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CHEMISTRY	Paper No. 14: Organic Chemistry –IV (Advance Organic Synthesis and Supramolecular Chemistry and carbocyclic rings)
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1. Learning Outcomes

After studying this module, you shall be able to understand:

- Adamantane and its structure
- Nomenclature of Adamantane
- Synthesis of Adamantane' Derivatives
- Property of Adamantane

2. Introduction

Adamanatne word derived from the Greek word *adamantinos* (relating to steel or diamond). Adamantane is a colourless, crystalline chemical compound with a camphor-like odour. Its formula is $C_{10}H_{16}$. Adamantane contains four cyclohexane rings which are connected and arranged in the "armchair" configuration. Adamantane is the most stable isomers among all the isomers with the formula $C_{10}H_{16}$, which include the similar structure of twistane. The arrangement of carbon in adamantine is same as in diamond crystal. The discovery of adamantane in petroleum in 1933 launched a new field of chemistry dedicated to studying the synthesis and properties of polyhedral organic compounds. Adamantane derivatives have found practical application as drugs, polymeric materials and thermally stable lubricants.

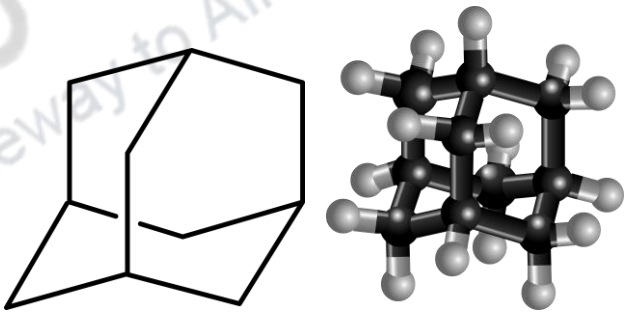


Figure 1: Structure of Adamantane.

3.Nomenclature of Adamantane

According to the rules of systematic nomenclature, adamantane should be called tricycle[3.3.1.1]decane. But, IUPAC recommends using the name "Adamantane". This molecule is composed of only carbon and hydrogen. Therefore, its 16 hydrogen and 10 carbon atoms can

be described by only two sites (labelled in figure 2). In figure 2, 1 show to 4 equivalent sites and 2 show to 6 equivalent sites. It has high T_d symmetry. Noradamantane and Homoadamantane is the closest structural analogs of adamantane, which respectively contain one less and one more CH_2 link than the adamantane.

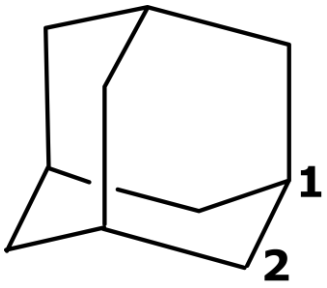


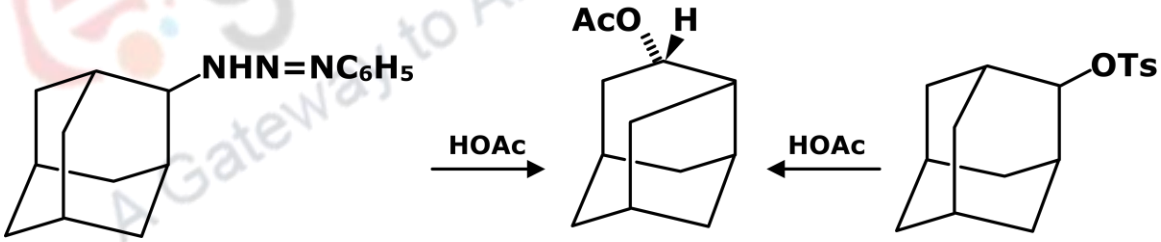
Figure 2: Numbering in adamantane

4. Synthesis of Adamantane's Derivatives

Protoadamantanes:

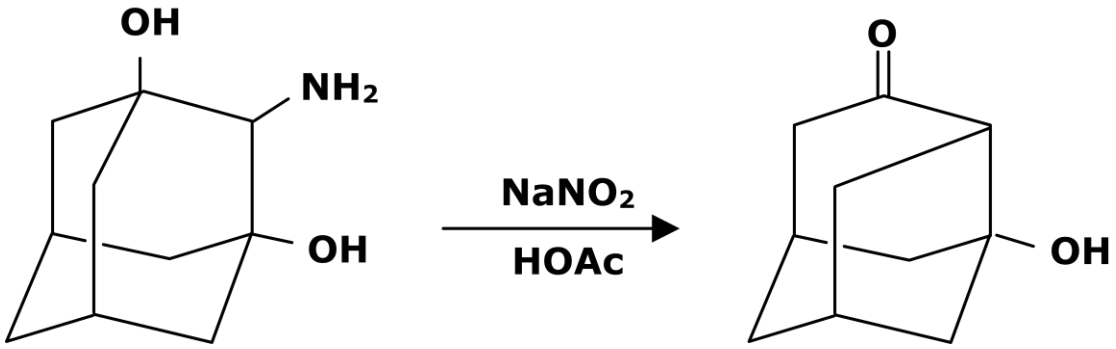
1. Rearrangement of the Adamantane Nucleus:

Exo-4-protoadamantyl acetate occurred after the acid catalysed deamination of 2-adamantyl phenyltriazene (Scheme 1). Acetolysis of 2-adamantyl tosylate give rise to 0.5% yield of the same acetate. The major product is the unrearranged 2-adamantyl acetate was found in both cases.



