroadamantane (**51**) with a mixture of formic acid, SF_4 and HF in dichloromethane yielded trifluoromethyl-containing adamantanes (*e.g.*, compound **99**) rather than the corresponding carboxylic acids. These are formed as the result of reactions of intermediate carboxylic acids with SF_4.[147]



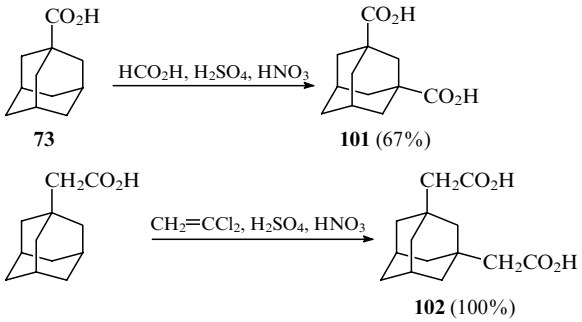
Studies of the reaction of 2-fluoroadamantane-2-carboxylic acid (**100**) with SF_4 and HF were undertaken to clarify the mechanism of these transformations.[148] This reaction afforded 4,4-difluoro-1-trifluoromethyladamantane (**99**), thus supporting the reaction scheme proposed earlier.[147]



Dicarboxylic acids of the adamantane series were also synthesised by the Koch–Haaf reaction. Thus adamantane-1,3-dicarboxylic acid was obtained from 1,3-dibromoadamantane (**19**) or 3-bromoadamantane-1-carboxylic acid (**72**).[16, 122]

A two-step synthesis of adamantane-1,3-dicarboxylic acid and (3-carboxymethyl-1-adamantyl)acetic acid from adamantane (**1**) or the corresponding monocarboxylic acids has been proposed.[172–175]

Adamantane-1,3-dicarboxylic acid (**101**) or (3-carboxymethyl-1-adamantyl)acetic acid (**102**) can be prepared from the corresponding monocarboxylic acids. In these cases, the reactions are carried out in a mixture of nitric and sulfuric acids with formic acid or CO and dichloroethylene as the carboxylating reagents for the former and the latter, respectively.[173]

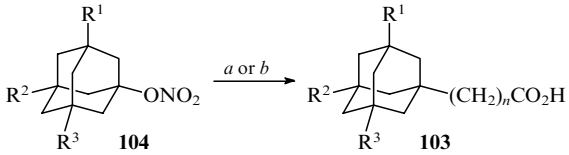


Using regression analysis, it was established that the best yields of the acids **101** (94%) and **102** (66%) starting from adamantane (**1**) are achieved with a mixture of nitric and sulfuric acids in 60% oleum.[174]

Dicarboxylic acids of the adamantane series, like the acid **102**, are of interest as starting materials in the synthesis of polyamides and polyesters.[176–178]

Adamantanecarboxylic acids can be prepared from the corresponding nitrates. Thus adamantane-1-carboxylic acid (**73**) has been obtained in 94% yield from 1-adamantyl nitrate (**12**) and formic acid in sulfuric acid.[104, 179]

The preparation of carboxylic acids **103** from aryl- and alkyl-substituted adamantyl nitrates **104** has been described.[180–182]



R^1, R^2, R^3 = H, Alk, Ar;
(*a*) HCO_2H, H_2SO_4 (d = 1.84 g cm^{-3}), n = 0;
(*b*) $CH_2=CCl_2$, H_2SO_4, n = 1.

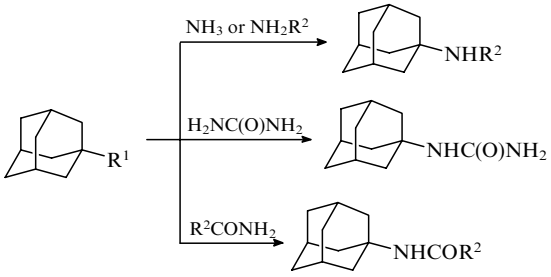
Using this approach, the corresponding dicarboxylic acids have been obtained from nitrates of 3-hydroxyadamantane-1-carboxylic and (3-hydroxy-1-adamantyl)acetic acids, however, more concentrated sulfuric acid was required in this case.[183]

A mixture of 1-formyladamantane and ethyladamantane-1-carboxylate results from the formylation of adamantane in CH_2Br_2 in an atmosphere of CO in the presence of superacid systems as catalysts.[184]

VI. Aminoadamantanes

The great interest in the synthesis of amino-substituted adamantanes is caused first of all by the discovery that 1-aminoadamantane hydrochloride (**80**) is active against influenza virus.

