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Contents

Recent Developments in the Chemistry of Adamantane and Related Polycyclic Hydrocarbons

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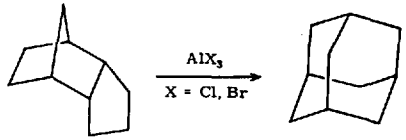
I. Introduction

Even before its discovery in petroleum in 1933 [1], adamantane *(1)* was especially intriguing to organic chemists because of its high symmetry (tetrahedral, point group *Td*) and because of its relationship to the structure of the diamond. Since first becoming readily available in 1956 through the chance observation that tetrahydrodicyclopentadiene *(2)* rearranges to adamantane *(1)* in the presence of aluminum halide catalysts,[2, 3] the development of the chemistry of diamonoid molecules has been both rapid and rewarding.



(1)

2 *1*

An earlier review [4] from this laboratory has summarized the initial, "collective" phase of this development. As a sequel, we propose not only to review the recent synthetic developments but also to emphasize the many applications of diamonoid substrates for testing various theories of physical-organic chemistry [5].

II. The Preparation of Diamonoid Substrates by the Rearrangement of Polycyclic Hydrocarbons

A. Lewis Acid Catalyzed Rearrangements

1. General Aspects

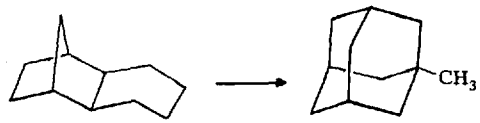
The most useful and general approach for the preparation of diamonoid molecules arises from Lewis acid catalyzed rearrangements of polycyclic hydrocarbons. The ubiquitiy of these rearrangements coupled with the availability of several highly selective direct substition reactions which may be subsequently applied to the rearranged hydrocarbons (see Section V.A. 1,2), makes a wide variety of diamonoid substrates readily available. The need for direct, multistep syntheses arises only when special substitution patterns not available *via* the substitution approach are required (see Section V.A. 3).

Although *Lewis acids* have long been known to produce extensive rearrangements in saturated hydrocarbons,[7] few examples of the successful synthesis of more complex molecules by such rearrangement routes may be found in the older literature [2, 3, 4]. This is due to the fact that such reactions, proceeding by ionic chain mechanisms, ordinarliy give complex mixtures of products governed by the relative thermodynamic stabilities of the individual components [8]. Moreover, under the more strenuous conditions, not only isomerizations but also degradations and other side reactions take place.

The exceptional success of these rearrangements for the preparation of diamonoid systems arises as the result of two unique properties of the molecules themselves. First, although a large number of by-products are formed in the adamantane rearrangement *(2 → 1)*, for example, pure adamantane is *easily isolated* from this mixture even though it is present as a minor component because of its high melting point (269 °C, the highest ever recorded for a saturated hydrocarbon) and its high crystallinity. In fact, the ease with which the adamantane in the reaction mixture will form a beautifully crystalline inclusion complex with thiourea [9, 10] has recently led to the suggestion [11] that the preparation of adamantane is suitable for use as an introductory organic chemistry experiment. Second, the fact that the diamonoid hydrocarbons are always the *most stable hydrocarbons* of comparable composition known requires that the thermodynamic control which governs these rearrangements must produce an equilibrium mixture which, in the absence of degrada-

tions and other side reactions, lies strongly in favor of the diamonoid structures.

This second factor is responsible for the extreme generality with which polycyclic hydrocarbons rearrange to diamonoid compounds. Thus, although all early examples of such rearrangements involved fairly strained starting materials[4, 12] (*eg.* Eq. (1–3) *cf.* Ref.[4, 12]), Schneider and coworkers[13–15]



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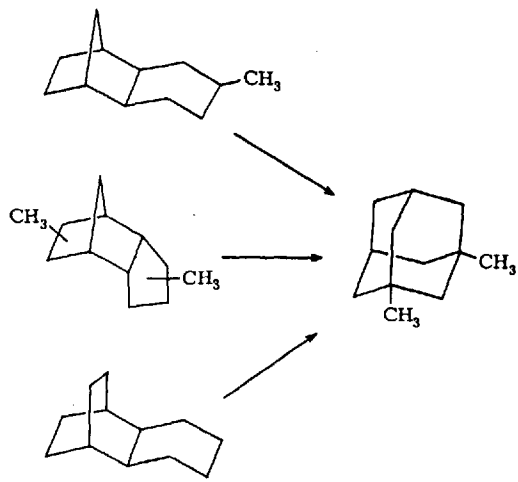
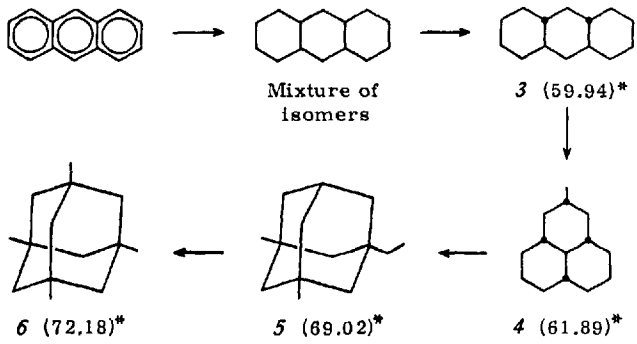


(3)

have clearly shown that the thermodynamic driving force alone is sufficient to cause even those polycyclic hydrocarbons classically considered to be strain free to rearrange to diamonoid compounds in excellent yields. This is most dramatically illustrated by the rearrangement of the *perhydroanthracenes* obtained from the hydrogenation of the aromatic hydrocarbon as illustrated in Scheme 1. Although *trans-syn-trans*-perhydroanthracene may adopt an energetically "ideal" chair-chair-chair conformation, 3,

Scheme 1

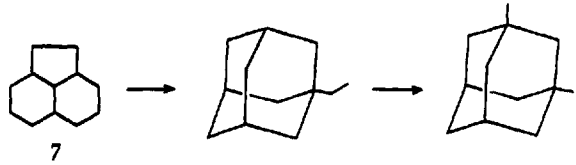


*Estimated $-\Delta H_f^\circ$ (g) in kcal/mole (see text)

the increase in chain branching experienced in each successive step in the rearrangement provides the driving force for the final formation of 1, 3, 5, 7-tetramethyladamantane *(6)*. The estimated heats of formation of *3–6* included in Scheme 1 based on the best available gas phase group increments for cyclic hydrocarbons [142] illustrate this point: $-\Delta H_f^\circ$(g) = 59.94 kcal/mole for *3* while the corresponding value for *6* is 72.18 kcal/mole. Choosing the proper conditions, any of the intermediates (*3, 4,* or *6*) could be isolated as these thermodynamic considerations would predict [13, 14].

Analogous results are also obtained with the hydrogenated forms of *acenapthene (7), fluorene (8)* and *phenanthrene (9)* as shown in Eq. (4–6) [13-15]. In each case (Scheme 1 and Eq. (4–6)) significant amounts of non bridgehead alkyladamantanes were obtained as the first formed adamantanes [14, 15]. Further rearrangement led to the build-up of the indicated intermediates. In all cases, the first all bridgehead adamantane intermediate contained a 1-ethyl group [14, 15].

As would be expected, the rearrangements of these perhydroaromatics are considerably slower than those of the more strained alkyl-substituted adamantane precursors [15]. In general, the success of these rearrangements



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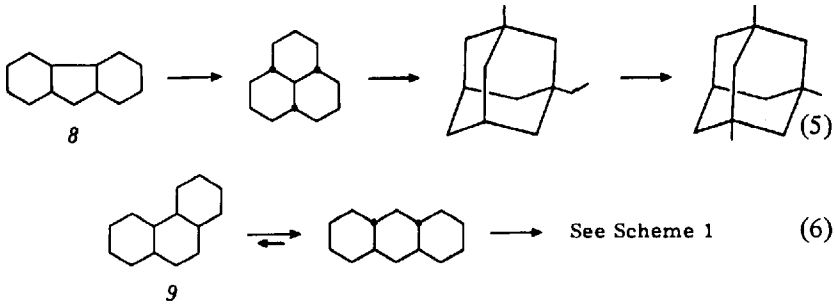


(6)

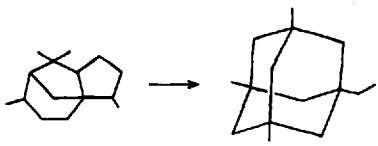
depends to some extent on the *nature of the catalyst* used. It is known that aluminum halide catalyzed rearrangements of hydrocarbons require the presence of an initiator [16]. Thus, rigorously purified substrates will not rearrange in the presence of aluminum bromide and hydrogen bromide alone [16]. Trace impurities such as olefins or alkyl halides must be present to act as initiators for these reactions [17]. The ideal catalyst, then would be one that had a built-in initiator which at the same time would not be prone to rapid deactivation through termination reactions such as polymerization.

Schneider and coworkers [14, 18, 19] appear to have been the first to utilize the enhanced efficacy of such complex catalysts in connection with their rearrangements of the perhydroaromatics discussed above. Their catalyst was a product of the cleavage of branched low molecular weight paraffin hydrocarbons by anhydrous aluminum halides in an atmosphere of the corresponding hydrogen halide. Williams [20] developed a similar, easier to prepare catalyst by treating either *sec*-butyl bromide or *t*-butyl bromide with aluminum bromide in cyclohexane at room temperature using a 2 : 1 ratio of aluminum bromide to alkyl bromide. In general, both catalysts significantly enhance the yields of diamonoid compounds obtained in these rearrangement reactions. For example, adamantane has been prepared in yields of 30 [21] to 66 % [22] using such techniques.

In addition to the prolonged lifetime of the complex catalysts, such enhanced yields are also made possible by improved catalyst-hydrocarbon contact. Aluminium chloride is insoluble in hydrocarbons: catalysis occurs in this case by surface contact with the solid. While the complex catalysts are also insoluble in hydrocarbons, they are liquids; the ease of mixing is therefore greatly facilitated.

Once the thermodynamic equilibria are achieved in these rearrangements the adamantanoid product compositions can be readily predicted. Methyl groups are more stable at the l-position than at the 2-position since the degree of chain branching is greater in the former and the latter suffer from *axial*-cyclohexane interactions [14, 23]. Other alkyl groups are less stable than methyl for similar reasons. Hence, alkyl groups rearrange to methyls provided bridgehead positions are available [14, 15, 24] as in the conversion of the 1-ethyl to 1,3-dimethyl groups

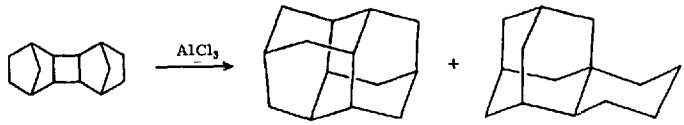
in Scheme 1 and Eq. (4–6) above. When bridgehead positions are not available, bridgehead attachment takes presidence over the formation of methyl groups. Thus, dihydrocedrene *(10)*, a readily available C_{15} hydrocarbon, rearranges in 93 % yield to 1-ethyl-3,5,7-trimethyladamantane *(11)* [25]. C_{16} tricyclics, on the other hand, have a marked tendency to fragment by loss of three carbons [26], 1,3,5-trimethyladamantane is the main product.



10 *11*

Perhaps the most startling demonstration of the significance of the *thermodynamic stability of bridgehead substituted adamantanes* is provided by the observation that a wide variety of diverse starting materials, including cholesterol, Nujol (refined petroleum oil) and squallene, rearrange to a variety of alkyladamantanes in small to moderate yields *via* an aluminium halide catalyzed cracking process [27]. These results are summarized in Table 1. Thus we see that although the rearrangement of tricyclic hydrocarbons containing 10 or more carbons is preferred for the preparation of specific adamantoid molecules, a wide variety of starting materials may, in fact, be employed including functionalized acyclic, monocyclic and polycyclic hydrocarbons [27].

Thermodynamic considerations lead one to except, then, that any number of adamantalogs (*i. e.* higher adamantanes) should also be readily prepared by rearrangement. Following the guiding principle that the most favorable synthetic materials are those that have the same molecular composition and number of rings as the desired product, both *diamantane (12)*, formerly called "Congressane", [28] and *triamantane (13)* have been prepared. Thus, the *exo-trans-endo* pentacyclic photodimer of norbornene, *14*, rearranges to diamantane *(12)* in ~ 1% yield when treated with $AlCl_3$ [29]. The assigned structure is confirmed by X-ray crystallography [30].



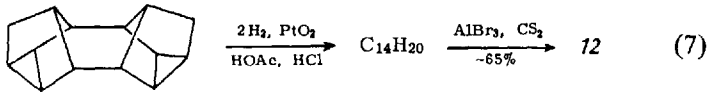
14 *12* *12a*

Table 1. *Summary of various better alkyladamantane rearrangement runs* [27] (Reproduced from Ref. 27).

Reactant	Wt, g	Solvent, g	Catalyst	Wt, g	Time hr	Temp, °C ± 10°	Wt dist product [a]	Product analysis [b]							
								Me	Me_2	Me_3	Me_4	MeEt	Me_2Et	Me_3Et	Other
Cholesterol	10	CH[g])	$AlBr_3$[c])	80	75	130	4.5	1	16	26	35	Tr	3	12	7
Cholesterol	10	None	$AlBr_3$[c])	80	47	130	0.8	3	18	25	43		1	3	7
Cholesterol	11	CS_2, 22	$AlBr_3$[c])	90	75	120	1.1	1	7	21	52	Tr	2	7	10
Cholesterol	10	None	$AlBr_3$[c])	50	70	120	1.0	2	15	30	35	Tr	2	6	10
Nujol	10	None	$AlBr_3$[c])	50	90	130	1.1	1	12[d])	28[d])	33[d])		4	14	8
Nujol	20	None	$AlCl_3$	50	170	145	0.9	2	10	16	13	4	13	20	22
Cedrene	15.5	None	$AlBr_3$[c])	62	64	120	5.2	2	24	11	12		2	43	6
Cedrene	31	None	$AlCl_3$[c])	90	66	120	13.6	1	7	4	3		3	76[e])	6
Abietic acid	10	CS_2, 20	$AlBr_3$[c])	80	75	120	0.2	Tr	7	19	64		12	5	3
Camphene	10	None	$AlBr_3$[c])	10	53	110	0.9			M[f])	M[f])				
Cyclohexane	10	None	$AlBr_3$[c])	41	69	110	1.9				M[f])				
Cyclohexene	11	CH[g]), 10	$AlCl_3$	20	70	110	3.0				M[f])				
Caryophyllene	11	None	$AlBr_3$[c])	41	86	110	1.4				M[f])				
Squallene	15	None	$AlCl_3$[c])	107	90	120	0.8			M[f])	M[f])				

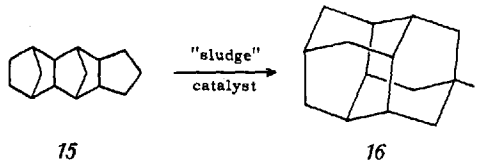
a) Boiling point range generally 75–110° (10 mm).
b) With 300 ft Golay DC-200 column. The alkyl groups are all at bridgehead positions.
c) Sludge catalyst.
d) Compounds isolated by preparative glc and identified by nmr and mass spectroscopy.
e) Compound isolated by fractional distillation and identified by nmr.
f) Main products.
g) CH = cyclohexane

While use of the William's sludge catalyst, discussed above, and the *exo-trans-exo* isomer of *14* dramatically improves the isolable yield of diamantane (from 1 to ~10 %), [20,31] the preparative utility of this reaction is limited. This problem is overcome using a different precursor. Hydrogenation of the "Binor-S" dimer of norbornadiene followed by rearrangement (Eq. (7)) gives diamantane in an average overall yield of 65 % [31].