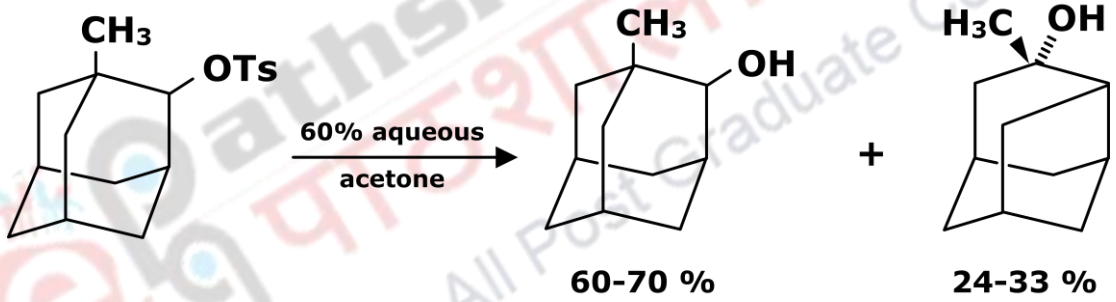
Scheme 1: Synthesis of 4-protoadamantyl actate

4-Protoadamantyl acetate may be converted *via* the alcohol to 4-protoadamantanone, which gives protoadamantane upon Wolf-Kishner reduction. While, Deamination of 2-aminoadamantan-1-ol, catalysed by the nitrous acid provide 92% yield of 4-protoadamanatanone. Furthermore, 56% yield of 8-hydroxy-4-protoadamantanone was obtained after the deamination of 2-aminoadamantane-1,3-diol (Scheme 2).



Scheme 2: Synthesis of 8-hydroxy-4-protoadamantanone.

Hydrolysis of 1-methyl-2-adamantyl tosylates gives 4-methyl-exo-4-protoadamantanol in approximately 30 % yield (Scheme 3).

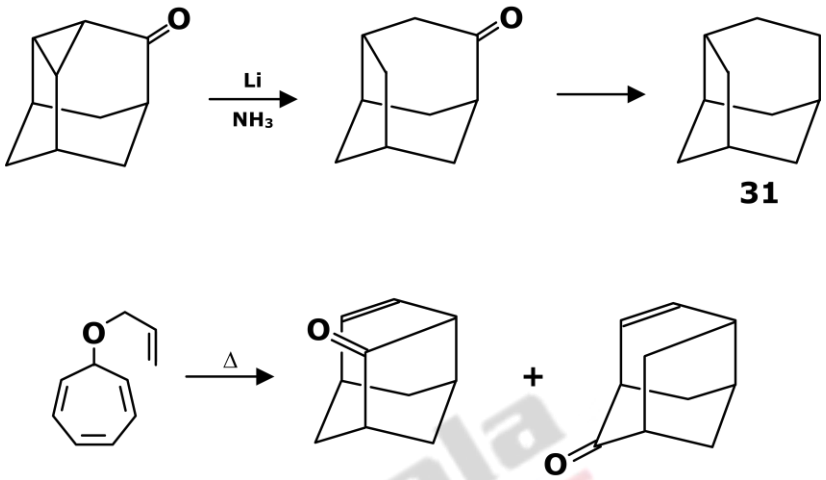


Scheme 3: Hydrolysis of 1-methyl-2-adamantyl tosylates gives 4-methyl-exo-4-protoadamantanol

After the reduction of 4-protoadamantanone with lithium aluminium hydride, it gives 2:1 mixture of endo-4-protoadamantanol and its exo-4-isomer. This stereochemical assignment is consistent with the relative solvolytic reactivities of derivatives of these alcohols. The addition of methyl Grignard to 4-protoadamantanone provide 2 : 1 mixture of 4-methyl-exo-4-protoadamantanol and it corresponding endo epimer.

2. Protoadamantane by Ring Closure Reaction:

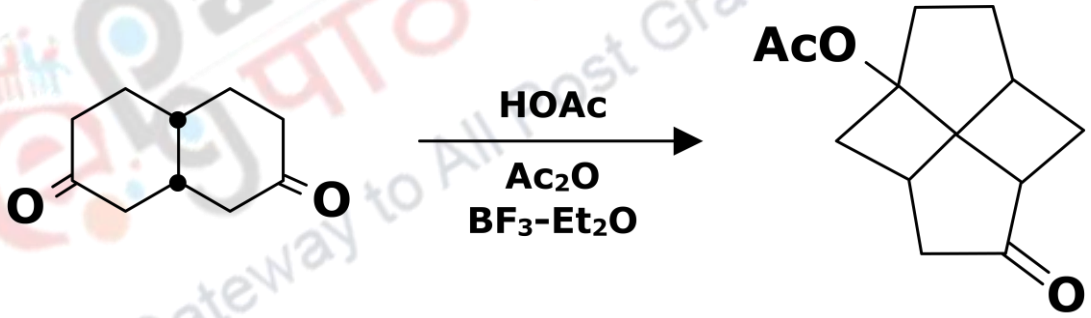
Protoadamantyl derivatives can be synthesized by several ring closure reaction. The reduction of 8,9-dehydroadamantane with lithium in ammonia provides 5-protoadamantone and the pyrolysis of 7-allyloxycyclopentatriene gives two unsaturated protoadamantanones (Scheme 4).



Scheme 4: Synthesis of protoadamantanone and its isomer.

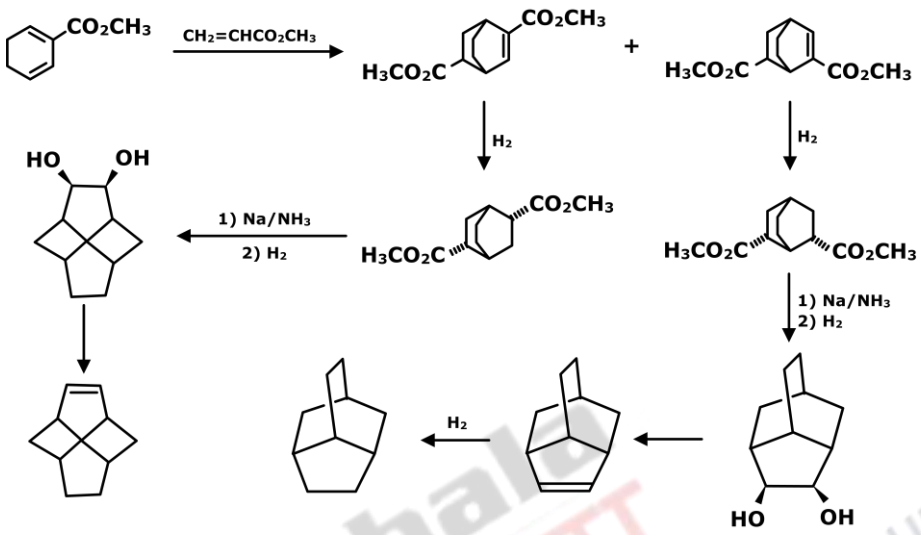
Twistanes:

Twistane derivatives may be easily prepared in one step from the cis decalin-2,7-dione (Scheme 5).