Amines of the adamantane series are obtained by the reactions of 1-bromoadamantane (**2**), 1-hydroxyadamantane (**4**) or 1-adamantyl nitrates with ammonia, amines, amides or nitriles of carboxylic acids, urea, *etc.*



R^1 = Hal, OH, ONO_2; R^2 = H, Alk, Ar.

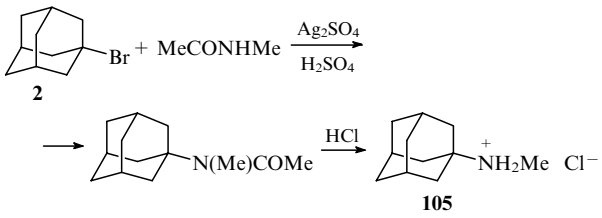
Oleum, concentrated H_2SO_4 or HNO_3 are used as an electrophilic medium. *N*-Adamantylamides are converted into the corresponding amines by alkaline or acid hydrolysis. 1-Aminoadamantane is synthesised from 1-bromoadamantane (**2**) under the action of ammonia at 200 °C for 6 h.[185]

The preparation of compounds of the general formula $AdNR^1R^2$ [R^1, R^2 = H, Ph, Alk(C_1–C_{12}), AlkO, cyclo-Alk, HetAr, *etc.*] has been described.[186] Thus 1-dodecylaminoadamantane was obtained by the reaction of 1-bromoadamantane (**2**) with dodecylamine for 8 h.

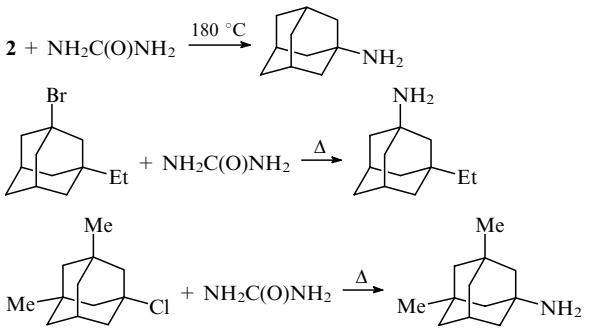
1-Aminoadamantane can be synthesised under fairly mild conditions with the use of amides, *e.g.*, formamide. The reaction of 1-bromoadamantane (**2**) with formamide is carried out in concentrated H_2SO_4.[187, 188] *N*-(1-Adamantyl)formamide thus formed is converted into 1-aminoadamantane under the action of 10% NaOH or 20% HCl. This method served as the basis for the manufacture of 1-aminoadamantane hydrochloride (**80**) (Amantadine, Mydantan and Symmetrel).[189]

The reactions of 1-hydroxyadamantane with alkylamides in trifluoroacetic acid have been proposed for the preparation of *N*-[1-(1-adamantanyl)alkyl]amides.[190]

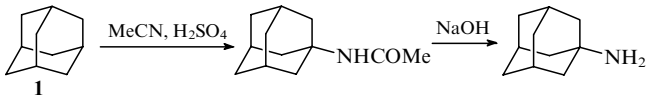
N-Alkyl-1-aminoadamantanes, including 1-methylaminoadamantane hydrochloride (**105**), were obtained from the bromide **2** and *N*-alkylacetamides.[191] In these reactions, silver sulfate was used as an electrophilic catalyst.



The synthesis of aminoadamantanes by the reactions of urea or its alkyl derivatives with 1-halogenoadamantanes has been described in some patents.[192–194] As a rule, the reactions are carried out at high temperature.