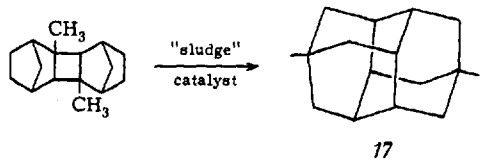


(7)

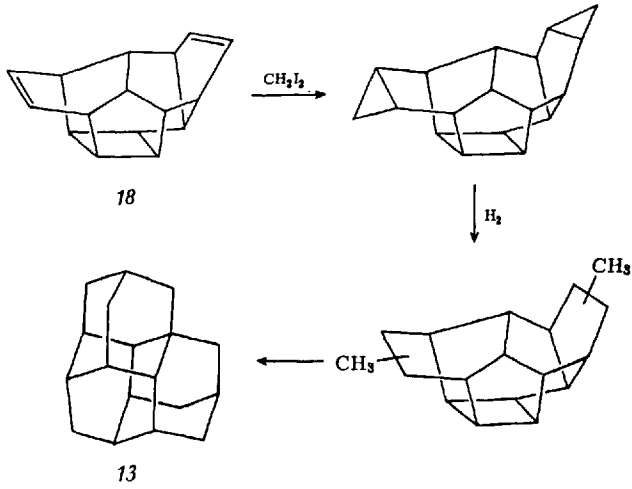
Similar rearrangement routes lead to alkylated *diamantanes.* The C_{15} pentacyclic hydrocarbon, *15*, rearranges to 4-methyldiamantane *(16)* [26] while the corresponding 4,9-dimethyl compound, *17*, is obtained as illustrated in Eq. (8) [32, 265].



(8)

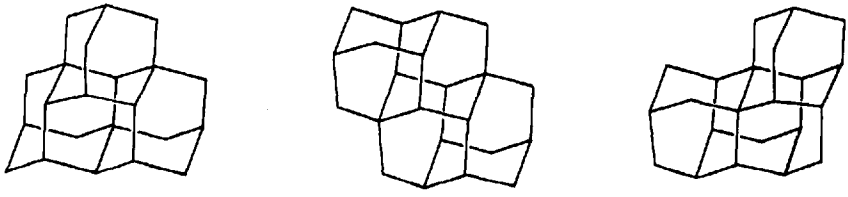


Triamantane (13) is obtained from the rearrangement of the heptacyclic dimer of cyclooctatetraene *(18)*, after it has been elaborated to the C_{18} level by Simmons-Smith cyclopropanation and subsequent hydrogenolysis (Eq.(9)) [33]. The structure of the product, obtained in 5% yield, is again confirmed by an X-ray analysis [34].



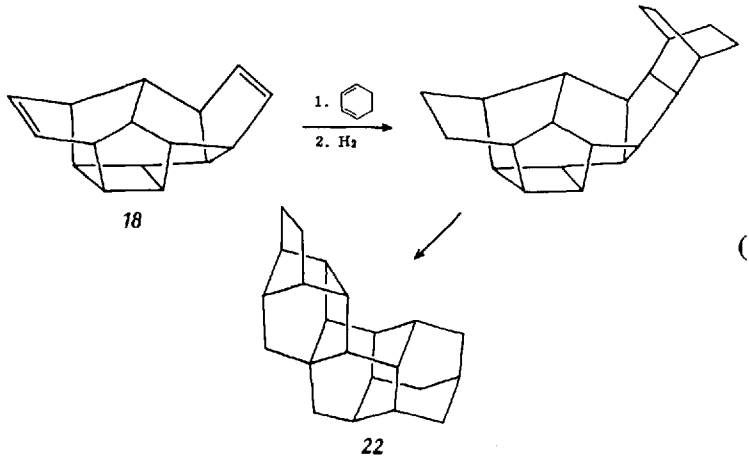
18 *13* (9)

Although the synthesis of even higher members of the adamantane to diamond series may be possible *via* similar approaches, the task will be further complicated by the possibility of isomers. Thus, there are three possible isomers of *tetramantane; iso*-tetramantane *(19), anti*-tetramantane *(20)* and *skew*-tetramantane *(21).* These three forms may be thought of as analogous to the three structural plus conformational isomers of butane just as adamantane, diamantane, and triamantane may be thought of as corresponding, respectively, to methane, ethane, and propane.



19 *20* *21*

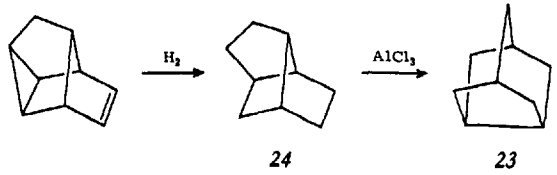
To date, attempts to prepare any of the *tetramantane isomers* have not been successful. In fact, one such attempt has provided the first example where thermodynamic control alone was not sufficient to give the desired product. Elaboration of the cyclooctatetraene dimer *(18)* to the desired C and H level followed by hydrogenation and rearrangement (Eq. 10)) gave *22* instead of one or more of the tetramantane isomers [35].



(10)

Although all three tetramantane isomers must be considerably more stable than *22*, the structure of which incorporates norbornane, noradamantane *(23)*, bicyclo [3.2.1] octane and diamantane units, prolonged treatment with the aluminum halide sludge catalyst results only in the destruction of *22* with no further rearrangement observed [35]. Apparently the failure to rearrange further is due to an energy barrier associated with the next step in the rearrangement which is much higher than those associated with degradative processes.

One other farily strained adamantoid molecule which has been found to be readily available *via* the rearrangement route is *noradamantane (23)*. Brexane *(24)*, a C_9 tricyclic hydrocarbon, rearranges smoothly in the presence of $AlCl_3$ to the lower adamantane homologue, *23*, in 75 % yield (Eq. (11)) [36]. This rearrangement, however, is consistent with thermodynamic principles. (See Section III. E and Scheme 8 for other preparations of this hydrocarbon).

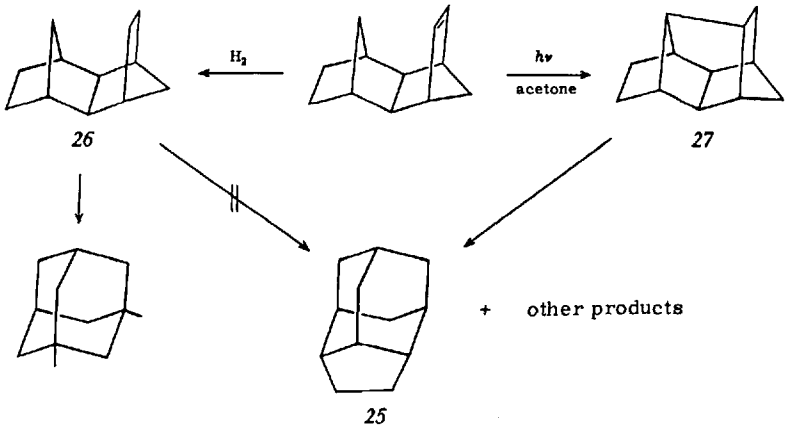


(11)

Finally, *2, 4-ethanoadamantane (25)*, recently found in petroleum [37], may also be prepared by rearrangement. In this case, however, the tetracyclic hydrocarbon, *26*, which had originally been expected to rearrange to *25*, gave only tricyclic alkyladamantanes *via* a ring opening disproportionation process [38]. This side reaction

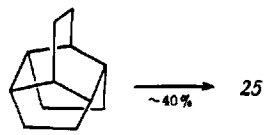
may be compensated for, however, by employing the pentacyclic dodecane, *27*, as starting material. Rearrangement of *27* gives ethanoadamantane *(25)* along with several, as yet unidentified products [38]. These results are summarized in Scheme 2.

Scheme 2

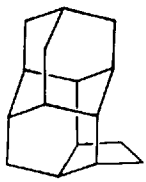


Such disproportionation reactions are often competing processes in the Lewis acid catalyzed rearrangements of polycyclic hydrocarbons. For example, the main product of the rearrangement of any isomer of *14* ($C_{14}H_{20}$) is a tetracyclic ($C_{14}H_{22}$) product, tentatively assigned structure *12a*, and not the pentacyclic diamantane [31]. In general, the tendancy toward disproportionation increases with the strain of the starting material.

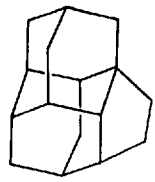
Recognition of this fact leads to significant improvements in the utility of rearrangement reactions for the preparation of diamonoid hydrocarbons. This is illustrated by the high yields of diamantane now obtainable as illustrated in Eq. (7) [31]. Similarly, in contrast to *26*, the tetracyclic dodecane, *28*, [38a] rearranges quite cleanly to ethanoadamantane *(25)* in 40% yield [38b].



Using the least strained starting material of proper atomic composition, a wide variety of additional diamonoid hydrocarbons should be potentially available. The successful preparation of at least one of the two possible



28 A



28 B

ethano-bridged diamantanes *(28A)* has already been reported [38c]. Other compounds, such as nordiamantane, bisnordiamantane and the higher adamantalogs (*e. g.* tetramantane), should be obtainable by similar rearrangement routes.

2. Mechanistic Considerations

The principle of the Lewis acid catalyzed rearrangements of hydrocarbons is well documented [4,8]. Lewis acids react with a promotor deliberately added or present as an impurity in the reaction mixture to form carbonium ions which initiate intermolecular hydride transfers involving the hydrocarbon. These hydride transfers appear to be fairly unselective processes. While the expected tertiary > secondary > primary selectivity order is observed, the differences are significantly reduced relative to typical carbonium ion reactions. Possibly this is due to a hydride transfer mechanism which involves a pentacoordinate carbon transition state in which charge development on carbon would be minimized [38d].

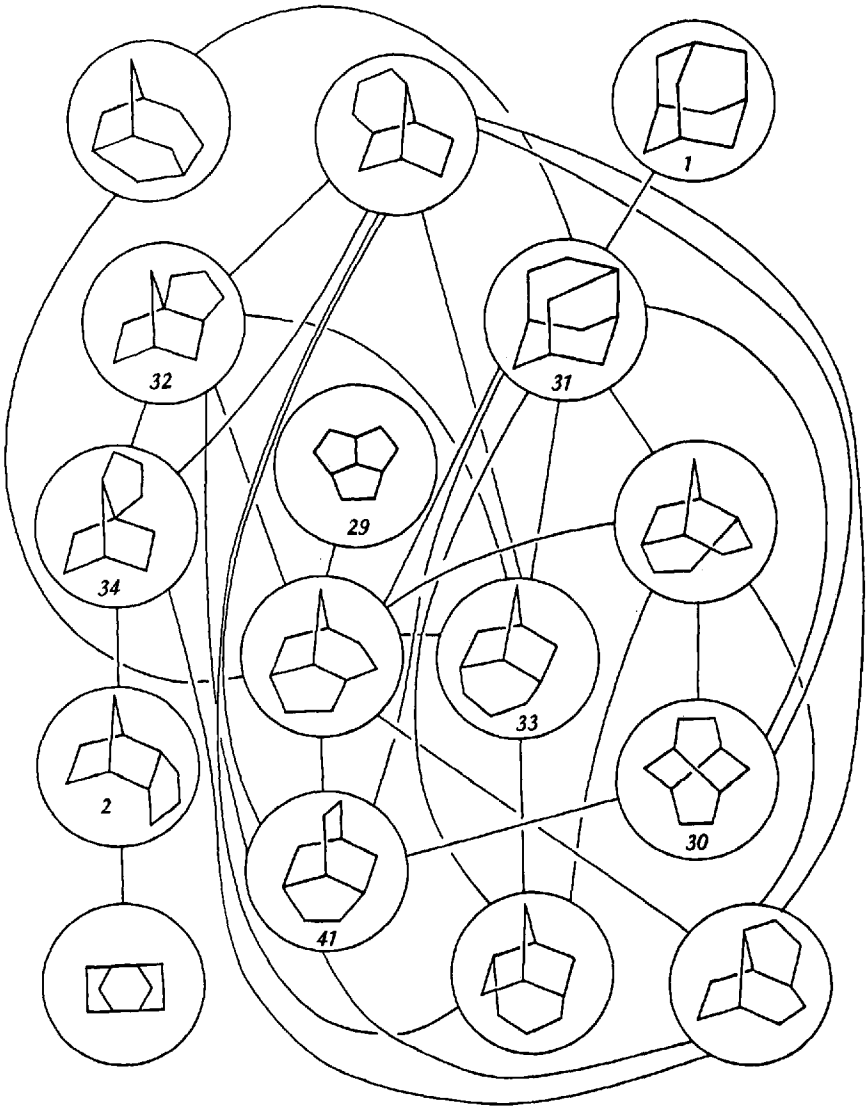
The *alkyl carbonium ions* which result from these reversible, relatively unselective hydride abstractions then undergo a series of 1,2- (Wagner-Meerwein) or 1,3- (protonated cyclopropane) rearrangements which eventually result in the formation of the thermodynamically most stable products. The number of different reaction sequences by which one may rationalize the formation of a given products is, of course, necessarily large. A variety of independent pathways are generally available for the interconversion of the isomers of a given species by successive alkyl shifts.

A *general mathematical treatment* has recently been developed which enables the construction of a graphical representation of such rearrangements[39]. This treatment has been applied to the rearrangement of tetrahydrodicyclopentadiene *(2)* to adamantane *(1)* [40]. Assuming that only 1,2-alkyl shifts are allowed and excluding steps which form either primary cations or unreasonably strained isomers, the intermediates which may be involved and the pathways by which they are interconverted are illustrated in Scheme 3 [40]. At least 2,897 independent pathways for the conversion of *2* to *1* are possible [40]. Clearly no single mechanism uniquely explains the rearrangement of tetrahydrodicyclopentadiene to adamantane. The availability of many rearrange-

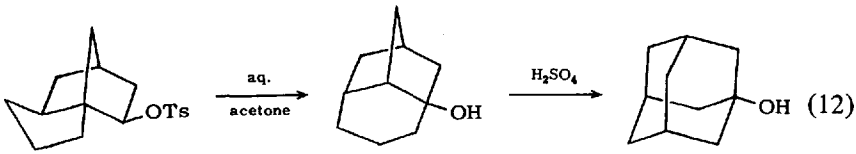
ment pathways illustrates why a wide variety of precursors should all give the same end product.

Several of the rearrangements in Scheme 3 have experimental precedents. Treatment of tricyclo [5.2.1.0 ^{4,10}] decane *(29)* [41], tricyclo [4.4.0.0 ^{3,8}] decane ("twistane") *(30)* [40], and tricyclo [4.3.1.0 ^{3,8}] decane ("protoadamantane") *(31)* [42] with aluminium chloride gives, in each case, high yields of adamantane.

Scheme 3 (after Ref. [40])



Less direct precedents are also available for the rearrangement of both *exo*-1,2-trimethylenenorbornane *(32)* and *endo*-2,6-trimethylenenorbornane *(33)* to adamantane. Solvolysis of *exo*-1,6-trimethylene-*exo*-2-norbornyl tosylate in aqueous acetone at room temperature gives nearly quantitative yields of *endo*-2,6-trimethylene-*exo*-2-norbornanol [Eq. (12)], which, when treated with sulfuric acid, produces 1-adamantanol [43].



(12)

The high yields and mild reaction conditions of each of these rearrangements to adamantane or 1-adamantanol constrast sharply with the low yields and relative severe reaction conditions required for the conversion of tetrahydrodicyclopentadiene *(2)* to adamantane *(1)* [4, 40-43]. Qualitatively, the ease of rearrangement to adamantane decreases in the following order: *31* [42] > *30* [40] > *29* [41] > *2*.

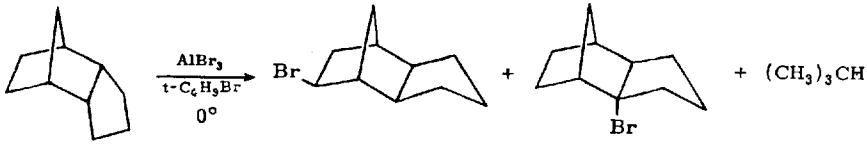
This observation has led to the speculation that the distance property of the graph represented in Scheme 3 has chemical significance. The minimum number of steps required for the rearrangement of *31, 30, 29* and 2 parallels the ease with which rearrangement occurs. In kinetic and thermodynamic terms, for this suggestion to be valid, the interconversion of all adjacent isomers must be reversible except for the final formation of adamantane, the rate constants for all interconversions must be nearly equal and the energies of all isomers must be nearly the same [40]. These assumptions must be regarded as being highly artifical.