Scheme 5: Synthesis of Twistane derivative.

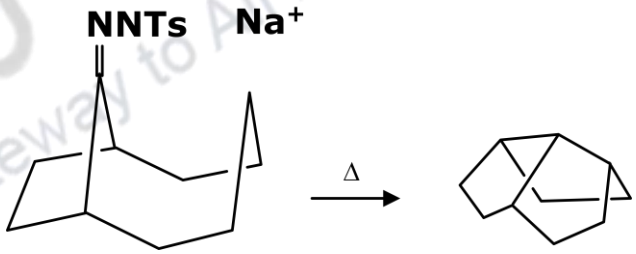
The wide variety of substituted twistanes by conventional techniques after selective removal of resulting 1-acetoxy-5-twistanone. The multistep synthetic route also developed for the synthesis of optically active twistane. The synthetic method also provide route for the synthesis of tricyclo decane (Scheme 6).



Scheme 6: Synthesis of twistane and tricyclo decane.

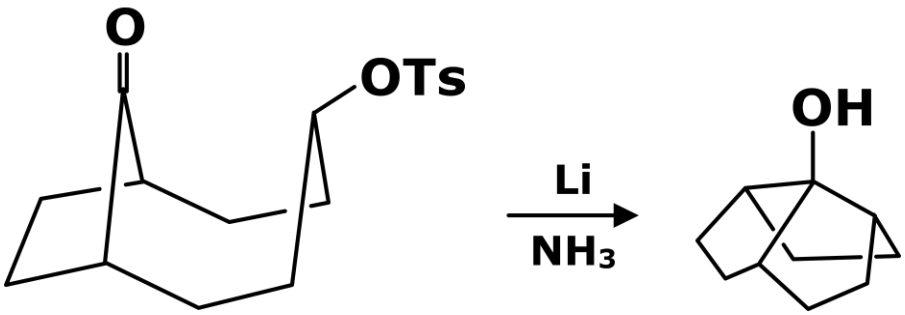
Tricyclo [5.2.1.0 4, 10] decanes :

Tricyclo decane can be synthesized by the pyrolysis of the sodium salt of the tosylhydrazone of 10-bicycto[5.2.1]decanone (Scheme 7).



Scheme 7: Synthesis of Tricyclo decane

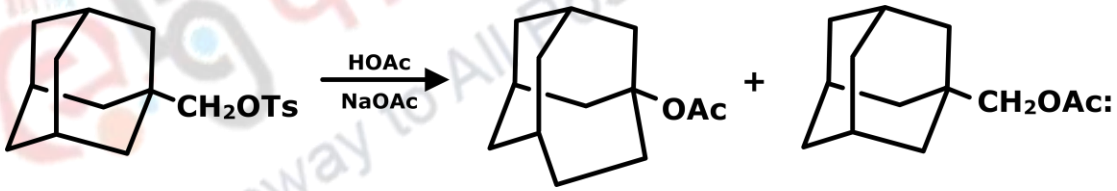
Furthermore, a transannular ring closure also a useful route for the synthesis of tricycle dacane derivative. Tricycle decanol can be synthesized by the ring closure of keto tosylate (Scheme 8).



Scheme 8: Synthesis of tricycle decanol.

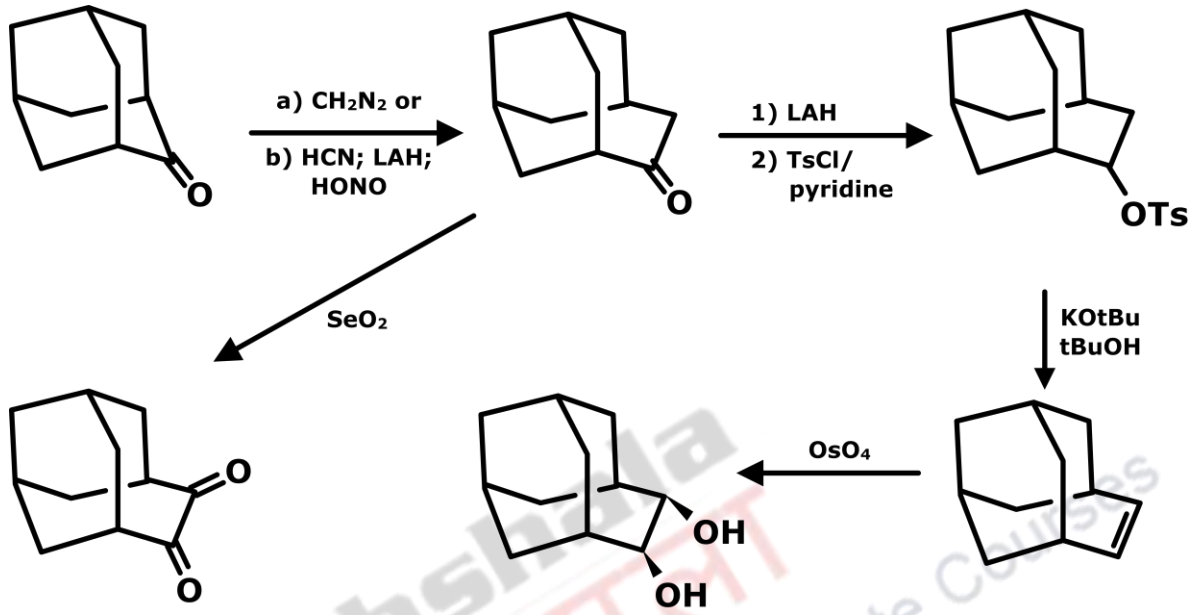
Homoadamantanes:

Ring Expansions of Adamantane: Homoadamantane derivatives are most readily obtained from ring expansions of appropriately substituted adamantanes. Carbonium ion reactions of adamantly carbonyl systems have been well known route to give 3-homoadamantyl derivatives. The mixture of 3-homoadamantyl acetate and 1-adamantylcarbinyl acetate were obtained after the solvolysis of 1-adamantylcarbinyl tosylate in acetic acid-sodium acetate. In more nucleophilic media (e.g. water-diglyme-NaOH) only 3-homoadamantanol is observed (Scheme 9).



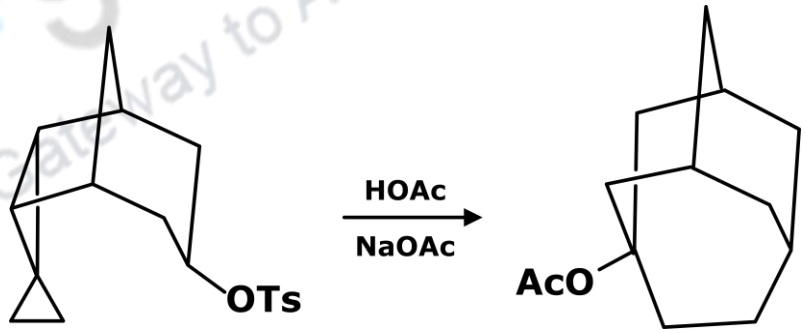
Scheme 9: Synthesis of 3-homoadamantanol derivative.

4-homoadamantanone is also obtained from the Tiffeneau-Demjanov-1-ol and diazomethane homologues of adamantanone. Homoadamantane and variety of 4-mono and 4,5-disustituted homoadamantanes also synthesized by these ring expansions reaction (Scheme 10).



Scheme 10: Synthesis of variety of 4-mono and 4,5-disustituted homoadamantanes

Ring Closure Reaction: Ring closure reaction is also synthetic route of homoadamantane derivatives. The first involves transannular cyclopropyl participation in the solvolysis, after acetolysis only one product 3-homoadamantyl acetate is observed (Scheme 11).

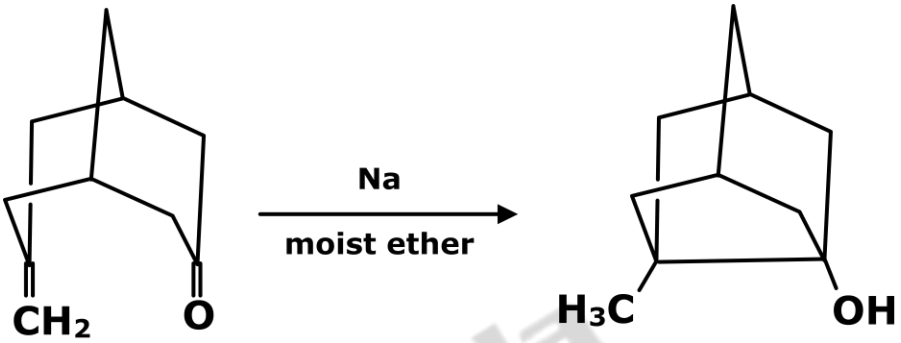


Scheme 11: Ring closure reaction.

Noradamantanes :

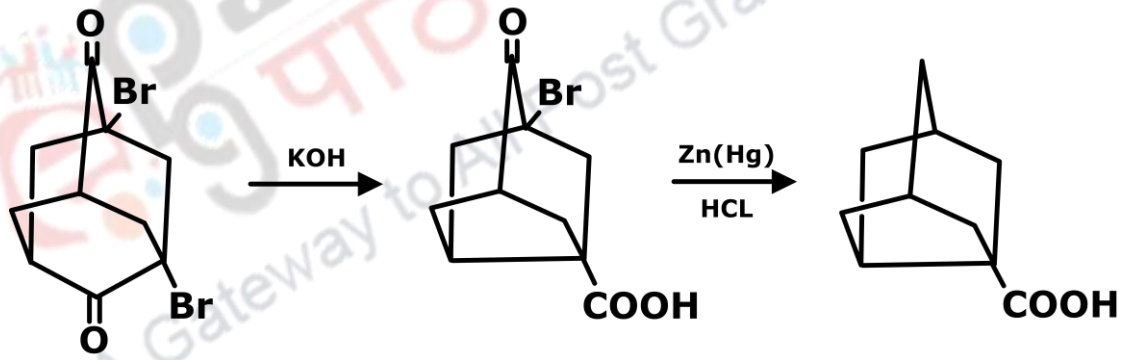
The ring closure reaction is useful reaction for the synthesis of noraadamantane. It involves a transannular ring closure of the bicyclo [3.3.1]nonyl system. Thus, 7-methyl-3-noradamantanol is

obtained from the treatment of 3-keto-7-methylenebicyclo [3.3.1]nonane with sodium in moist ether (Scheme 12).



Scheme 12: Ring closure reaction.

Furthermore, The single Favorskii ring contraction of 1,5-dibromoadamantane-2,6-dione also enables the preparation 3-substituted noradamantanes as shown in scheme 13.



Scheme 13: Synthesis of substituted 3-noradamantanes.

Bisnoradamantanes :

Bisnoradamantane derivatives are also synthesized by the Favorskii ring contraction of 1,3-dibrompadamanatane-2,6-dione (Scheme 14).