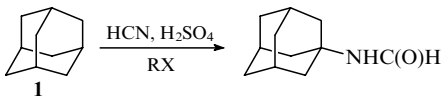


Stetter *et al.*[195] were the first to have studied the reactions of 1-bromo- (**2**) and 1-hydroxyadamantane (**4**) with acetonitrile in the presence of acid catalysts (the Ritter reaction). 1-Acetamidoadamantane was obtained by these reactions in 61% yield. Diethylene glycol was used as a medium for the alkaline hydrolysis of 1-acylaminoadamantane.[196]



The reaction of hydrocyanic acid with adamantane (**1**) in sulfuric acid in the presence of a hydride ion acceptor leads to 1-formamidoadamantane. The influence of the reaction conditions on the yield of this product has been studied by Haaf.[197]

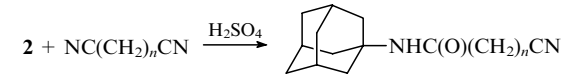
The reaction is carried out at 21–26 °C in an excess of 96%–100% H_2SO_4 using the molar ratio adamantane : acceptor : HCN = 0.1 : 0.4 : 1.7.



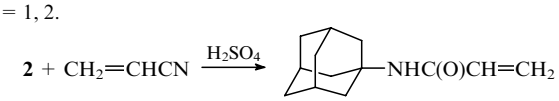
R	X	Solvent	Time /h	Yield (%)
Bu^t	OH	n-hexane	1.5	78
EtCHMe	OH	the same	2.0	75
Bu^i	OH	cyclohexane	1.0	60
Bu^t	Cl	CCl_4	1.5	42

In the reaction of adamantane with acetonitrile under similar conditions, 1-acetamidoadamantane was obtained in 36% yield.[197]

Nitriles of not only aliphatic monocarboxylic acids, but also of saturated dicarboxylic acids (maleic, adipic) and unsaturated monocarboxylic acids, *e.g.*, acrylic, have been used in the reactions with 1-bromoadamantane (**2**).[198]

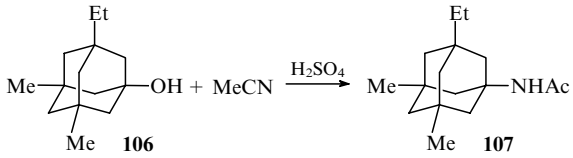


n = 1, 2.

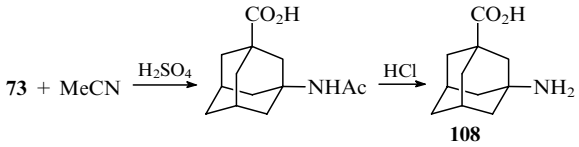


Adamantyl cation can be generated in the Ritter reaction using $NOPF_6$.[199] The reactions of 1-bromoadamantane (**2**) with acetonitrile and propionitrile in the presence of $NOPF_6$ and subsequent hydrolysis resulted in *N*-adamantylamides.

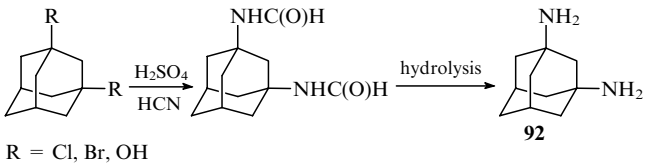
Alcohols react nicely with acetonitrile in the presence of H_2SO_4. Thus 3-ethyl-1-hydroxy-5,7-dimethyladamantane in the reaction with acetonitrile in sulfuric acid gives the corresponding acetamide **107**.[200]



The preparation of 3-aminoadamantane-1-carboxylic acid (**108**) from adamantane-1-carboxylic acid (**73**) has been described.[201]

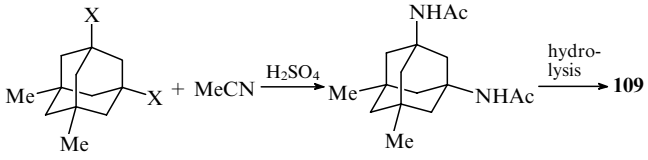


Diamines are of particular importance for the chemistry of polymers. Methods for the synthesis of diaminoadamantanes have been reported in several patents.[102, 202, 203] Thus 1,3-diaminoadamantane (**92**) was prepared by the ammonolysis of 1,3-diiodoadamantane. The reaction is carried out at 260 °C under a pressure above 1000 atm.[102] 1,3-Diaminoadamantane (**92**) is also synthesised by the reactions of hydrocyanic acid with 1,3-dichloro-, 1,3-dibromo- or 1,3-dihydroxy-adamantanes in sulfuric acid.[202]