Thermodynamic equilibria are independent of the route by which they are established (provided such routes are available). The rates with which such equilibria are achieved depend on the energies of the transition states involved. The strain energies of the intermediates in the adamantane rearrangement will be reflected in the transition states for their formation. If one step in the rearrangement involves the formation of an excessively strained intermediate not only will the overall rearrangement be retarded but also undesirable side reactions including fragmentation and catalyst deactivation, will be able to compete more effectively.

The most probable pathway for the conversion of *2* to adamantane based on the available precedents discussed earlier would appear to involve the following sequence: *2* → *34* → *32* → *33* → *31* → *1* [40].

Inspection of molecular models suggests that *34* may be the most strained intermediate in this sequence. Formation of *34* would, therefore, be the rate deter-

mining step. This suggestion is consistent with the observation that no intermediates can be detected in the rearrangement of *2* to *1* [3,44]. Even at 0 ° the necessary driving force for the *exo-endo* equilibrium of *2* and for the ionization required for the rearrangement to *34* is available as indicated by the formation of bromide *35* in Eq. (13). No further rearrangement is observed under these conditions, however.

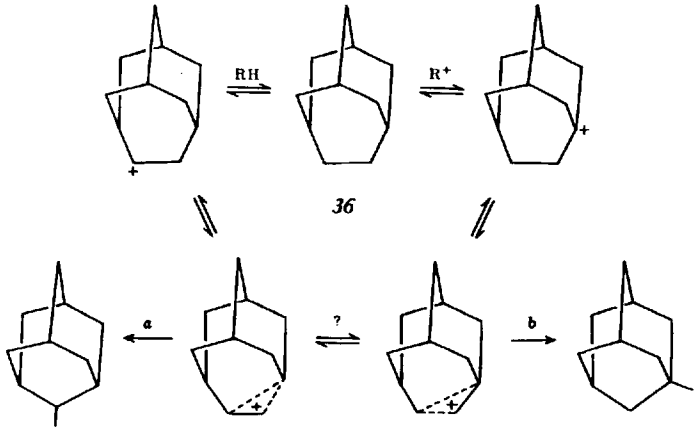


endo-*2* *35* (13)

Future determinations of the strain energies of the $C_{10}H_{16}$ isomers, illustrated in Scheme 3, as well as their corresponding cations (*e. g.* by calculation) [95] should help clarify the relative ease with which each of the isomers rearranges to adamantane. The true significance of the formal description of the adamantane rearrangement (Scheme 3) [40] lies, for the moment, in the fact that a rational framework for the discussion of the mechanism of the reaction is established.

Additional mechanistic problems are encountered upon extension of the discussion to the rearrangements of *larger tricyclic alkanes* such as the perhydroaromatics discussed earlier (Scheme 1 and Eq. (4–6)) [13-15] and the rearrangement of homoadamantane to 1-methyladamantane (Scheme 4) [23]. As illustrated in Scheme 4, the first formed alkyl adamantanes in all of these re-

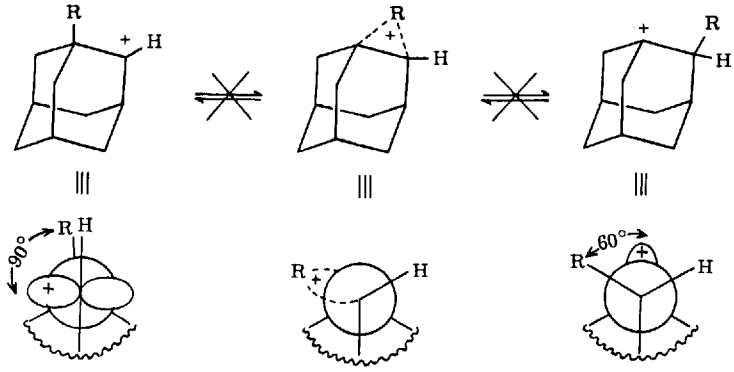
Scheme 4



arrangements include significant amounts of nonbridgehead isomers [13–15, 23]. Although the rearrangement of 2-methyladamantane to 1-methyladamantane is a facile process, labeling experiments have shown steps *a* and *b* in Scheme 4 to be essentially irreversible [46, 47] while direct 1,2-alkyl shifts do not occur on the adamantyl nucleus.

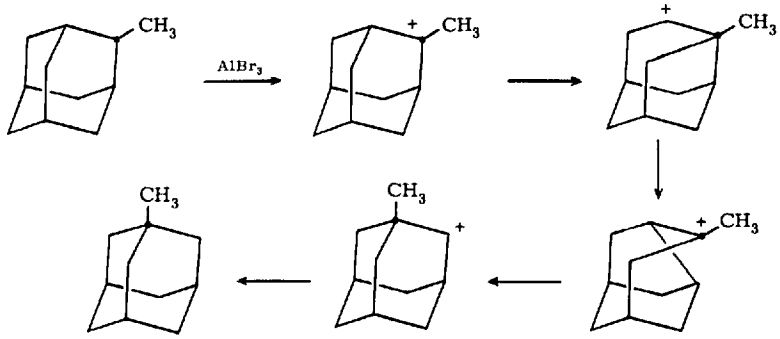
Direct 1,2-alkyl shifts would involve badly distorted transition states since the relationship between the vacant orbitals and the migrating groups is very unfavorable (Fig. 1). This situation is circumvented

Fig. 1



by means of a skeletal rearrangement similar to that illustrated in Scheme 5 for the rearrangement of 2-methyladamantane to the corresponding bridgehead isomer [47]. As would be predicted on the basis of this scheme, labeling

Scheme 5



experiments have shown that the alkyl group remains attached to the same ring carbon throughout the rearrangement (see Scheme 5) [47].

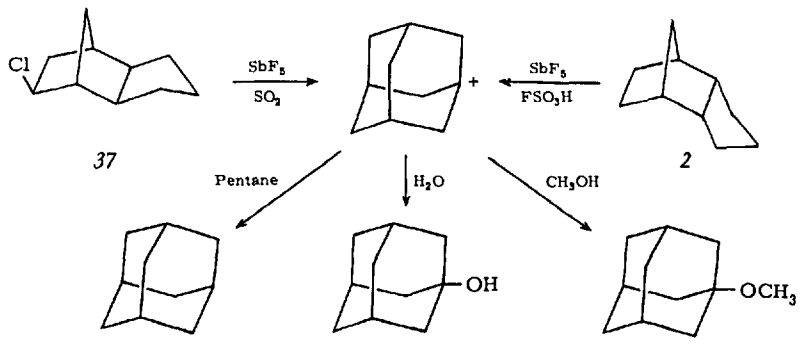
Vigorous conditions have been found to cause similar skeletal rearrangements *in adamantane itself.* Thus, treatment of adamantane-2-^{14}C[48] with aluminum bromide in carbon disulfide at 110° C for 8 hours gives rise to nearly 80 % net scrambling of the tertiary and secondary carbons[49]. The mechanism for this degenerate isomerization possibly is similar to that depicted in Scheme 5.

B. Rearrangements in Highly Acidic Media

Several rearrangements of tricyclic systems analogous to those catalyzed by Lewis acids have also been observed, as might be expected, in more highly acidic media such as SbF_5-SO_2 and SbF_5-FSO_3H-SO_2 mixtures. In contrast to the Lewis acid catalyzed rearrangements, carbonium ion formation in these media is generally considered to be irreversible[50]. The ions, once formed, are stable. The mechanistic pathways available for these rearrangements may, therefore, be greatly reduced.

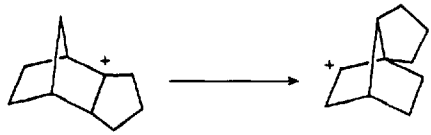
Treatment of either *exo*-2-chloro-*exo*-5,6-trimethylenenorbornane *(37)* in SbF_5-SO_2[50] or *endo*-2,3-trimethylenenorbornane *(2)* itself in SbF_5-FSO_3H[51] results in high yields of the 1-adamantyl cation which may be quenched with pentane, water or methanol to give adamantane, 1-adamantanol or 1-methoxyadamantane, respectively (Scheme 6). No 1-adamantyl products are obtained under the same conditions at low temperature, however. Instead, only 2,3-

Scheme 6



trimethylene-2-norbornyl products of undetermined stereochemistry are observed[50]. This behavior is similar to that observed under Lewis acid conditions[44] (*cf.* also the Koch carboxylation of *exo*-5,6-trimethylene-*exo*-2-

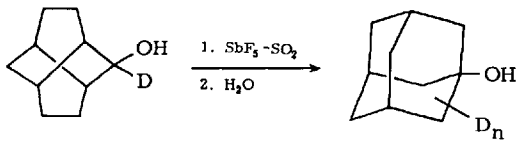
norbornanol [52] and again suggests that the Wagner-Meerwein rearrangement depicted in Eq. (14) is the rate determining step of the overall rearrangement.



(14)

Reversible, random carbonium ion formation is not required to explain the rearrangements of both *2* and *37* to adamantane in the highly acidic media. Sequential 1,2 alkyl shifts coupled with the well documented [53] 6,2- and 3,2-hydride shifts of the norbornyl system permit a rearrangement pathway analogous to that discussed earlier as the most likely route for the Lewis acid catalyzed rearrangement of *2* to adamantane.

The rearrangements of several *twistane derivatives* to adamantyl cations under the same conditions, on the other hand, appear to involve reversible, random carbonium ion formation, at least to a limited extent. Rearrangement of 2-twistanol-2-d *(38)* occurs with considerable intermolecular hydrogen scrambling (Eq. (15)) [40]. Similar intermolecular rearrangements are observed when a 50 : 50 mixture of 1-adamantanol and 1-adamantanol-3,5,7-d_3 in SO_2 is treated with SbF_5 [40].

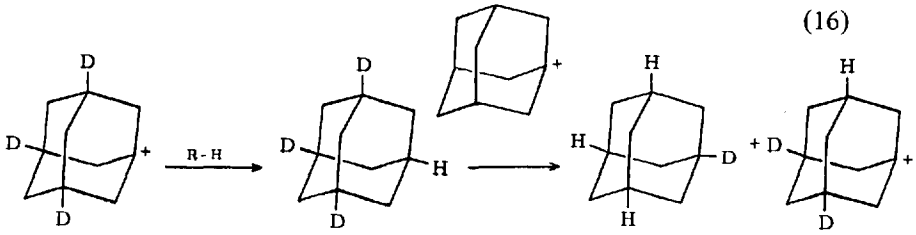


38 (15)

$n = 0-3$

The precise mechanism of these intermolecular reactions is not known. Transient disproportionation processes, although well documented in less acidic media (see below and Section V.A.1), seem unlikely if alkyl cations alone are involved. Two possible explanations for the observed results may be considered. Small amounts of polymeric impurities may be present in the reaction mixture which could serve as a hydride source, catalyzing the intermolecular reaction as indicated in Eq. (16) [40]. Alternatively, the intermolecular reactions may result from inefficient mixing during reaction initiation. In this case, unionized alcohols would serve as the hydride source. This latter alternative is consistent with the observation [40] that the deuterium in the 1-adamantanol obtained from the rearrangement of *38* is distributed between bridgehead and methylene positions. Unless more than one re-

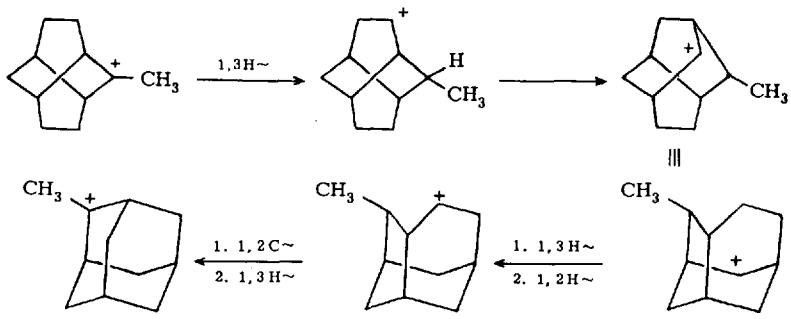
(16)



arrangement pathway is available, some of the intermolecular transfers observed must have preceeded rearrangement.

2-Methyl-2-twistanol rearranges to the 2-methyl-2-adamantyl cation in SbF_5/SO_2 solutions [40]. The mechanism of this rearrangement can be most readily depicted in terms of 1,3-hydride shifts (protonated cyclopropanes) as illustrated in Scheme 7. Control experiments have shown that the 3-methyl-1-adamantyl cation is not involved in the rearrangement. It is stable to the rearrangement conditions despite the fact that relative solvolytic reactivities suggest that the 2-methyl-2-adamantyl cation is more stable by nearly 6 kcal/mole [55, 56].

Scheme 7



The failure of the 3-methyl-1-adamantyl cation to rearrange to its thermodynamically more stable isomer in strong acid media is atypical. Cations generated in strong acid media generally rearrange rapidly to their most stable form. In the present case, rearrangement is apparently prohibited (strongly retarded) by an energy barrier which is inaccessably high under normal conditions.

This energy barrier may be associated with the inhibition of 1,2-shifts on the adamantane nucleus [57]. As discussed earlier, 1,2 shifts on the adamantyl nucleus are unfavorable due to the near orthogonal relationship between a vacant orbital and the migrating group (see Fig. 1). No evidence of 1,2-hydride

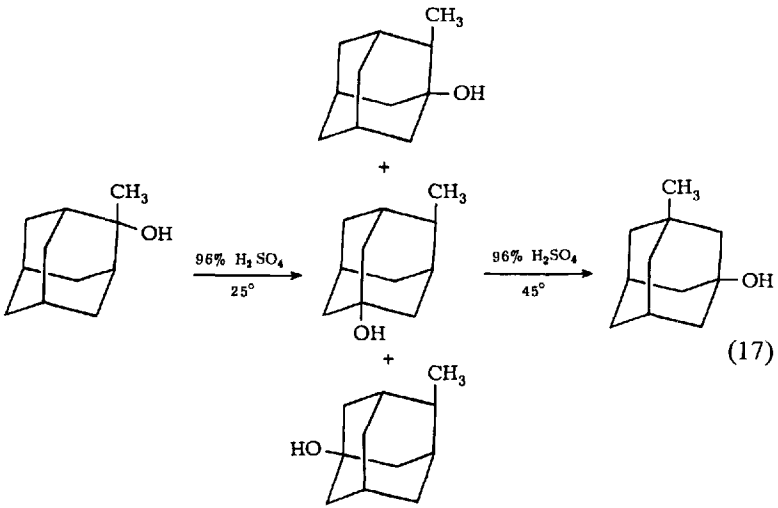
shifts even at high temperatures is indicated by the nmr spectra of the 1-adamantyl cation [50, 51, 58-60].

The *2-adamantyl cation* on the other hand, does rapidly rearrange to its tertiary isomer in strong acid media [39, 61]. The energy barrier for this rearrangement should be decreased by at least 5 kcal/mole relative to the reverse process based on the relative solvolytic reactivities of the corresponding bromides in 80 % ethanol at 25° C [55, 62]. Long reaction times at high temperatures may be sufficient to allow experimental observation of the rearrangement of 3-methyl-1-adamantyl cation to the 2-methyl-2-adamantyl isomer.

Of course, the intramolecular nature of the rearrangement of the 2-adamantyl cation to its tertiary isomer has not been established. Intermolecular processes similar to those discussed above in connection with the 1-adamantyl cation may be involved, and, in fact, seem likely [60].

Rearrangements of tricyclic systems in concentrated sulfuric acid are often unlike those observed in SbF_5-SO_2 solutions. Not only do intermolecular hydride shifts occur readily with ordinary substrate concentrations, but also the stabilities of the product *alcohols* control product distributions in sulfuric acid, whereas the stabilities of the *carbonium ions* are the controlling factors in SbF_5-SO_2 solution.

Thus, in contrast with the results in SbF_5-SO_2, *2-methyl-2-adamantanol* undergoes extensive rearrangement in concentrated sulfuric acid [63, 64]. The results are summarized in Eq. (17). Similar rearrangements are observed [57, 65] during Koch-Haaf carboxylation reactions carried out in sulfuric acid [66]. The intermolecular nature of these reactions is indicated by the fact that high dilution conditions suppress the rearrangements [57].