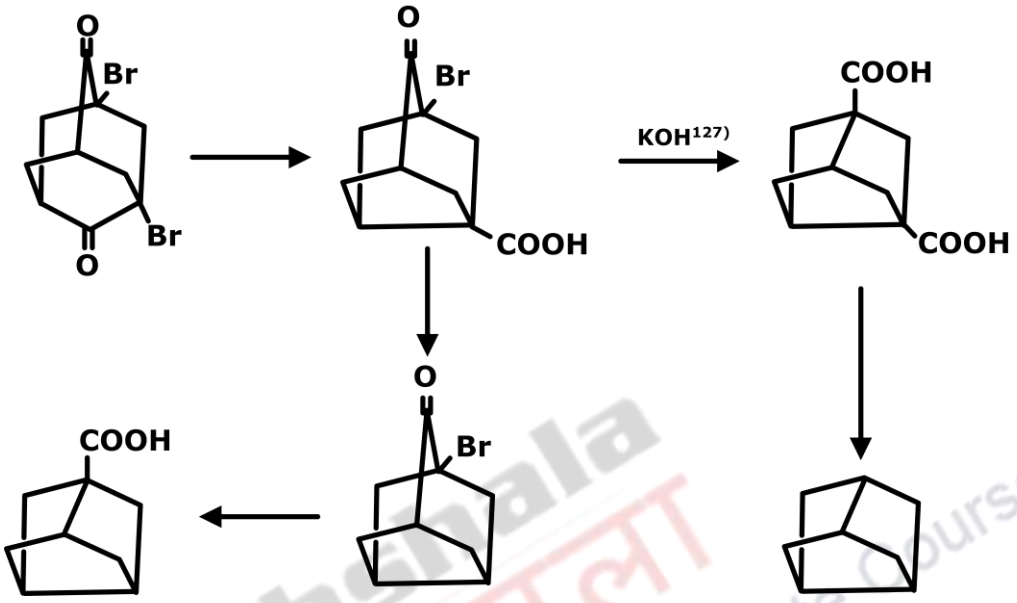
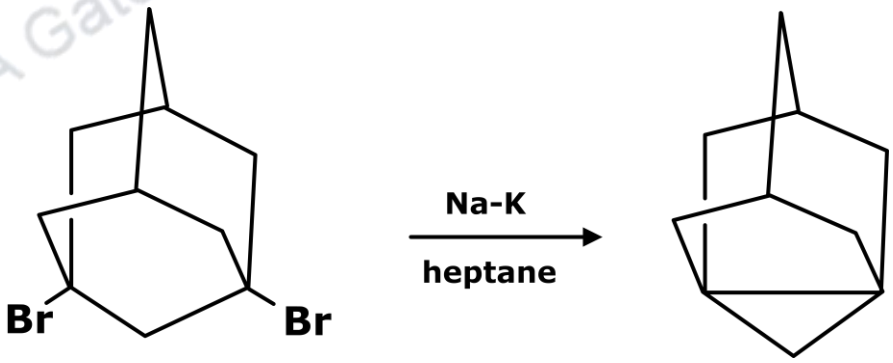


Figure 3: Synthesis of Noradamantane (Scheme 14)

Dehydroadamantanes and Dehydrohomoadamantanes :

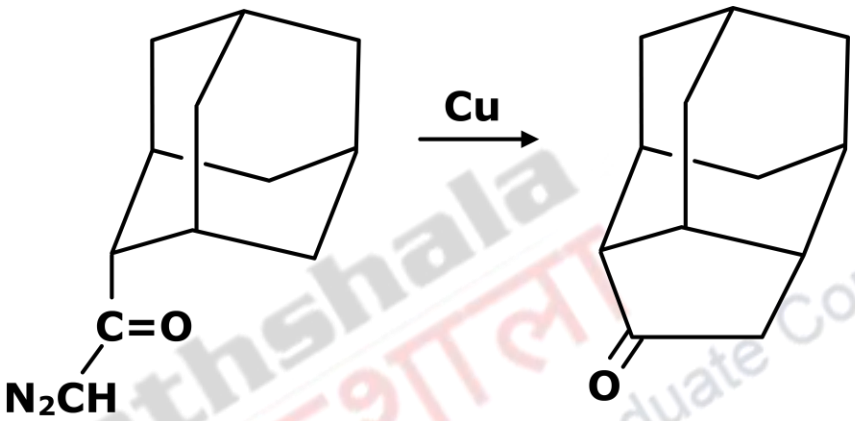
Carbene insertion or 1,3 reductive eliminations reaction widely used for the synthesis of dehydroadamanatanes. Pyrolysis of the dry sodium salt of the tosylhydrazone of adamantanone gives good yields of 2,4-dehydroadamantane and by the treatment of 1,3-dibromoadamantane with sodium, the 1,3-dehydroadamantane was obtained (Scheme 15).



Scheme 15 Synthesis of 1,3-dehydroadamantane.

Ethanoadamantanes :

A ring closure reaction of a substituted adamantane occurred during the synthesis of ethanoadamantane via Lewis acid catalysed rearrangement of various polycyclic hydrocarbons. Carbine insertion reaction illustrated during the treatment of 2-adamantyl diazoketone with copper (Scheme 16).



Scheme 16: Synthesis of Ethanoadamantane.