R = Cl, Br, OH

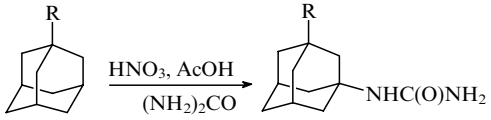
Diaminodimethyladamantane (**109**) is obtained by the reactions of 1,3-dichloro-and 1,3-dibromo-5,7-dimethyl-adamantanes with acetonitrile.[203]



X = Cl, Br.

Nitrates of the corresponding alcohols can also be used as starting compounds in the synthesis of aminoadamantanes. Thus 1-acetamidoadamantane is formed in the reaction of 1-adamantyl nitrate (**12**) with acetonitrile.[204]

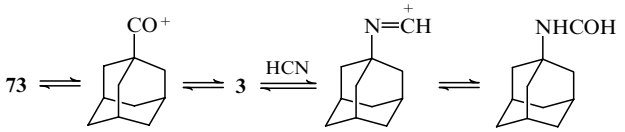
It was later shown that adamantane (**1**) and its homologues can be functionalised with urea in a mixture of acetic acid and HNO_3.[205] The isolation of only the *N*-alkylation products of urea provides evidence in favour of the intermediacy of carbocations.



R = H, Me, Et.

Carboxylic acids can also serve as starting compounds in the synthesis of the corresponding aminoadamantanes.[206] Thus adamantane-1-carboxylic acid (**73**) in 100% sulfuric acid produces the adamantyl cation (**3**), which then reacts with HCN or RCN

providing *N*-adamantylformamide or *N*-adamantylacetamide in 56% and 51% yields, respectively.



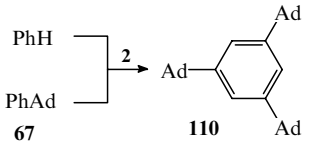
VII. Aryladamantanes

Halogenoadamantanes, adamantanols and their *O*-nitrates are used for the alkylation of aromatic compounds with adamantane.

The reaction of bromoadamantane (**2**) with benzene has been used by Stetter *et al.*[15] to prepare phenyladamantane (**67**). The synthesis of some other adamantane-substituted aromatic compounds was also described.[207, 208]

Either adamantane with several phenyl groups or benzene bearing up to three adamantyl substituents are formed in the reaction of 1-bromoadamantane (**2**) with benzene in the presence of Lewis acids, depending on the ratio of the reactants.[209, 210]

1,3,5-Triadamantylbenzene (**110**) has been synthesised by the reaction of benzene or 1-phenyladamantane (**67**) with 1-bromoadamantane (**2**) in liquid SO_2 in the presence of $AlCl_3$.[210] A small amount of *p*-diadamantylbenzene was also isolated.



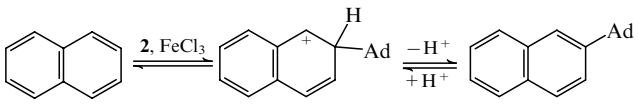
1,3,5-Triphenyladamantane and 1,3,5,7-tetraphenyladamantane have been synthesised by the reaction of 1-bromoadamantane (**2**) with benzene in the presence of *tert*-butyl bromide and a catalytic amount of $AlCl_3$.[209]

It was shown [211] that the reaction of 1-bromoadamantane (**2**) with toluene in the presence of water resulted only in 4-(1-adamantyl)toluene, while a mixture of 4-(1-adamantyl)toluene and 3-(1-adamantyl)toluene was obtained in the presence of $ZnCl_2$ or $FeCl_3$.