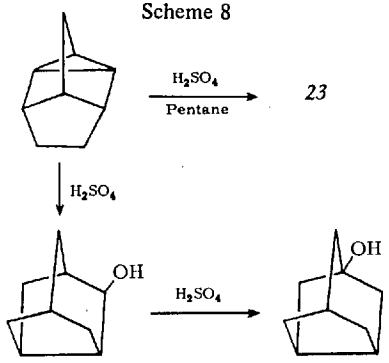


(17) [64]

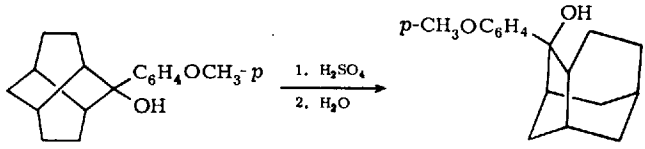
Similar results are obtained with 2-adamantanol which rearranges to 1-adamantanol (> 98 %) at 28°C in sulfuric acid. An equilibrium mixture containing small amounts of 2-adamantanol is rapidly achieved from either direction [67, 68]. This isomerization is one of the mechanistic bases for the preparation of adamantanone by the reaction of adamantane with sulfuric acid at 77°C (see Section V.A.1) [57, 67, 69]. The Koch-Haaf carboxylation of 2-adamantanol similarly results in predominant 1-adamantyl carboxylic acid formation unless highly dilute reaction conditions are employed [57, 70].

Synthetically useful skeletal rearrangements in concentrated sulfuric acid are also occasionally encountered. For example, treatment of *tetracyclo [4.3.0.0 ^{2,3}.0 ^{3,7}] nonane* (deltacyclane) with sulfuric acid in the presence of pentane (which serves as a hydride donor) results in good yields of noradamantane *(23)* [72]. In the absence of pentane, 2-noradamantanol is obtained [73] which, on longer reaction times, subsequently rearranges (presumably intermolecularly) to 1-noradamantanol [72]. These reactions are summarized in Scheme 8.

Scheme 8



Treatment of *2-anisyl-2-twistanol* with sulfuric acid (Eq. (18)) results in the formation of a protoadamantyl derivative [40] (see also Section III.A.1). The mechanism of this rearrangement may be similar to that depicted in Scheme 7



(18)

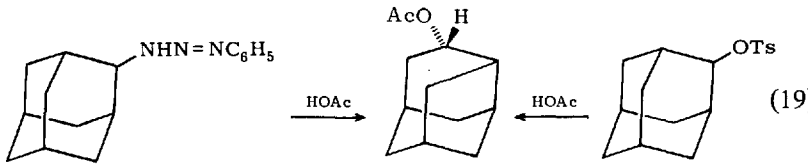
for the rearrangement of the corresponding methyl compound. In this case, however, the product distribution is apparently controlled by the stability of the resulting benzylic cation.

III. Synthesis and Chemistry of Polycyclic Hydrocarbons Related to Adamantane

A. Protoadamantanes

1. Rearrangement of the Adamantane Nucleus

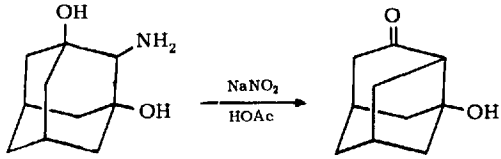
Despite the high stability of the adamantyl nucleus, several reactions of substituted adamantanes have been found to give skeletally isomerized tricyclo-[4.3.1.0 ^{3,8}] decyl (protoadamantyl) products. The most extensively studied reactions to date are those arising from the 2-adamantyl cation. Acid catalyzed deamination of 2-adamantyl phenyltriazene gives a 7.5 % yield of *exo*-4-protoadamantyl acetate (Eq. (19)) [74]. Acetolysis of 2-adamantyl tosylate gives rise to a 0.5 % yield of the same acetate. In both cases, the major product is the unrearranged 2-adamantyl acetate. 4-Protoadamantyl acetate may be converted



(19)

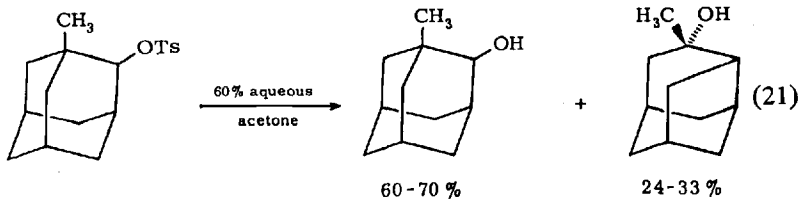
via the alcohol to 4-protoadamantanone which gives protoadamantane upon Wolf-Kishner reduction [74].

The carbonium ion rearrangements become much more synthetically useful when cation stabilizing substituents are present. Nitrous acid deamination of 2-aminoadamantan-1-ol [75] gives 4-protoadamantanone in 92 % yield [76]. Similarly, deamination of 2-aminoadamantane-1,3-diol [77] gives 8-hydroxy-4-protoadamantanone in 56 % yield (Eq. (20)) [78]. Hydrolysis of 1-methyl-2-



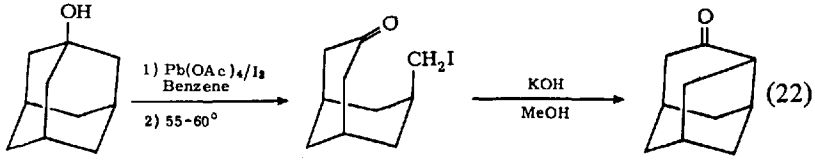
(20)

adamantyl tosylates [76] gives 4-methyl-*exo*-4-protoadamantanol in approximately 30 % yield (Eq. (21)) [76].



(21)

The difficulty associated with the preparation of the starting materials for these carbonium ion reactions decreases their general utility for the preparation of protoadamantyl derivatives. A recently reported isomerization of the 1-adamantyloxy radical conveniently overcomes this problem. Thermolysis of 1-adamantanol hypoiodite, prepared *in situ* in dry benzene, gives *endo*-3-iodomethylbicyclo [3.3.1] nonane-7-one, which, when treated with base, gives 4-protoadamantanone (Eq. (22)) in an overall yield from 1-adamantanol of approximately 30 % [79, 79a].



(22)

Lithium aluminum hydride reduction of 4-protoadamantanone gives a 2 : 1 mixture of *endo*-4-protoadamantanol and its *exo*-4-isomer [76, 78, 79]. This stereochemical assignment is consistent with the relative solvolytic reactivities of derivatives of these alcohols. *Exo*-4-protoadamantyl 3,5-dinitrobenzoate solvolyses approximately 10^4 times faster than the corresponding *endo* isomer [76].

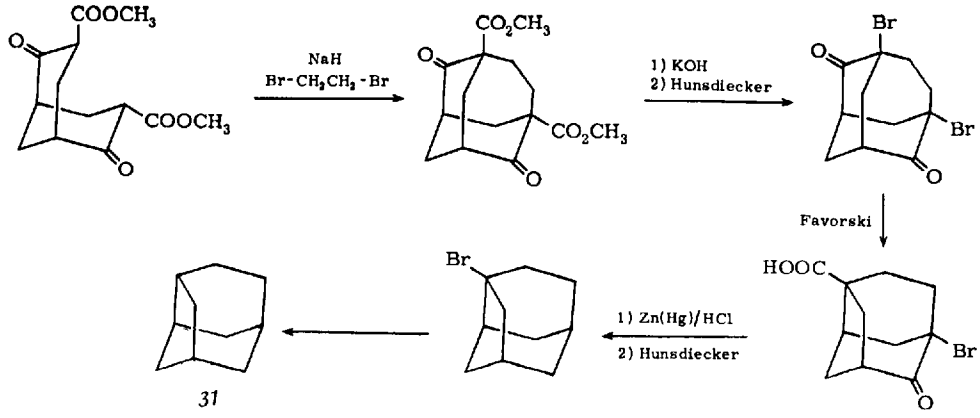
Addition of methyl Grignard to 4-protoadamantanone gives a 2 : 1 mixture of 4-methyl-*exo*-4-protoadamantanol and the corresponding *endo*-epimer [76]. This mixture rearranges nearly quantitatively to 1-methyl-2-adamantanol when treated with acid [76].

2. Protoadamantane by Ring Closure Reactions

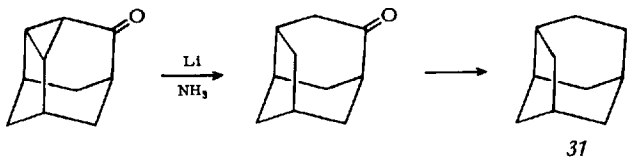
In addition to the skeletal rearrangements of the adamantane nucleus described above, several ring closure reactions have also been developed for the

preparation of protoadamantyl derivatives. Scheme 9 illustrates an early example [80], an approach analogous to that employed in the first successful synthesis of adamantane [81]. Additional examples include the reduction of

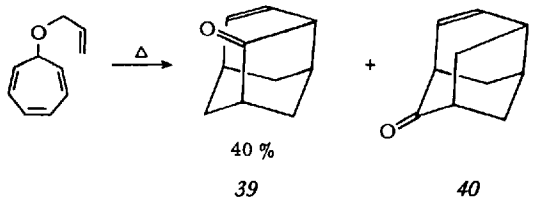
Scheme 9



8,9-dehydroadamantane [82] with lithium in ammonia which gives 5-protoadamantanone (Eq. (23))[40] and the pyrolysis of 7-allyloxycycloheptatriene (Eq. (24)) which results in the formation of two unsaturated protoadamantanones, *39* (tricyclo [4.3.1.0 ^{3,8}] dec-4-en-2-one) and *40* (tricyclo [4.3.1.0 ^{3,8}]-



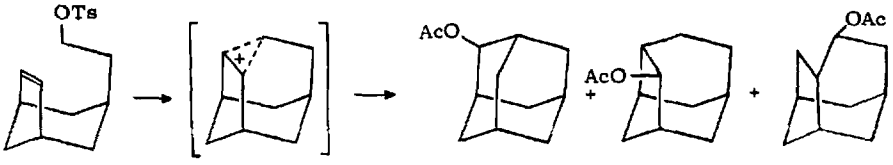
(23)



(24)

dec-4-en-10-one). Wolff-Kishner reduction of *39* plus *40* gives protoadamantene while hydrogenation of the mixture gives the two isomeric ketones which may be separated by column chromatography [83].

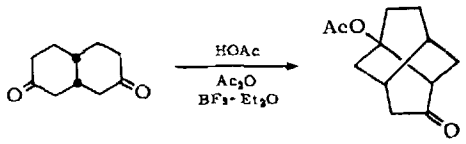
Finally, a solvolytically initiated π-route ring closure to a protoadamantyl cation has been found to give minor amounts of protoadamantyl products (Eq. (25)) [84].



(25)

B. Twistanes

Twistane derivatives (tricyclo [4.4.0.0^{3,8}] decanes) may be prepared in one step from the readily available *cis*-decalin-2,7-dione (Eq. (26)) [85, 86].

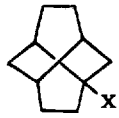


(26)

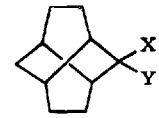
The functional groups of the resulting 1-acetoxy-5-twistanone may be selectively removed, enabling the preparation of a wide variety of 1- [86, 87] and 4- [85] substituted twistanes by conventional techniques. Table 2 summarizes all twistane derivatives which have been reported.

Multistep syntheses based on the earlier work of Whitlock [40, 89] have also been developed which enable the preparation of optically active twistane [90] and twistene [91]. In the latter case, the method of synthesis

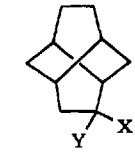
Table 2. *Twistane derivatives*



X	Ref.
OAc	86)
OH	86)
Cl	86)
COOH	86)
$COCH_3$	86)
NHAc	86)
NH_2	86)
Br	87)
OEt	87)
$p\text{-}CH_3C_6H_4SO_2O$	87)



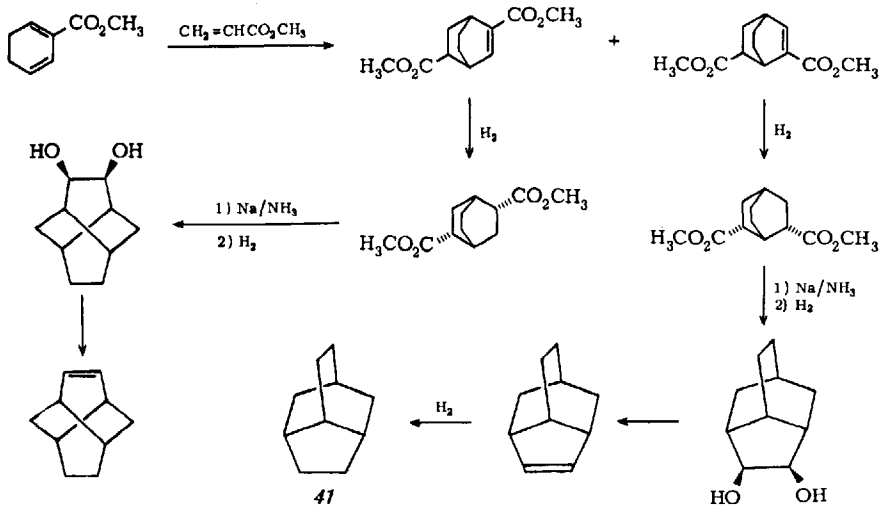
X	Y	Ref.
=O		40)
OH	H	40)
OH	CH_3	40)
OH	$p\text{-}CH_3OC_6H_4$	40)



X	Y	Ref.
=O		85, 88, 90)

(Scheme 10) also provides a route to tricyclo [4.3.1.0 ^{3,7}] decane *(41)*.

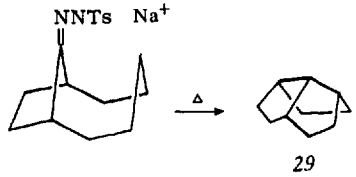
Scheme 10



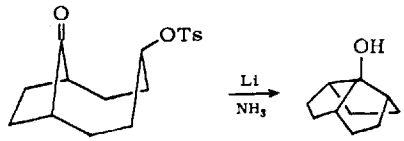
C. Tricyclo [5.2.1.0 ^{4,10}] decanes

Pyrolysis of the sodium salt of the tosylhydrazone of 10-bicyclo[5.2.1]decanone provides a remarkably easy synthesis of tricyclo [5.2.1.0 ^{4,10}] decane

(29) as illustrated in Eq. (27). A transannular ring closure of keto tosylate *42* has similarly been employed for the preparation of 10-tricyclo [5.2.1.0^{4,10}]-decanol (Eq. (28)) [93].

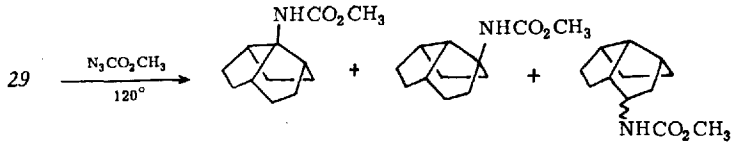


29 (27)

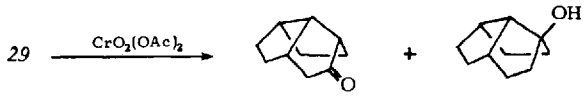


42 (28)

Direct substitution of hydrocarbon *29 via* both carbomethyloxynitrene insertion (Eq. (29)) and chromyl acetate oxidation (Eq. (30)) has been studied. The nitrene insertions are fairly unselective. On a per bond basis, both tertiary



(29)



(30)

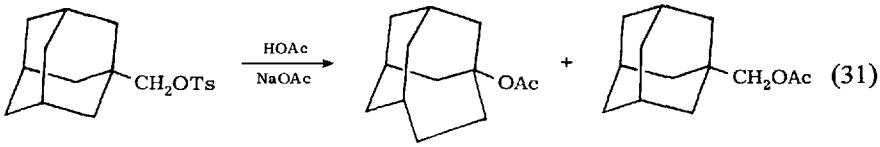
sites are attacked about 4 times more readily than the methylene positions. Tertiary/secondary ratios of this order are quite typical [94]. The chromyl acetate oxidation, on the other hand, appears to be highly selective. No 10-position oxidation products are observed at all.