5. Properties of adamantane and it's derivatives

Thermodynamic Properties:

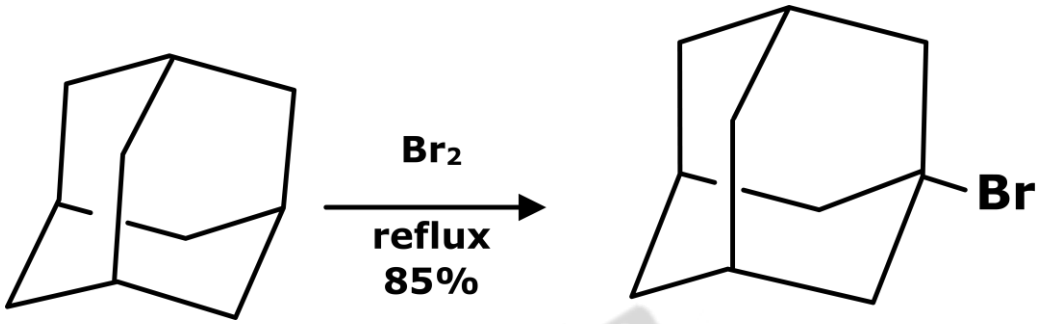
The driving force for the Lewis or strong acid catalysed rearrangements of polycyclic hydrocarbons to adamantoid systems is provided by the high thermodynamics stability of the adamantyl ring system. So, we can say the adamantane is the most stable tricyclic hydrocarbon. Due to the high degree of branching in the ring system and from the nearly ideal conformations of the atoms in the molecule, this thermodynamic stability occurred.

Chemical Property

Ionic Reaction:

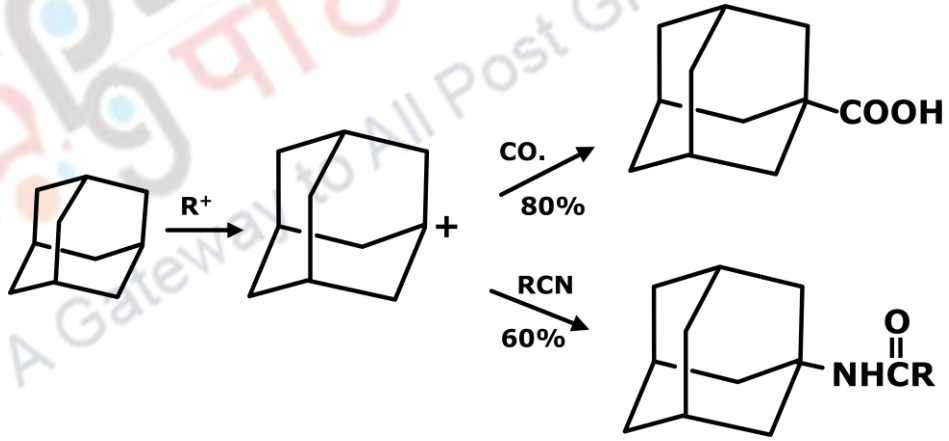
Although the bridgehead positions of many polycyclic hydrocarbons have been found to be quite unreactive toward nucleophilic substitutions, the 1-adamantyl cation may be generated with relative ease. Since, tertiary 1-adamantyl cation is more stable compared to the secondary 2-cation. At the bridgehead position, the carbonium substitution reaction strongly occurred. In the

absence of the free radical catalysts, the bromination reaction provide high yield of 1-bromoadamantane (Scheme 17).



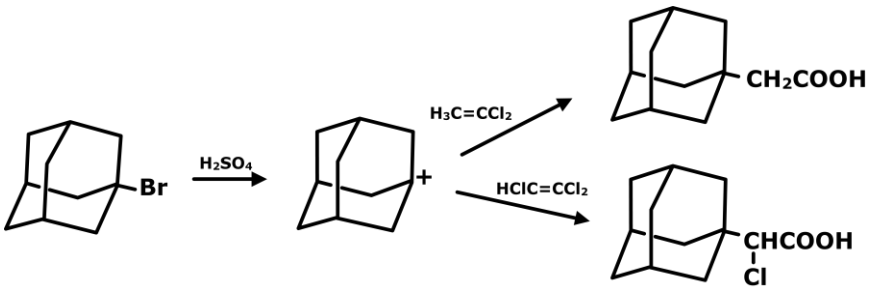
Scheme 17: Synthesis of 1-bromoadamanatane.

In another reaction, which involves the initial generation of the 1-adamantyl cation either by means of hydride transfer to the t-butyl cation or from 1-bromo- or 1-hydroxyadamantane, followed by trapping of the cation by carbon monoxide and acetonitrile, respectively (Scheme 18) may be used to introduce a carboxylic acid and amino function.



Scheme 18: Introduction of a carboxylic acid and amino functional group.

1,1-dichloroethylene and 1,1,3-trichloroethylene can also be used for the trap of 1-adamantyl cation and give the *1-adamantyl acetic acid* and *α-chloro- l-adamantyl acetic acid* respectively (Scheme 19).



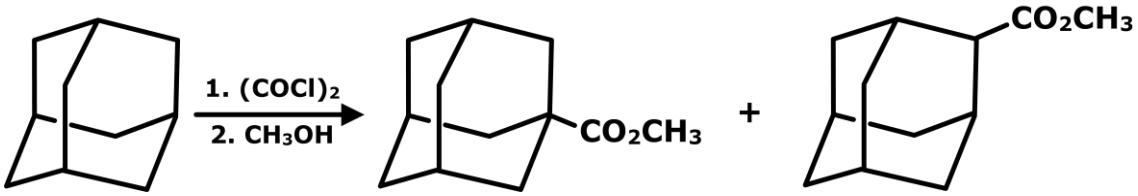
Scheme 19: Reaction to yield *1-adamantyl acetic acid* and *α-chloro- l-adamantyl acetic acid*

Free Radical Reactions:

In contrast to the specific ionic reactions of diamonoid hydrocarbons discussed above, free radical substitutions are much less selective. Thus, free radical reactions provide a method for the preparation of a greater number of the possible isomers of a given hydrocarbon than might be available by ionic processes. Generally, it is difficult to separate the complex product mixture. Consequently, there are few examples of the synthesis of specific derivatives of diamonoid hydrocarbons by this method.

For example, *photochlorination* of adamantane in $CC1_4$ gives 37 % 1-chloroadamantane and 73 % of the secondary isomer , Due to the decreased symmetry of substituted adamantanes, free radical substitutions of these substrates gives rise to even more complex product mixtures.