1-Bromoadamantane (**2**) reacts also with naphthalene, 2-methylnaphthalene, biphenyl, anthracene, phenanthrene and fluorene to give the corresponding substituted adamantanes.[212]

The reactions of naphthalene and its derivatives with 1-bromoadamantane (**2**) were the subject of several studies.[213–219]

Thus the reaction of 1-bromoadamantane (**2**) with naphthalene in the presence of $FeCl_3$ at 60–140 °C leads to 2-(1-adamantyl)naphthalene. The second molecule of adamantane is introduced either in the 6- or 7-position.[215]

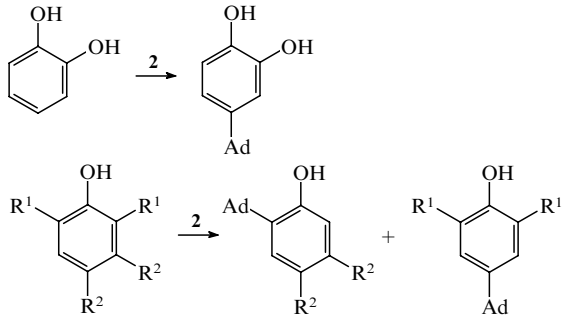


According to Stewart–Breigleb models of 1- and 2-adamantylnaphthalene, the molecule of the former is much more sterically hindered due to the spatial interaction of the hydrogen at the C(2) atom of the adamantane fragment and the H(8) atom of naphtalene.

Attempts to obtain 2-(1-adamantyl)naphthalene by the isomerisation of 1-(1-adamantyl)naphthalene were unsuccessful. 2-(1-Adamantyl)naphthalene has been synthesised by the reaction of 1-hydroxyadamantane (**4**) with naphthalene in the presence of phosphoric anhydride.[216] *N*-Acetyl-1-aminonaphthalene is alkylated under these conditions with hydroxyadamantane to give the corresponding 4-adamantyl-1-aminonaphthalene.[216]

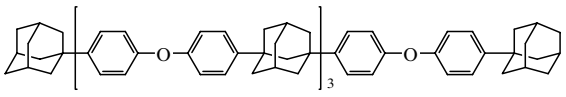
Phenol, anisole, catechol, 2,6- and 3,4-dimethylphenols, *o*-, *m*- and *p*-cresols, diphenyl ether and others were also reacted with 1-bromoadamantane (**2**).[220–227]

Thus phenol, 2,6- and 3,4-dimethylphenols and catechol react with 1-bromoadamantane (**2**) in the absence of a catalyst.[222]



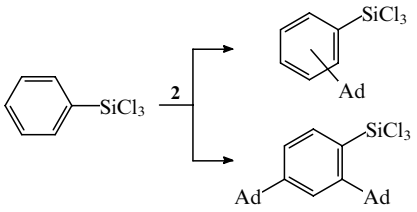
R^1, R^2 = Me; R^1 = H, Me.

2,6-Di(*tert*-butyl)phenol and 2-methoxyphenol react with 1-bromoadamantane (**2**) at 130–140 °C to form 4-adamantylphenols. The alkylation of *m*-aminophenol with 1-bromoadamantane (**2**) leads to adamantane-substituted *m*-aminophenol.[223] 4,4′-Diadamantyldiphenyl ether is formed upon heating of 1-bromoadamantane (**2**) with diphenyl ether in carbon disulfide in the presence of aluminium chloride. In the presence of zinc chloride and at elevated temperature, the oligomer **111** becomes the major product.[207, 223]



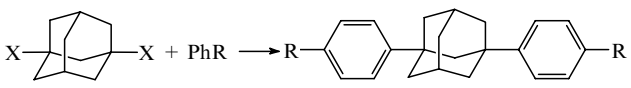
111

The possibility of alkylation of phenylchlorosilanes with 1-bromoadamantane (**2**) has been demonstrated.[228]



It should be noted that the reaction of 1-bromoadamantane (**2**) with methyl(phenyl)dichlorosilane results in a mixture of mono- and polyadamantylbenzenes.[228]

1,3-Dichloro- and 1,3-dibromo-adamantanes react with aryl(alkyl)chlorosilanes at 160–200 °C in the presence of $ZnCl_2$ to give 1,3-di(alkylchlorosilylalkyl)phenyladamantanes **112**.[229] 1-(Alkylchlorosilylalkyl)phenyladamantanes are also formed in appreciable yields.