Possibly this is due to a greater charge development in the transition states of the chromyl acetate oxidations. Solvolysis reactions at the 10-position are known to be highly unfavorable [95]. The solvolytic reactivity of 10-tricyclo [5.2.1.0^{4,10}] decyl tosylate is retarded relative to 1-adamantyl tosylate by a factor of approximately 10^6 at 70°C in acetic acid.

D. Homoadamantanes

1. Ring Expansions of Adamantane

Homoadamantane derivatives are most readily obtained from ring expansions of appropriately substituted adamantanes. Carbonium ion reactions of *adamantylcarbinyl systems* have long been known to give 3-homoadamantyl derivatives as the major product [4]. Thus, solvolysis of 1-adamantylcarbinyl tosylate in acetic acid-sodium acetate gives a mixture of 3-homoadamantyl acetate (93.2 %) and 1-adamantylcarbinyl acetate (6.8 %) as indicated in Eq. 31 [96, 97]. In more nucleophilic media (*e.g.* water-diglyme-NaOH) only 3-homoadamantanol is observed [96].



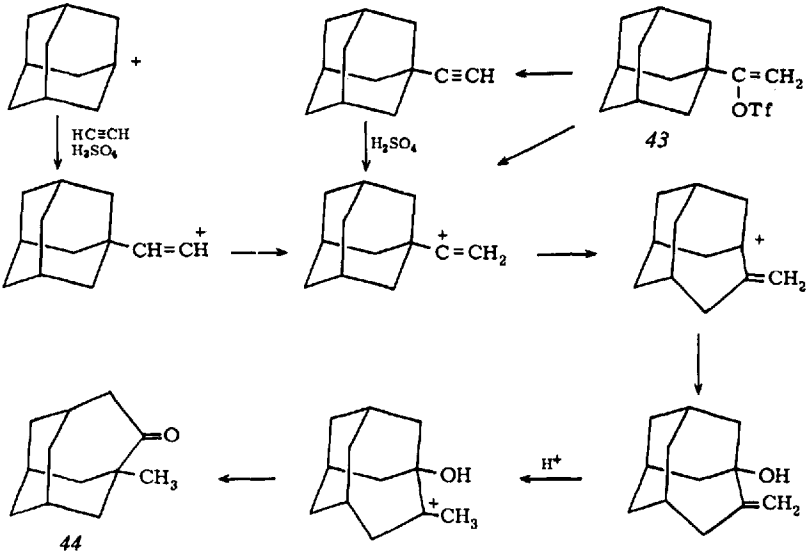
(31)

The Koch-Haaf carboxylation of 1-adamantylcarbinol gives rise to a similar ring expansion. Under dilute reaction conditions, 3-homoadamantyl carboxylic acid is obtained as the only product. More concentrated reaction conditions allow intermolecular hydride shifts to occur. A product mixture consisting of both 3-homoadamantyl carboxylic acid and the corresponding 1-acid is obtained [137]. In the analogous Ritter reaction (*cf.* Eq. (55)), intermolecular hydride shifts are not detected. In this case, the overall reaction seems to be thermodynamically controlled, with the major product at long reaction times being the unrearranged 1-adamantylcarbinyl acetamide [137a].

Analogous carbonium ion initiated rearrangements also occur when the rearrangement terminus may be formally represented as a vinyl cation. The solvolysis of 1-adamantylvinyl triflate *(43)* [98], the interaction of the 1-adamantyl cation with acetylene in sulfuric acid [99] and the treatment of 1-adamantyl-acetylene with sulfuric acid [100] all lead to the formation of *3-methyl-4-homoadamantanone (44).* The mechanisms of these rearrangements are summarized in Scheme 11.

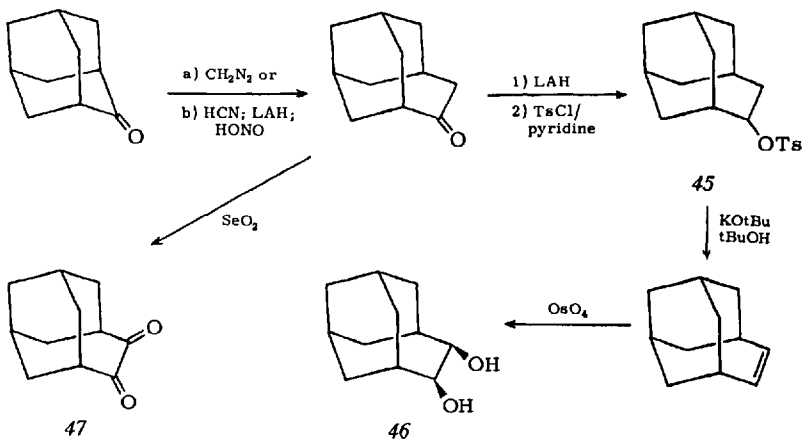
4-Homoadamantanone is also obtained from the Tiffeneau-Demjanov [101, 102] and diazomethane [103, 104] homologations of adamantanone [67, 69]. These ring expansions enable easy access to homoadamantane *(36)* and a variety of 4-mono and 4,5-disubstituted homoadamantanes. Some of this chemistry is summarized in Scheme 12.

Scheme 11



Several of the physical and chemical properties of the homoadamantane derivatives depicted in Scheme 12 are notable. The 4-homoadamantyl cation obtained during acetolysis of 4-homoadamantyl tosylate undergoes degenerate Wagner-Meerwein rearrangements before collapsing to a mixture of 4-homoadamantene and 4-homoadamantyl acetate products [101, 103]. These rearrangements are analogous to the semi-pinacolic rearrangement shown in Scheme 11.

Scheme 12



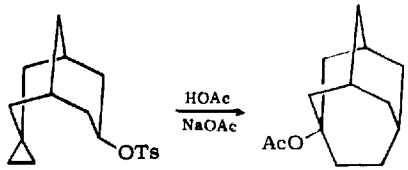
Evidence concerning the preferred conformation of homoadamantane (twisted C_2, or untwisted, C_{2v}) [105] is derived from the strength of the intramolecular hydrogen bond in *cis*-4,5-homoadamantanediol (46), [103] from the x-ray diffraction analysis of 4,5-homoadamantanedione *(47)* [106] and from a first order analysis of the vinylic portion of the nmr spectra of homoadamantene [104]. The results in all cases suggest a slightly twisted conformation for the homoadamantane ring system.

Finally, benzylic acid rearrangement of *47* to *2-hydroxyadamantane-2-carboxylic acid* provides a useful approach for the preparation of adamantane derivatives ring labeled in the 2-position [48]. Starting with labeled diazomethane, 50 % of the label will be retained in the regenerated adamantyl nucleus. Treatment of the 2-hydroxy-2-adamantane carboxylic acid prepared in this manner with thionyl chloride gives the starting adamantanone labeled in the 2-position [48]. The Wolff rearrangement of 5-diazo-4-homoadamantanone has similarly been employed for the preparation of ring labeled 2-adamantyl derivatives [46].

Beckmann and Schmidt rearrangements of adamantanone oxime [104, 107-109] and adamantanone [110-111], respectively, have also been studied. While certain conditions give rise to the expected 4-aza-5-homoadamantanone [107-109], a number of conditions have been found to give rise to anomalous fragmentation and rearrangement products [104, 109, 110]. These unexpected reactions are useful for the preparation of 2,4-disubstituted adamantanes and will be discussed in Section V.A.3.

2. Ring Closure Reactions

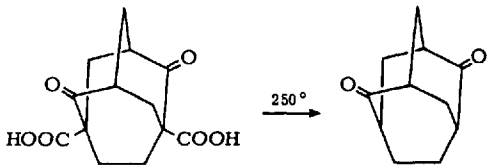
Although not competitive synthetically with the methods discussed above two interesting applications of ring closure reactions for the synthesis of homoadamantane derivatives have been reported. The first involves transannular cyclopropyl participation in the solvolysis of *48*; acetolysis gives 3-homoadamantyl acetate as the only observed product (Eq. (32)) [112]. Comparison of the acetolysis rate of *48* (2.14 x 10^{-4} sec^{-1}, 25°C) with that of *exo*-3-bicyclo[3.3.1]nonyl tosylate (5.82 x 10^{-5} $sec.^{-1}$, 25°C) [113, 114]



48 (32)

suggests that the cyclopropane ring may not be involved to as great an extent in the rate determining step of the solvolysis as originally interpreted [112].

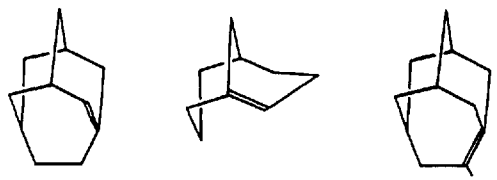
The second ring closure route to homoadamantane derivatives involves the preparation of the diester *49* discussed above (*cf.* Scheme 9). It is interesting to note that the corresponding acid, *50*, readily decarboxylates at 280°C (Eq. (33)) [80]. The adamantane derivative corresponding to *50* does not decarboxylate even at 500°C [80]. The contrasting behavior of these two



50 (33)

systems is attributed to a *resonance stabilization* of the incipient carbanion in the homoadamantane system (the dihedral angle between the C-C bond of the carboxyl group and the π-bond orbitals of the carbonyl function is approximately 70° which is not possible in the adamantane nucleus (dihedral angle near 90° [80, 115].

This result suggests that the anti-Bredt's rule olefin *51* may be an isolable compound. A number of bicyclic bridgehead olefins (*e.g. 52*) have recently been prepared, and their stabilities related to the corresponding *trans*-monocyclic olefins [115, 116]. The stability of *51* should correlate, then, with the

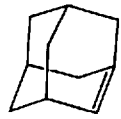


51 *52* *53*

stability of *trans*-cycloheptene. Bicyclic analogues of *trans*-cycloheptene have been reported [117].

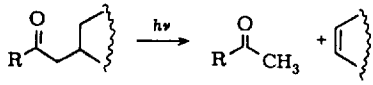
The isomeric homoadamantene, *53* (R=H), should also be isolable, since it is also a *trans*-cycloheptene analogue. An attempt to observe bridgehead deuterium incorporation *via* the corresponding enol (*53*, R=O^-) during the treatment of 4-homoadamantanone with KO*t*Bu in DO*t*Bu was not successful, however [103]. One must suspect that the conditions were not sufficiently vigorous.

The stability of *adamantene (54)* should correspond roughly to that of *trans*-cyclohexene. While the transient intermediacy of *trans*-cyclohexene during the photolysis of cyclohexene has been postulated [118], no evidence for the intermediacy of *54* during the photolysis of 1-adamantylacetone is



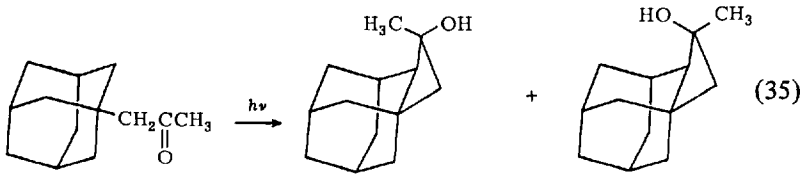
54

observed [119]. Instead of the typical Norrish type II elimination (Eq. (34)) commonly observed, irradiation of 1-adamantylacetone resulted in the for-



(34)

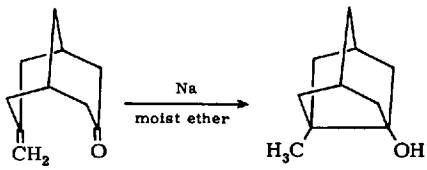
mation of two isomeric cyclobutanols (Eq. (35)) [119].



(35)

E. Noradamantanes

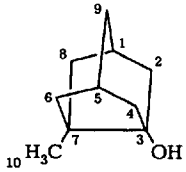
In addition to the facile aluminum halide and sulfuric acid catalyzed rearrangement routes to noradamantane and substituted noradamantanes discussed above (see Eq. (11) and Scheme 8), a variety of ring closure reactions have also been employed for the preparation of these systems. The most useful reaction for this purpose involves a transannular ring closure of the bicyclo [3.3.1]nonyl system. Thus, 7-methyl-3-noradamantanol is obtained [120] from the treatment of 3-keto-7-methylenebicyclo[3.3.1]nonane [121] with sodium in moist ether (Eq. (36)).



(36)

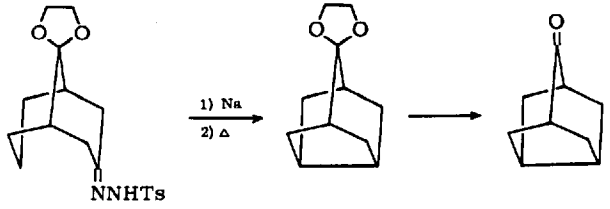
The structure of the product obtained from this reaction has been confirmed by X-ray analysis [122]. Details of this analysis are summarized in Table 3.

Table 3. *X-ray analysis of 7-methyl-3-noradamantanol* [122]



C_8-C_1-C_2	99.5	C_2-C_3-C_7	104.5
C_8-C_1-C_9	112	C_1-C_9-C_5	113
C_9-C_1-C_2	111	C_8-C_7-C_6	102
C_1-C_2-C_3	99.8	C_8-C_7-C_3	105
C_2-C_3-C_4	108	C_1-C_8-C_7	99.8

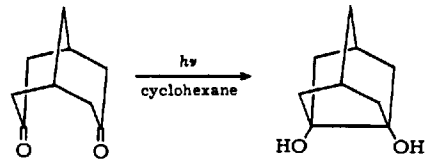
Analogous transannular *carbene insertion reactions* have also been reported as illustrated in Eq. (37). Both 9-noradamantanone [123] and N-methyl-9-aza-noradamantane [124] have been prepared in this manner.



(37)

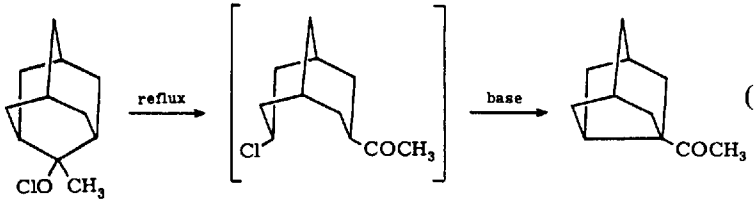
Photochemically induced transannular ring closure of bicyclo[3.3.1]-nonane-3,7-dione to 3,7-noradamantane diol is illustrated in Eq. (38) [125].

An extremely easy synthesis of 3-substituted noradamantanes is derived from the cleavage of the 2-methyl-2-adamantyloxy radical. Pyrolysis of 2-



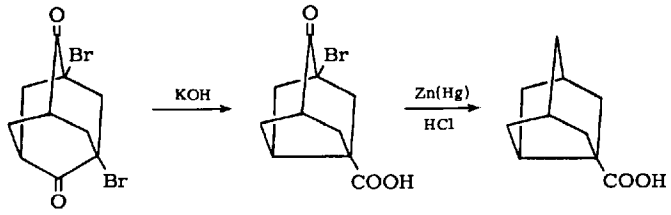
(38)

methyl-2-adamantanol hypochlorite in dry carbon tetrachloride followed by elution of the crude reaction product over basis alumina gives 3-noradamantane methyl ketone in 66 % overall yield [79]. The course of this rearrangement is summarized in Eq. (39).



(39)

The single Favorskii ring contraction of 1,5-dibromoadamantane-2,6-dione *(55)* also enables the preparation 3-substituted noradamantanes as illustrated in Eq. (40) [126]. Unfortunately, the starting material, *55*, is difficult to prepare. The synthetic utility of this reaction is therefore limited relative to those previously discussed.