Occasionally, special circumstances permit a simple separation of the products which result from such free radical substitutions. Thus, *chlorocarbonylation* of adamantane followed by a methanolic work-up (Scheme 20) results in a nearly 1 : 1 ratio of 1- and 2-methyl adamantane carboxylates which may be separated readily by fractional distillation.

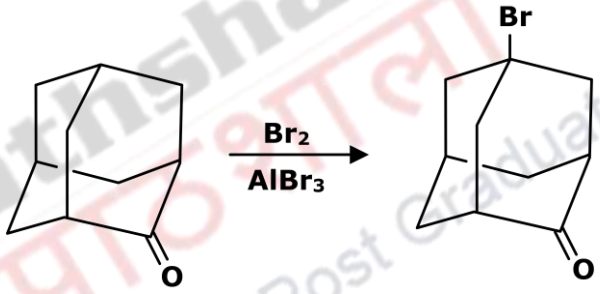


Scheme 20: Chlorocarbonylation of adamantane.

1,2-, 1,4-, 2,4- and 2,6-Disubstituted Adamantanes :

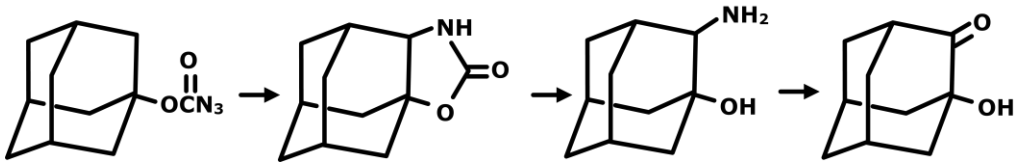
While the preparation of bridgehead (mono-, di-, etc.) and methylene substituted adamantanes is extremely easy, polysubstituted adamantanes in which one of the substituents is at a methylene position are much less readily prepared. In general, special techniques must be developed for each specific substitution pattern.

1,4 disubstituted derivatives can be easily prepared from the *2-Substituted* adamantanes, it provide convenient precursors for the preparation of 1,4-disubstituted derivatives. Deactivation of the adjacent bridgehead positions by the methylene substituent directs ionic substitution to the other bridgehead sites. Thus, treatment of adamantanone with bromine in the presence of $A1Br_3$ for 10 days gives 5-bromo-2-adamantanone in 90 % yield (Scheme 21).



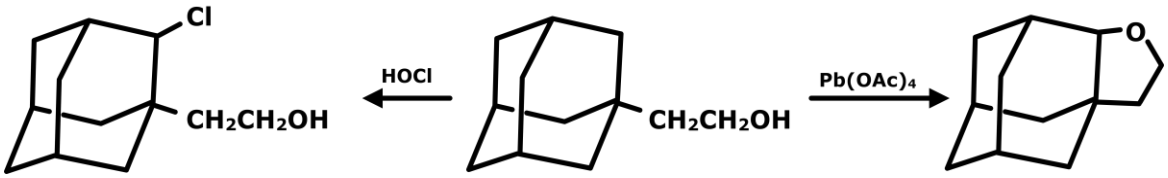
Scheme 21: Synthesis of 5-bromo-2-adamantanone

The internal cyclization reaction of a bridgehead substituent provide 1,2 disubstituted adamantanes. 1-hydroxy-2-adamantanone was synthesized by the photolysis of the azidoformate (Scheme 22) by followed internal cyclization and formation of nitrene intermediate.



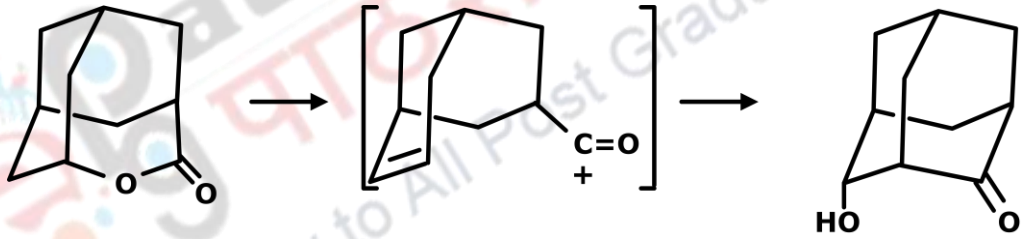
Scheme 22: Synthesis of 1-hydroxy-2-adamantanone.

Furthermore, same type of internal cyclization occurred during the reaction of 2-(1-adamantyl)-ethanol and lead tetraacetate or with the HOCl, it give 1,2 disubstituted adamantanone (Scheme 23).



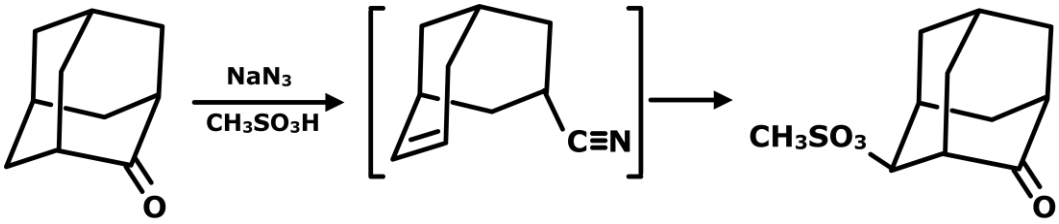
Scheme 23: Internal cyclization

2,4-disubstituted adamantanes prepared by the ring closure reaction of bicycle nonanes. Thus lactone rearrange in 50% sulfuric acid to 4-hydroxy-2-adamantanone via the acylium ion (Scheme 24).