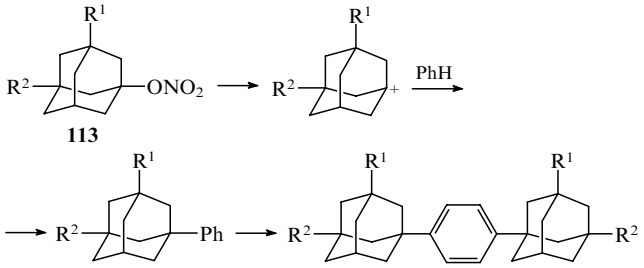
112

X = Cl, Br; R = CH_2SiMe_3, $C_2H_4SiMe_3$, $C_2H_4SiMeCl_2$, $C_2H_4SiCl_3$, CH_2SiMe_2Cl, $CH_2SiCHCl_2$, CH_2SiCl_3.

1,3-Dibromoadamantane was found to be more reactive than its 1,3-dichloro-analogue and aryl(alkyl)chlorosilanes can be arranged according to their reactivity in the following order: $PhCH_2SiMe_3 > PhC_2H_4SiMe_3 > PhC_2H_4SiMeCl_2 > PhC_2H_4SiCl_3 > PhCH_2SiCH_2Cl > PhCH_2SiMeCl_2 > PhCH_2SiCl_3$.

Mono- (**12**) and dinitrate **13** were also used as the alkylating reagents. The nitrate **12** readily reacts with benzene, toluene, ethylbenzene, *p*- and *m*-xylenes and anisole yielding the corresponding mono- and di-substituted adamantanes.[230] The preparation of 1,3-diaryladamantanes from the dinitrate **13** was also described.[230]

The nitrates **113** were used in the synthesis of diadamantyl-substituted arenes.[180]



113

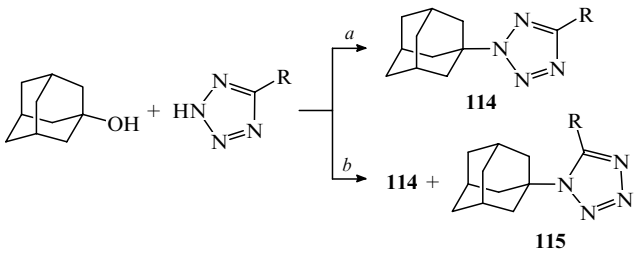
R^1 = Me, Et; R^2 = H, Me.

Reactions of 1-adamantyl nitrate (**12**) with such heterocyclic compounds as thiophene, 2-nitrothiophene, thiophene-2-carboxylic acid, furan and 2-furoic acid have been described.[231] The alkylation was carried out in concentrated sulfuric acid at -5 °C; the corresponding 1-hetaryladamantanes were obtained in 40% – 60% yields.

Data concerning the relative reactivities of 1-bromoadamantane (**2**), 1-hydroxyadamantane (**4**) and its nitrate **12** in the reaction with isopropylbenzene have been reported.[232] The highest yield of *p*-adamantylisopropylbenzene was obtained from adamantyl nitrate.

In recent years, an efficient procedure for the introduction of the adamantyl substituent into the aromatic ring of crown ethers by their direct alkylation with hydroxyadamantane in the presence of boron trifluoride diethyl etherate as a catalyst has been developed.[233]

1-Hydroxyadamantane (**4**) has been used as an alkylating reagent for 1,2,4-triazoles and 5-R-tetrazoles.[234 – 236] Its reactions with tetrazoles in 85% sulfuric acid gave the corresponding 2-(1-adamantyl)tetrazoles **114**, while a mixture of 2-(1-adamantyl)tetrazoles **114** and 1-(1-adamantyl)tetrazoles **115** was formed in 94% sulfuric acid.



114

114 +

115

(*a*) 85% H_2SO_4; (*b*) 94% H_2SO_4.

The studies of the reactions of adamantanes in electrophilic media have expanded the general concept of the mechanism of C – H bond activation and made it possible to develop preparative methods for the synthesis of halogen-, hydroxy- and nitroxy-substituted adamantanes. The latter are of particular interest as starting materials. Among the methods of adamantane functionalisation, the reactions with urethanes, amides and nitriles in nitric acid or its mixtures with AcOH or Ac_2O are worth especial attention. Some of these reactions have formed the basis for technological processes in the manufacture of pharmaceuticals Remantadinum and Mydantan.

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