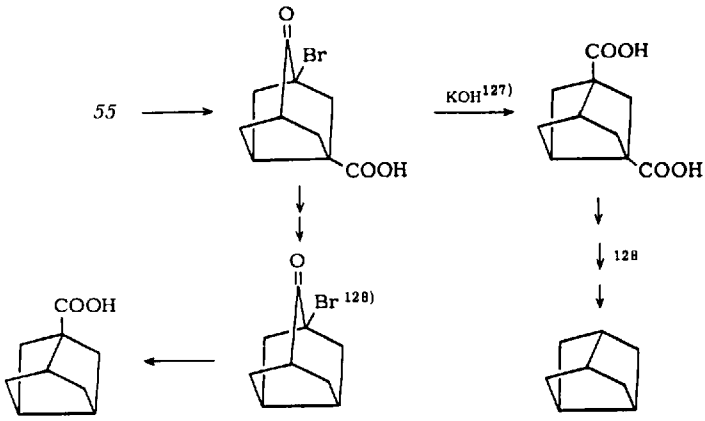
55

(40)

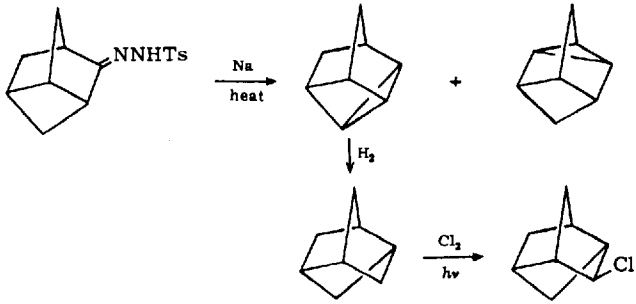
F Bisnoradamantanes

Favorskii ring contractions of 1,3-dibromoadamantane-2,6-dione *(55)* [127, 128] also provide synthetic approaches to bisnoradamantane derivatives as illustrated in Scheme 13.

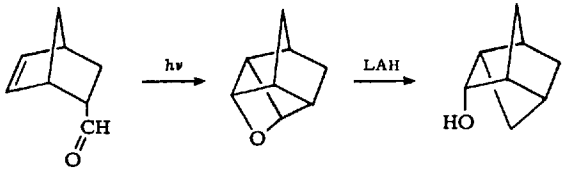
Scheme 13



More recently, other approaches to this interesting ring system have also been developed. These are illustrated in Eqs. (41) [129, 130] and (42) [131]. As indicated, photochlorination of the parent hydrocarbon occurs only at the methylene positions [130]. The correspondence between free radical and carbonium ion reactivities at the bridgehead positions of polycyclic hydrocarbons suggests that the bridgehead position of bisnoradamantane should also be highly unreactive in carbonium ion processes [132].



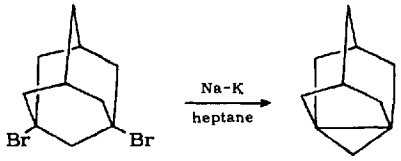
(41)



(42)

G. Dehydroadamantanes and Dehydrohomoadamantanes

Dehydroadamantanes are most readily obtained from either carbene insertion reactions or from 1,3-reductive eliminations. Pyrolysis of the dry sodium salt of the tosylhydrazone of adamantanone gives good yields of 2,4-dehydroadamantane [133]. The unstable 1,3-dehydroadamantane is obtained from the treatment of 1,3-dibromoadamantane with sodium (Eq. (43)) [134].

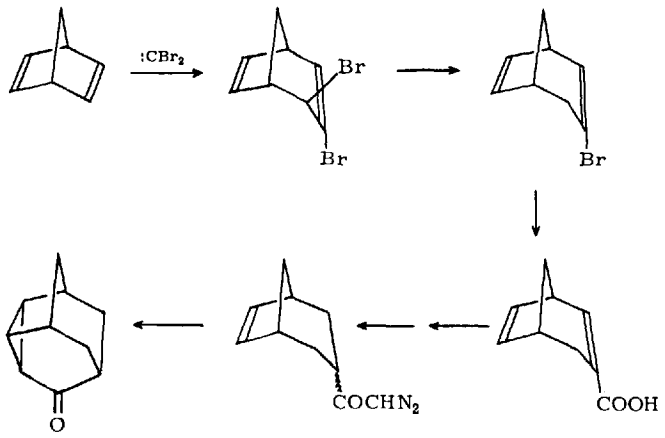


(43)

Both of the dehydroadamantane isomers undergo rapid electrophilic additions and may, in certain cases, provide useful syntheses of 2,4- and 1,3-disubstituted adamantanes. These reactions will be discussed in Section V.A.

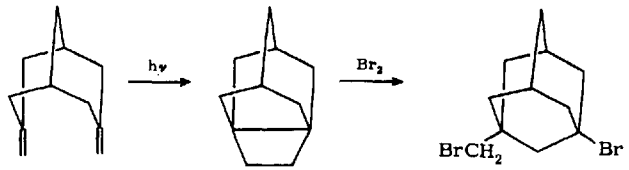
While ring closure reactions of the adamantane nucleus have not yet been reported for the preparation of substituted dehydroadamantanes, direct synthesis of *8,9-dehydro-2-adamantanone* has been accomplished as summarized in Scheme 14 [135].

Scheme 14



The stability and symmetry of the 8,9-dehydro-2-adamantyl cation have been investigated and comparison has been made with the cyclopropyl carbinyl cation itself [135]. For a complete discussion see Section V.B.1.

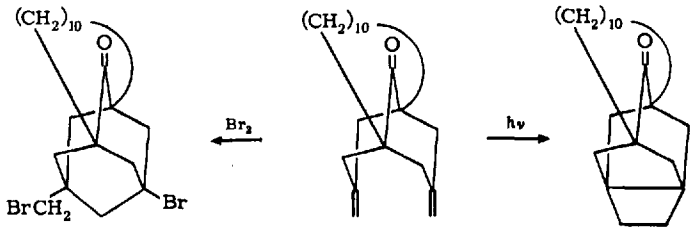
The most intriguing, and apparently general reaction for the preparation of dehydrohomoadamantanes involves the *(2+2) cycloaddition of 3,7-dimethylene-bicyclo[3.3.1]nonane.* Photolysis of the parent diene gives 3,6-dehydrohomoadamantane which, upon reaction with bromine, gives 1-bromo-3-bromomethyladamantane (Eq. (44))[136]. Thermodynamic control un-



(44)

doubtedly causes the rearrangement to the adamantane system during bromination. A similar rearrangement to 1-bromomethyladamantane is observed when homoadamantane itself is treated with molecular bromine[137].

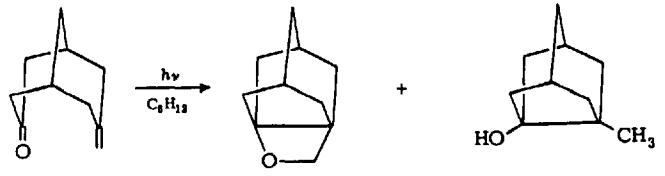
1,5-Decamethylene-3,7-dimethylenebicyclo[3.3.1]nonan-9-one *(56)* undergoes a similar photolytic cycloaddition reaction (Eq. (45))[138]. Bromination of the same diene gives the interesting bridged adamantanone *57*[138]. 3-Keto-



57 *56*

(45)

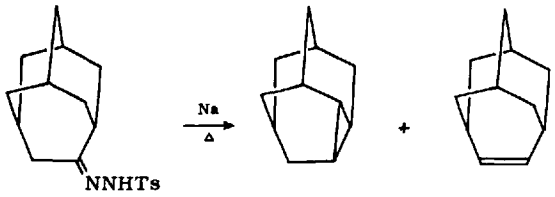
7-methylenebicyclo[3.3.1]nonane also undergoes a (2 + 2) cycloaddition reaction as illustrated in Eq. (46) [125].



(46)

Of the numerous dehydrohomoadamantanes which are conceptually possible, only one has yet been reported. Pyrolysis of the sodium salt of

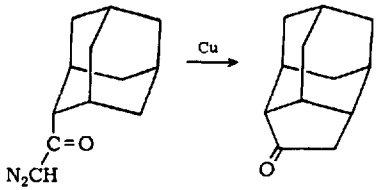
the tosylhydrazone of 4-homoadamantanone gave 2,4-dehydrohomoadamantane in addition to 4-homoadamantene (Eq. (47)) [139].



(47)

H. Ethanoadamantanes

In addition to the preparations of ethanoadamantane *via* Lewis acid catalyzed rearrangement of various polycyclic hydrocarbons described above (Section II. A.1), a ring closure reaction of a substituted adamantane has also been developed. Treatment of 2-adamantyl diazoketone with copper results in the intramolecular carbene insertion illustrated in Eq. (48) [140].



(48)

IV. Physical Properties

A. Thermodynamic

The driving force for the Lewis or strong acid catalyzed rearrangements of polycyclic hydrocarbons to adamantoid systems is provided by the high thermodynamics stability of the adamantyl ring system. In fact, adamantane is the most stable $C_{10}H_{16}$ tricyclic hydrocarbon possible. This thermodynamic stability is derived from the high degree of branching in the ring system and from the nearly "ideal" conformations of the atoms in the molecule. All bond angles are close to 109.5° (available X-ray diffraction data indicate an average bond angle of 109.4±.9° for adamantane [141] and 109.5±.7° for diamantane [36], the bonds around all adjacent carbons are ideally staggered, and all C-C bond lengths are similar to that found in diamond (1.534±.003Å) [30, 141].

Despite these structural features, the adamantane ring system is not strain-free [142]. Comparison of an estimated heat of formation for adamantane based on group increments derived from acyclic alkanes in completely skew-free conformations [142] with the experimentally determined value [143], indicates that adamantane is strained to the extent of 6.48 kcal/mole.

The source of the strain in adamantane is not readily apparent but appears to be due to features present in the rigid, cage structure of the molecule. Less rigid molecules, *e.g.* acyclic alkanes, cyclohexane and *trans*-decalin, are free to relax and to adopt conformations in which the best balance between angle, nonbonded and torsional strain is achieved. Thus, C-C-C bond angles of 112.4°, 111.3° and 111.5° are observed in straight chain hydrocarbons [144], isobutane [145] and cyclohexane [146], respectively. The rigidity of the adamantane molecule prevents any comparable relaxation. Nonbonded interactions are therefore accentuated in the adamantyl ring system [142].

Molecular mechanics calculations [147] of the strain in adamantane support this interpretation. Since such calculations are based on empirically derived parameters, however, a unique set of parameters for the representation of physical reality cannot be derived. Nevertheless, all available conformational analysis calculations demonstrate that the strain in adamantane may be quantitatively accounted for in terms of angle strain, which implicitly includes strain due to 1,3 nonbonded interactions since "ideal" bond angles derived from acyclic hydrocarbons are employed, and more remote nonbonded repulsions (either C...C

[142, 147] or H...H [148] depending on the parameterization) considered explicitly [142, 147, 148].

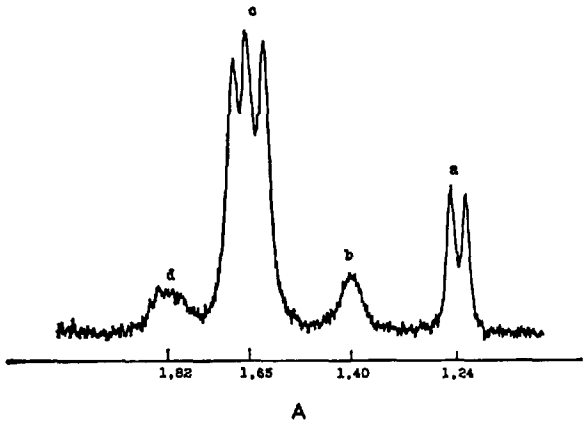
Magnification of nonbonded repulsions by the rigidity of the adamantane ring system is also exemplified by the magnitude of the skew interactions of methylene substituted adamantanes. The thermodynamic values for the aluminum bromide catalyzed equilibrium between 2- and 1-methyladamantane (see Scheme 5 for the mechanism of this rearrangement) are: ΔH = -3.44±.074 kcal/mole, ΔS = 3.2±2.3 eu and ΔG^{298° = 2.48±0.06 kcal/mole [23]. Correcting for the different degrees of branching in the two compounds using "skew-separate" [142] liquid state group increments, a value of 1.36 kcal/mole may be estimated for each liquid state skew interaction in 2-methyladamantane [23]. This may be compared with the liquid state skew interactions in *trans*-1,3-dimethyl cyclohexane and *cis*-1,4 dimethylcyclohexane of 0.87 and 0.82 kcal/mole, respectively [149]. The decrease in the number of degrees of freedom available for the relief of the skew interactions in 2-methyladamantane results in an increase in the magnitude of this interaction relative to the monocyclic cases.

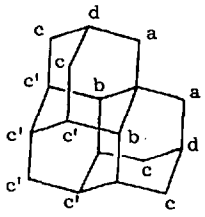
B. Spectral

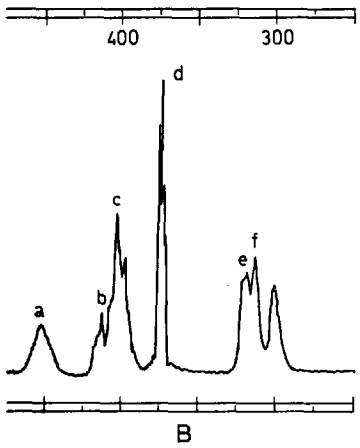
1. Nuclear Magnetic Resonance Spectra

The nmr spectra of diamonoid hydrocarbons display a wide range of complexities. The 60 MHz spectrum of adamantane consists of a sharp doublet (δ = 1.78 ppm, spacing = 1.7 cps) [150]. Only at 220 MHz are the signals due to the two types of hydrogens present cleanly separated (δ 1.78 and 1.74 ppm for bridgehead and methylene hydrogens, respectively) [151]. The 100 MHz spectrum of diamantane *(12)* consists of a single, relatively sharp signal (δ = 1.68 ppm) despite the three different types of hydrogens in this molecule [29]. The spectra of noradamantane *(23)*, triamantane *(14)* and homoadamantane *(36)* are increasingly more complex, however. The 60 MHz spectrum of noradamantane consists of three different absorptions. Resonances due to the two different types of bridgehead hydrogens (δ = 2.40 and 2.10 ppm) and to the methylene hydrogens (δ = 1.60 ppm) are well separated. Resonances due to the three different types of methylene hydrogens are not resolved even at 220 MHz, however [151]. The analyses of the complex 100 and 220 MHz spectra of triamantane [33] and homoadamantane [151] respectively, are summarized in Fig. 2.

The nmr spectra of bridgehead substituted adamantanes are generally readily analyzed since, for the most part, only minor spin-spin coupling is observed in these substrates. The chemical shifts induced by various bridgehead substituents are found to be remarkably additive [150]. Knowing the chemical shifts pro-







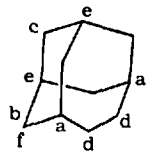


Fig.2. A. 100 MHz spectrum of triamantane. B. 220 MHz spectrum of homoadamantane. (After Ref. [33] and [151], respectively).

duced in the mono-substituted adamantanes, the chemical shifts of a wide variety of 1,3-, 1,3,5- and 1,3,5,7-polysubstituted adamantanes may be estimated accurately.

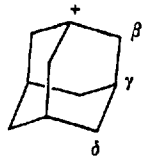
The chemical shifts of *1-substituted adamantanes* are correlated well with substituent electronegativity [150] as measured by σ^* [152] or group dipole moments [153]. Only the chemical shifts observed for the γ (bridgehead) position exhibit the normal inductive order, however; the chemical shifts of the β (adjacent methylene) and δ (far methylene) hydrogens appear to be anisotropy controlled [150].

Solvent effects upon the chemical shifts of 1-substituted adamantanes are also highly specific [150]. Aromatic solvents, especially benzene, give rise to significant solvent shifts of all resonances to a higher field. The β hydrogens, which are closest to the substituent, are affected least, however. The manner in which these geometrically specific effects are produced is not clear. No evidence for the existence of thermodynamic 1 : 1 complexes is found. Apparently, specific solvent ordering results from an interaction of the solvent with the dipole moment of the solute [154].

The nmr spectra of *2-substituted adamantanes* are far more complex than those of their bridgehead isomers [150, 155]. This is illustrated in Fig. 3 by comparing the nmr spectra of 1- and 2-hydroxyadamantane. The lower symmetry of the secondary derivatives gives rise to a larger number of nonequivalent protons. Spin-spin coupling also becomes more evident in these systems. The nmr spectra, therefore, generally consist of several broad, uncharacteristic signals. Use of the nmr shift reagent, tris (dipivalomethanato) europium II, serves to greatly simplify the 2-hydroxyadamantane spectrum, however, and, in addition, to enable the resolution of the two types of δ-protons of 1-adamantanol [156].