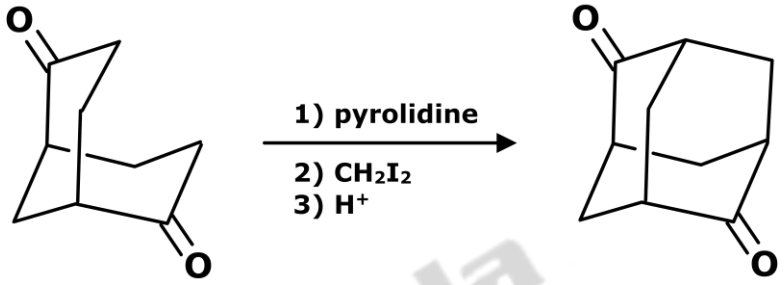
Scheme 24: Preparation of 4-hydroxy-2-adamantanone.

Similarly, the Schmidt reaction of adamantanone results in the overall formation of 4-methanesulfonyl-2-adamantanone presumably *via* the unsaturated nitrile (Scheme 25).



Scheme 25: Synthesis of 4-methanesulfonyl-2-adamantanone.

2,6-disubstituted adamantanes may be obtained from the direct synthesis or as minor components of specific ionic substitution reactions. Treatment of 2,6-bicyclo nonanedione with pyrolidine and methylene iodide followed by acid hydrolysis provides pure 2,6-adamantanedione (Scheme 26).



Scheme 26: Preparation of 2,6-adamantandione.

6. Application of Adamantane Derivatives in Pharmacology and Biochemistry

Applications of adamantane derivatives in the field of pharmacology have given added impetus to research in adamantane chemistry. Numerous derivatives have been shown to have *antiviral activity*.

The 1-adamantanamine-HCl salt useful for inhibits specific strains or influenza A, A1, A2 and C in tissue culture, chick embryos, and mice, the range of effectiveness of this drug has been considerably extended and similar antiviral activity has been found in man.

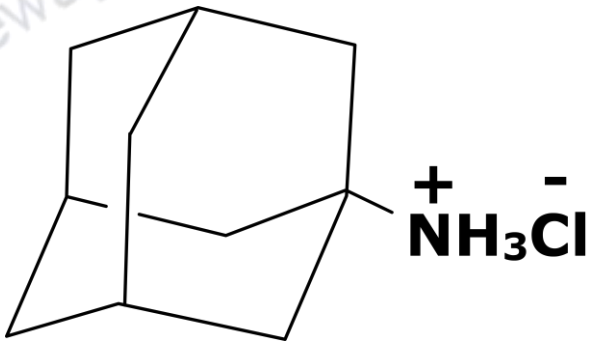


Figure 4: 1-adamantanamine-HCl salt.

The structure activity relationship also demonstrated by an alternative experiment. Since the *sedative property* of a drug requires that the drug be transported directly to the nervous system, a

decrease in hydrophobic bonding should result in an increase in sedative activity. The successive introduction of methyl groups to adamantane carboxamide (Figure 5) increase the sedative activity of the drug in mice.

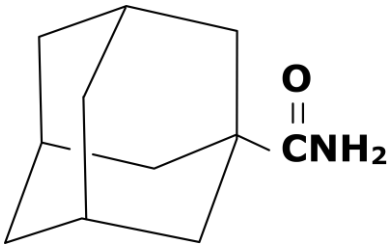


Figure 5: Adamantane carboxamide.

The adamantly substituted naphthoquinones (Figure 6) is found less effective antimalarials than the corresponding cyclohexyl substituted compound.

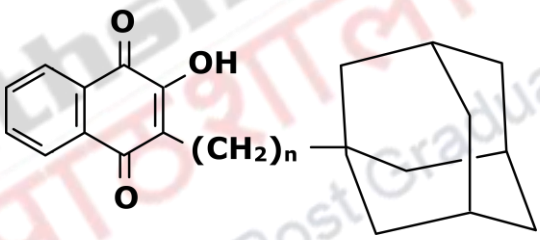


Figure 6: Adamantyl substituted naphthoduinone.

Similarly, the adamantly esters of pyridoxyl (Figure 7) are found to be comparatively weak growth inhibitors.

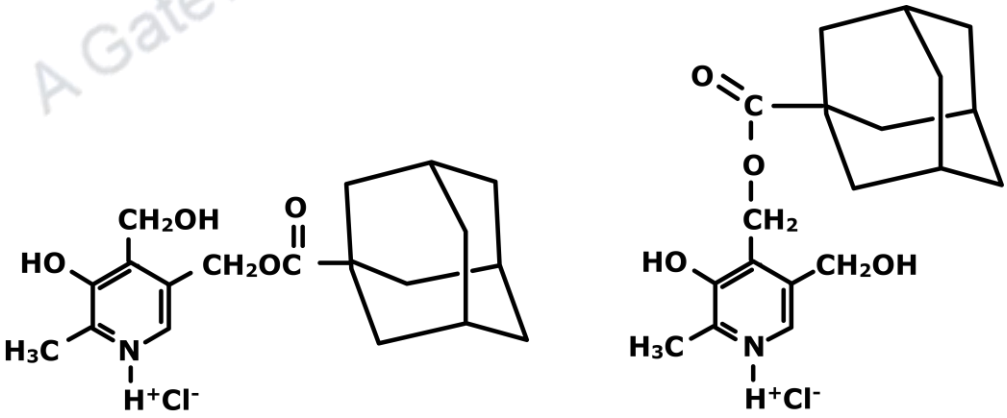


Figure 7: Adamantyl ester of pyridoxyl.

The 1-adamantyl chloroformate and 1-adamantoyl chloride (Figure 7) is useful blocking agents in biochemical syntheses.

Figure 8: 1-adamantyl chloroformate and 1-adamantoyl chloride

7. Summary

1. The chemistry of adamantane and related "cage-like" hydrocarbons has developed rapidly in recent years.
2. The chemistry of such systems is typically hydrocarbon in nature.
3. The particular utility of “cage-like” substrates in a variety of chemical investigations arises.
4. Adamantane and their derivatives widely used in various biological activity.