The nmr spectrum of 1-chloroadamantane in SbF_5-SO_2 [50] or of adamantane in SbF_5-FSO_3H [157] is attributed to the *1-adamantyl cation*. The essential characteristics of the spectrum are summarized in Table 4. Contrary to the normal observation where the hydrogens adjacent to the carbonium ion site experience the largest deshielding effect, the γ (bridgehead) hydrogens of the

Table 4. *The NMR Spectrum of the 1-Adamantyl Cation* [156, 157]

	δppm	Area	Assignment
	4.50	6	β
	5.42	3	γ
	2.67	6	δ

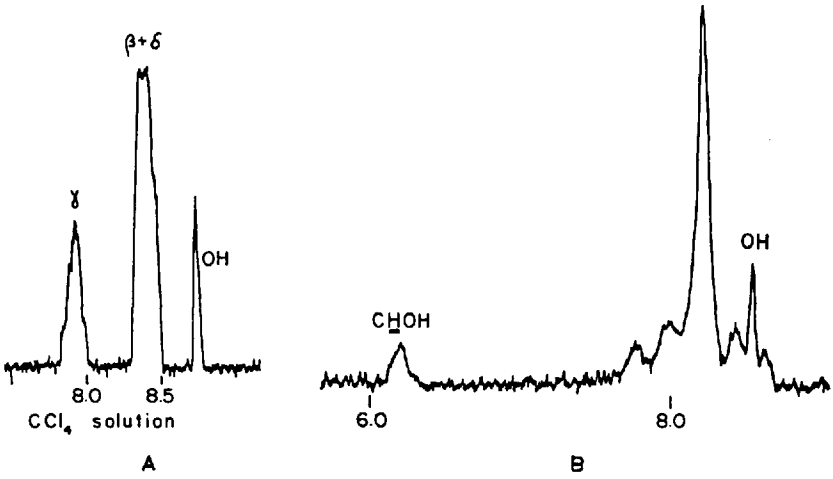
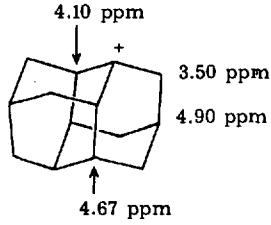


Fig. 3. 60 MHz spectra of 1-hydroxyadamantane (A) and 2-hydroxyadamantane (B). (Reproduced from Ref. [150]. *Cf.* Ref. [155]).

1-adamantyl cation appear furthest downfield. This "anomalous" chemical shift is also observed in the spectrum of the 1-diamantyl cation *(58)* obtained from the SbF_5-FSO_3H solution of diamantane [157].



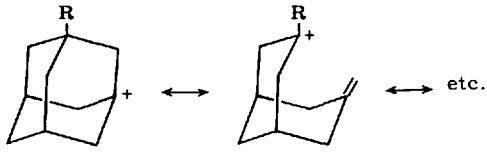
58

This γ-deshielding effect might be explained on the basis of a special cage effect which enables the back lobes of the bridgehead C-H bonds to overlap with the vacant *p*-orbital of the cation [156]. No direct experimental evidence exists which would substantiate this special cage effect, however. An earlier report of the observation of the esr spectrum of the adamantane radical anion [158] in which a five line spectrum was observed suggesting that the electron was within the adamantane cavity interacting with the back lobes of the four bridgehead C-H bonds has apparently proven not to be reproducible [159-161]. Although theoretical arguments have been cited in support of

this "backbonding" hypothesis [163], the operation of this special cage effect remains unverified.

C-C hyperconjugation appears to afford a more reasonable explantion for the apparent distribution of charge to the bridgehead positions of the 1-adamantyl cation. The valence bond picture commonly employed to illustrate hyperconjugation should be considered to conform to the definition proposed by Jensen and Smart [162]: *".. the movement of electrons and atoms is only slight but enough to provide stabilization at an adjacent developing electron-deficient center."*

Previously, it has been noted that the solvolysis rates of both 3-methyl-1-bromoadamantane and 3,5-dimethyl-1-bromoadamantane are slower than 1-bromoadamantane itself. This result was felt to be inconsistent with any mechanism which distributed positive charge to all bridgehead positions of the adamantyl cation under solvolysis conditions since the introduction of tertiary resonance contributors (*cf.* Eq. (49)) should enhance rather than retard solvolysis rates [56, 164].

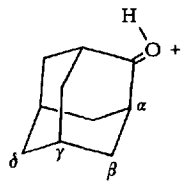


(49)

Substituent effects do not appear to be reliable probes for hyperconjugation, however. Even in the 2-norbornyl cation, where considerable C-C bond delocalization is generally considered to be present [165], substituents fail to indicate any electron deficiency at the 6-position of the developing 2-norbornyl cation [162, 166, 167]. Methyl substituent effects may also not be expected to provide a reliable test for C-C hyperconjugation in the 1-adamantyl system.

The nmr spectrum of the *2-adamantyl cation* has not yet been observed. All attempts to generate this species in strong acid solution have been foiled by an apparent 1,2 hydride shift to the 1-adamantyl cation as discussed in Section II.B [59, 61]. An analogy for the 2-adamantyl cation is provided by protonated adamantanone. The nmr spectrum of protonated adamantanone is illustrated in Table 5 [61, 168]. The spectrum of the 2-methyl-2-adamantyl cation has also been determined [54].

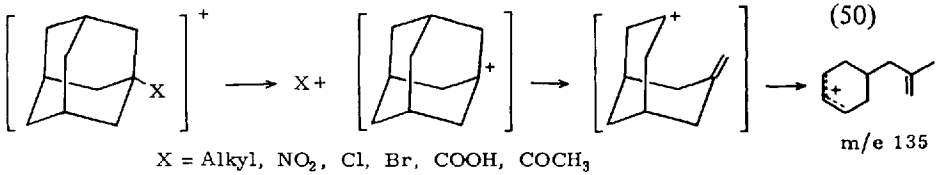
Table 5. *The NMR spectrum of protonated adamantone* [61, 168]

	δ ppm	Area	Assignment
	3.50	2	α
	2.73	8	β
	2.40	2	γ
	2.30	2	δ
	13.85	1	O-H

2. Mass Spectra

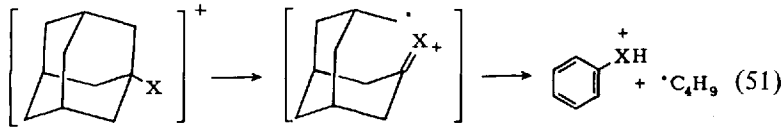
The mass spectra of diamonoid substrates are highly characteristic. The parent hydrocarbons exhibit a remarkable resistance to fragmentation. Large parent peaks which are also generally the base peaks are observed [4, 29, 33, 169].

1-Substituted adamantanes fall into two mass spectra classes [169]. The first group includes alkyl substituents and other functions (NO_2, Cl, Br, COOH, $COCH_3$) easily eliminated as neutral species from the molecular ions. The mass spectra of this group of compounds are practically identical, since they arise from decomposition of the adamantyl cation, $C_{10}H_{15}^+$ (Eq. (50)). The m/e 135 peak, corresponding to this ion, is the base peak, while the parent peak,



X = Alkyl, NO_2, Cl, Br, COOH, $COCH_3$

if it appears at all, is very weak. The second class of substituted adamantanes include those with C_6H_5, OH, NH_2 and similar functions capable off affording resonance stabilization to an adjacent positive charge [169]. These functions are not lost during fragmentation, and the spectra of members of this class are quite different from one another. In each case, however, the base peak is found to arise from a fragmentation which may be represented as shown in Eq. (51).



X = C_6H_5, OH, NH_2, $NHCOCH_3$

C. Physical Organic Chemical Applications

All bond angles in adamantane are nearly 109.5 ° (see above). Theory [170] predicts, therefore, that all carbon bonding orbitals should be nearly pure sp^3 hydrids. The situation in norbornane is quite different. Endocyclic bond angles of this molecule are considerably less than 109.5 ° [171]. The *p* character of the endocyclic carbon orbitals should be greater than that of the exocyclic orbitals [170].

The differences in the hybridizations of the exocyclic bridgehead bonds of adamantane and norbornane are reflected by the bridgehead C^{13}-H coupling constants observed for the two systems: $J_{C^{13}-H}$ = 120±1Hz for all hydrogens in adamantane [150]; $J_{C^{13}-H}$ = 139±1 Hz for norbornane [172]. These coupling constants correspond to 24 and 28 % s character for the exocyclic bridgehead C orbitals of adamantane and norbornane, respectively [173].

The differences in *s* character in the central bonds of 1,1'-binorbornane *(59)*, 1,1'-biapocamphane *(60)* and 1,1'-biadamantane *(61)* provide an opportunity to test factors which may affect C-C bond lengths. Three explanations have been suggested for the shortened C-C single bond observed in butadiene relative to n-butane: Conjugation (CH_2 = CH–CH=$CH_2 \rightleftarrows \dot{C}H_2$–CH=CH–$\dot{C}H_2$), decreased nonbonded interactions, and increased s character [172]. Conjugation in the saturated systems *59-61* was assumed to be inconsequential. The observed variations in the C-C central bonds of *59-61* (Table 6) were attributed to hydridization and nonbonded interaction effects alone. Thus, since the nonbonded interactions in *60* and *61* were assumed to be nearly the same, the shorter C-C bond length in *60* relative to *61* may be attributed to hybridization effects. Since the hybridization of the central bonds in *59* and *60* should be nearly the same, the shorter bond in *59*, may be attributed to a decrease in the severity of the nonbonded interactions in the molecule. By analogy, therefore, hydridization and nonbonded interaction effects were supported as the dominant effects which determine the C-C single bond length in butadiene as well [172].

Unfortunately, the neglect of conjugation in the saturated systems may be an oversimplification. This is illustrated by the contrasting effect of hybridization on the chemical shifts of bridgehead hydrogens and fluorine. Since an s orbital lies closer to the nucleus than does a *p* orbital, electronegativity increases with increasing s character. As a result, the chemical shifts of bridgehead hydrogens are observed to shift downfield as the s character of the C-H bond increases [174]. F^{19} chemical shifts, on the other hand, are observed to exhibit the opposite trend (Table 7) [175].

The observed trend in F^{19} chemical shifts may be due to an increased interaction of the nonbonded electrons of the fluorine atom with the greater p character of the endocyclic bonds in the more deformed systems [175]. A si-

Table 6. *Central bond lengths of 1,1'-binorbornane (59), 1,1'-biapocamphane (60) and 1,1'-biadamantane (61)* [172]

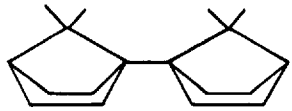
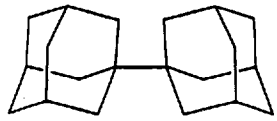
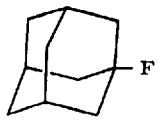
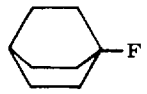
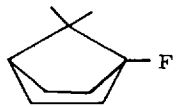
	Central bond length	% S character
 *59*	1.515	28
 *60*	1.544	28
 *61*	1.578	25

Table 7. *F^{19} chemical shifts of bridgehead fluorides* [175]

Compound	F^{19} chemical shift [a]
	132
	148
	194

[a] In CCl_4 relative to external CCl_3F.

milar interaction in 1,1'-binorbornane might contribute to the shortened central C-C bond of this compound.

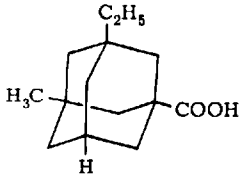
Substituent effects on the F^{19} chemical shifts of bridgehead adamantyl fluorides also show unexpected trends. A shielding effect is observed for both 3-methyl-1-adamantyl fluoride [176] and 3-carbomethoxy-1-adamantyl fluoride [177] relative to 1-adamantyl fluoride itself. Not only do these results indicate that methyl is acting as an electronegative substituent in this case (see Section V.B. 1 for a detailed discussion of the inductive property of alkyl groups in saturated substrates) but also, electronegative groups are found to *shield* the fluorine nucleus.

The same effect is also observed in the bicyclo[2.2.2]octyl system [175]. In this system, the effect has been attributed to a substituent induced structural perturbation. The electronegative fluorine and substituent repel each other resulting in enhanced *p*-character of the endocyclic C-C bonds. The C-F bond order may, therefore, be enhanced as discussed above for the unsubstituted polycyclic fluorides [175].

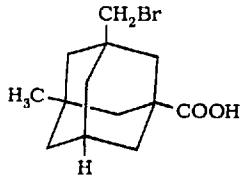
D. Optical Activity in Adamantane Derivatives

The four bridgehead positions of adamantane are formally analogous to the four tetrahedral valences of carbon. Adamantanes with four different bridgehead substituents are, therefore, chiral.

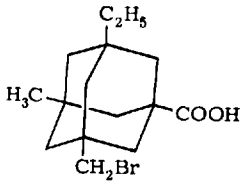
In general, small specific rotations should be expected for such adamantane derivatives since a large reduction in optical rotatory power should occur when pairwise interactions are greatly reduced by distance. The resolution of several tetrasubstituted adamantanes *(62-65)* has been attempted [178, 179, 247]. Mesured rotations, as expected [4] are quite low. Only *65*, the formal analogue of lactic acid, has been proven to be optically active [178, 179] by a confirmatory approach.



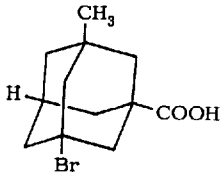
62



63



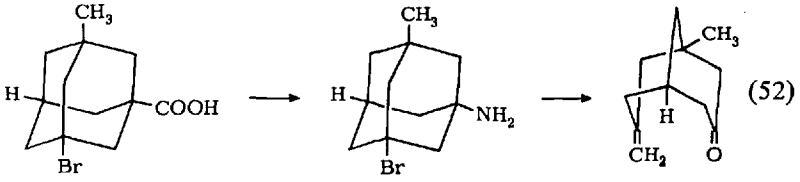
64



65

While a small specific rotation (< 1 °C) may be observed for this compound (optical purity unknown) [179], conversion of *65* to 1-methyl-3-methylene-7-

ketobicyclo[3.3.1]nonane as illustrated in Eq. (52) serves to amplify the experimentally observable rotation [178]. Possibly, a similar indirect approach may serve to demonstrate the successful resolution of *62–64* as well.



(52)

65

Quantitative conclusions regarding the reduction of optical rotatory power of these derivatives by the increased distance of the pairwise interactions must, of course, await optical purity determinations. Qualitatively, however, expectations are obviously confirmed [179].

Since the adamantane ring system is composed of three interlocking cyclohexane rings, all in the perfect chair conformation, β-substituted adamantanones are also ideal models for establishing quantitative substituent contributions to the *optical rotatory dispersion* of cyclohexanones in the undisturbed chair form. A variety of optically active β-equatorial and β-axial substituted adamantanones have been synthesized [180-184] and their circular dichroism determined [184–185]. In general, axial polar substituents (CO_2R, Cl, Br, I and N_3) exhibit anti-octant behavior (the positive Cotton-effect observed for β-equatorial-methyladamantanone is attributed to the R configuration) [181] while β-equatorial substituents obey the octant rule [184, 185]. The contribution of a β-axial methyl group to the Cotton-effect is found to be practically zero [183]. The β-equatorial substituted haloadamantanones, on the other hand, exhibit extraordinarily high circular dichroism absorptions. High order anisotropy terms explain these observations [186]. The rigidity of the adamantanone system has also been used to demonstrate that α-equatorial substituents make only very small small rotatory contributions [186a].

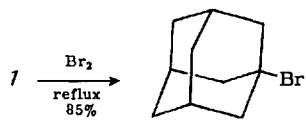
V. Chemical Properties

A. Substitution Methods

1. Ionic Reactions

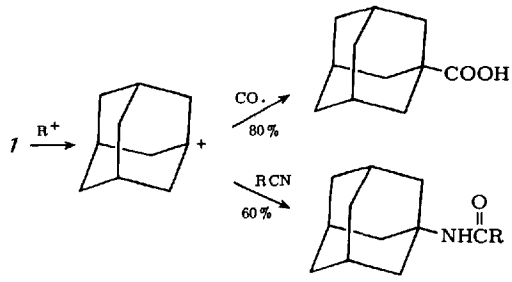
Although the bridgehead positions of many polycyclic hydrocarbons have been found to be quite unreactive toward nucleophilic substitutions [187], the 1-adamantyl cation may be generated with relative ease. Since the tertiary 1-adamantyl cation is considerably more stable than the secondary 2-cation, carbonium ion substitution reactions strongly favor the bridgehead positions (see, however, below).

Bromination in the absence of free radical catalysts, for example, gives high yields of 1-bromoadamantane (Eq. (53)) [188]. The Koch [189] and Ritter [188, 190] reactions, which involve the initial generation of the 1-adamantyl cation either by means of hydride transfer to the t-butyl cation or



(53)

from 1-bromo- or 1-hydroxyadamantane, followed by trapping of the cation by carbon monoxide and acetonitrile, respectively (Eqs. (54) and (55)), may be used to introduce a carboxylic acid and amino function. The bridgehead

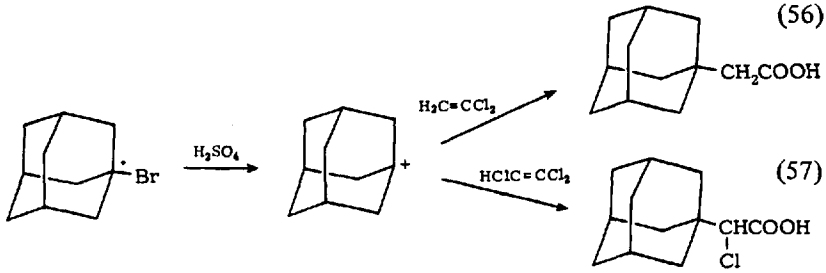


(54)

(55)

amines are also obtained from the reaction of trichloramine and aluminum chloride with adamantane [191].

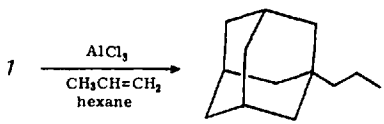
The 1-adamantyl cation is also trapped by 1,1-dichloroethylene [192] and 1,1,3-trichloroethylene [193] to give *1-adamantyl acetic acid* (Eq. (56)) and *α-chloro-1-adamantyl acetic acid* (Eq. (57)), respectively, after hydrolysis, and by olefins in the presence of hydride donors such as hexane to give alkyl



(56)

(57)

adamantanes (*e.g.* Eq. (58)) [194-196]. In a similar manner, the 1-adamantyl cation adds to acetylene to give 1-adamantyl acetaldehyde in addition to the



(58)

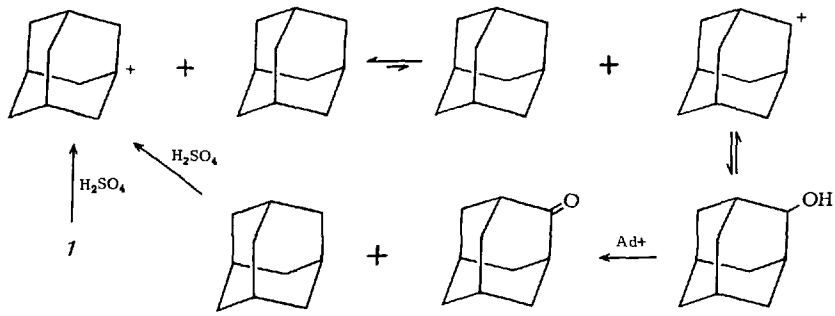
4-homoadamantyl rearrangement products discussed earlier (see Scheme 11) [99].

Analogous ionic substitutions work equally well on substituted adamantanes. A wide variety of mono-, di-, tri-, and tetra-bridgehead substituted adamantanes may be readily obtained.

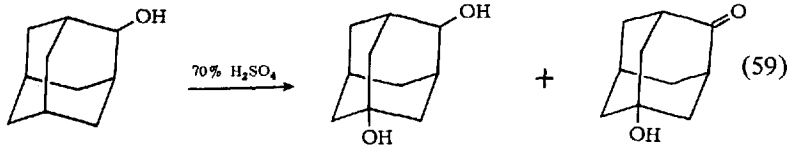
Under special conditions, an ionic substitution reaction also provides a convenient method for the funtionalization of the *methylene positions of adamantane.* Treatment of adamantane or 1-hydroxyadamantane with 96 % H_2SO_4 at 77 °C for 5 hours results in a 50–60% yield of adamantanone [67–69].

The mechanism of this reaction involves an equilibrium between the 1- and 2-adamantyl cations established *via* intermolecular hydride transfers. Direct 1,2-hydride shifts on the adamantyl nucleus are inhibited by the unfavorable stereoelectronic relationship between the vacant orbital and the migrating group as discussed previously (see Fig. 1) [57]. The 2-adamantyl cation, once formed, is trapped by water. The resulting 2-hydroxadamantane apparently then undergoes a disproportionation reaction with an adamantyl cation to give adamantanone and adamantane. The overall reaction is summarized in Scheme 15.

Scheme 15

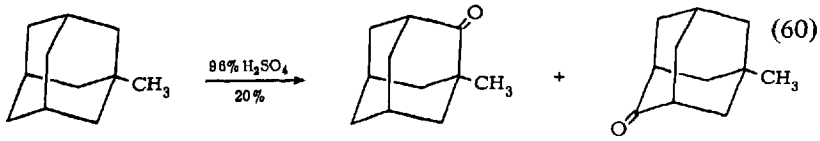


Treatment of 2-hydroxyadamantane with 70 % H_2SO_4 gives rise to similar *intermolecular hydride transfers.* In this case, however, 1-hydroxy-4-adamantanone is the major isolable product (Eq. (59))[197].



(59)

Oxidation of the methylene positions of alkyl substituted adamantanes works poorly. The synthetic utility of such reactions is further decreased by the isomeric product mixtures which result (Eq. (60)) [64].



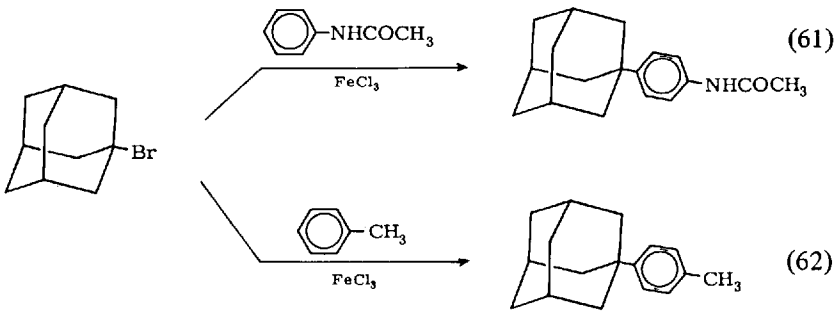
(60)

The general success of the direct ionic substitutions of the methylene positions of adamantane may be attributed to two main factors:

First, as discussed earlier in connection with the aluminum halide catalyzed rearrangements of hydrocarbons (Section II.A.2), intermolecular hydride transfer reactions appear to be fairly unselective processes. Apparently, charge development in the transition states of these reactions is minimized; a pentacoordinate carbon intermediate may be involved. As a result, the strong preference for the bridgehead positions exhibited by most ionic substitution reactions is partially overcome.

Second, the equilibrium between 1- and 2-hydroxyadamantane, once established, is effectively shifted further toward the methylene position by the oxidation of 2-hydroxyadamantane to adamantanone.

Once functional groups have been added to the adamantane nucleus, well known and reliable techniques may be used to convert them to a number of *other derivatives* [4]. 1-Bromoadamantane is converted smoothly to the corresponding alcohol by 10 % K_2CO_3 [188]. Friedel-Craft alkylations proceed normally with 1-bromoadamantane as the alkylating agent [198, 199]. The adamantyl residue is apparently directed to the *para* position only [198], although no detailed product analyses were reported (Eq. (61) and (62)). Such behavior is expected by analogy with the corresponding t-butyl compounds.

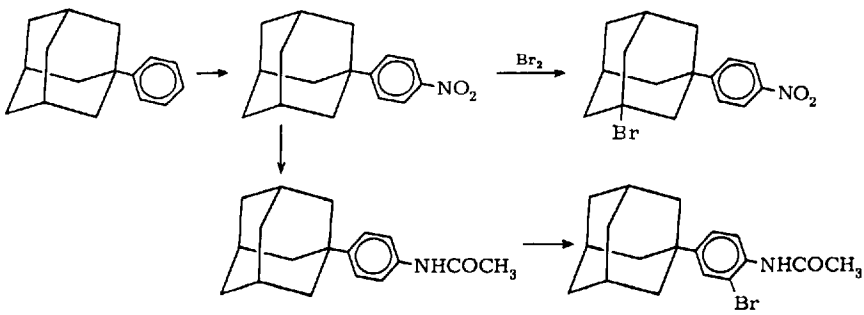


(61)

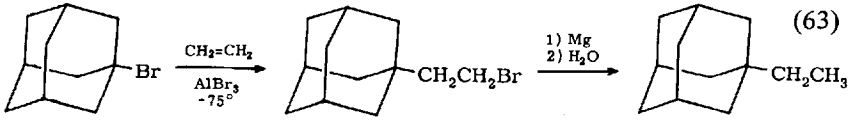
(62)

Nitration of 1-phenyladamantane occurs at the *para* position of the phenyl ring [198]. The resulting nitrobenzene brominates on the adamantane nucleus. If, however, the nitro group is converted to an acetamide function, bromine enters the aromatic ring (Scheme 16) [198].

Scheme 16

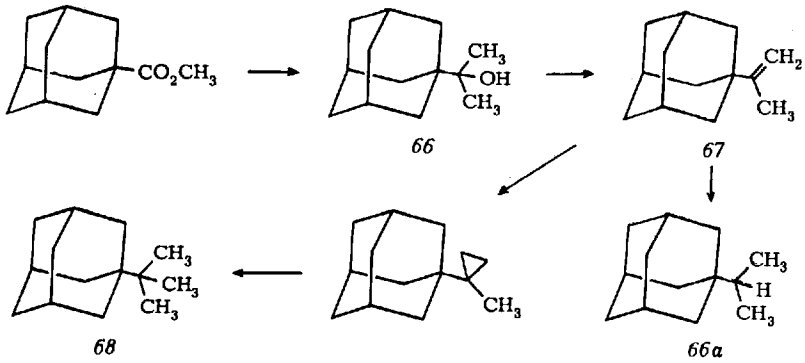


1-Bromoadamantane couples with CH_3MgBr in ethyl ether solution at 100 °C to give 1-methyladamantane in 83 % yield [201]. While similar coupling reactions are not synthetically useful or do not occur at all with other alkyl groups, simple alternative synthetic methods have been developed. Treatment of 1-bromoadamantane with $AlBr_3$ in the presence of ethylene at -75 °C to give 1-(β-bromoethyl)-adamantane [202] followed by reduction [200] results in good yields of 1-ethyladamantane (Eq. (63)). Wolf-Kishner [164] or Clemensen [203] reduction of commercially available methyl adamantyl ketone provides an alternative route for the preparation of this compound.

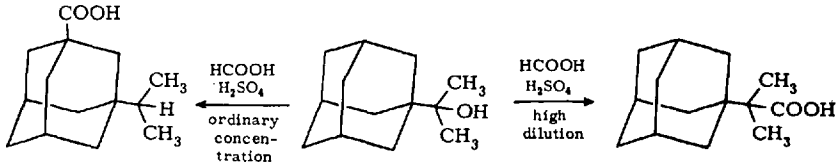


(63)

Conversion of the methyl ester of 1-adamantane carboxylic acid to 1-adamantyl dimethylcarbinol *(66)* by reaction with CH_3MgI followed by dehydration and subsequent hydrogenation provides a convenient route to 1-isopropyladamantane *(66a)* [164, 200]. Simmons-Smith cyclopropanation of 1-isopropenyladamantane *(67)* followed by hydrogenolysis of the cyclopropane ring gives 1-*t*-butyladamantane *(68)* [204]. An alternative synthesis



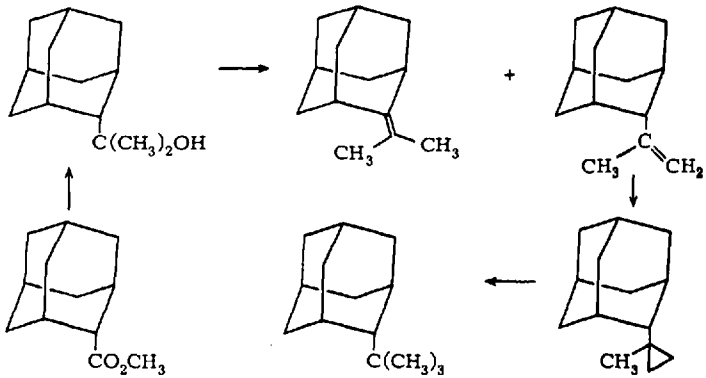
of *(68)* might involve 2-(1-adamantyl)-2-propionic acid *(69)* which is obtained from the Koch-Haaf reaction of *66* in 65 % yield under high dilution conditions [205]. It is interesting to note that when *66* is subject to ordinary Koch-Haaf carboxylation conditions, 3-isopropyl-1-adamantane carboxylic acid *(70)*, derived from intermolecular hydride shifts, is the only product observed [205].



70 *66* *69*

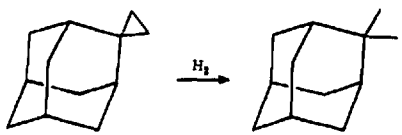
Functional group manipulations are equally successful for the preparation of a wide variety of 2-substituted adamantanes. Starting with the methyl ester of 2-adamantane carboxylic acid [57, 206], 2-*t*-butyladamantane *(71)* may be prepared in a manner anlogous to that described above for the synthesis of the bridgehead isomer (Scheme 17) [204]. These reactions illustrate the

Scheme 17



71

remarkable ease and specificity of the hydrogenolysis of cyclopropane rings as a technique for the introduction of quaternary carbon atoms.
In an analogous manner, 2,2-dimethyladamantane *(72)* may be prepared by the hydrogenolysis of the spiro cyclopropane derivative, *73* [204, 204a].



73 *72*

The structure of the adamantane nucleus requires that substituents at the 2-position of adamantane be axially disposed to one rigid chair cyclohexane. The

strain introduced by the axial-*t*-butyl substituent described above must be quite large. Molecular mechanics calculations predict a strain of 5.4 kcal/mole due to axial-*t*-butyl in the conformationally more mobile chair-cyclohexane itself[207]. Nevertheless, direct formation of 2-*t*-butyl-2-adamantanol by *t*-butyl lithium addition to adamantanone is observed [208]. Obviously, additions to the carbonyl function of adamantanone may be expected to be of general utility.

Introduction of functional groups to the adamantane nucleus after the hydrocarbon itself has been prepared is clearly a general and useful approach for the preparation of a wide variety of adamantane derivatives. Tables 8 – 12, summarize additional 1- and 2- substituted adamantanes which have been obtained in this manner.

Table 8. *1-Substituted Adamantanes* (see also Ref. [4]).

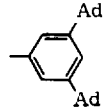
1-Substituent	Ref.	1-Substituent	Ref.
F	176)	C_6H_4-p-CH_3	198)
CH_2Br	96)	$CH(CN)_2$	215)
CH_2OEt	96)		216)
CH_2OAc	96)		
OCOCl	209)		
$OCONHNH_2$	209)		
$CON(CH_3)CH(CH_3)CH_2C_6H_5$	210)	CH_2CH_2OH	217, 233)
$CH_2N(CH_3)CH(CH_3)CH_2C_6H_5$	210)	CH_2COOH	202)
$CONHCH(CH_3)CH_2C_6H_5$	210)	CH_2CH_2COOH	202)
$CH_2NHCH(CH_3)CH_2C_6H_5$	210)	$CH_2(CH_2)_2COOH$	202)
	211)	$CH_2(CH_2)_3COOH$	202)
		$CH_2(CH_2)_4COOH$	212, 202)
$(CH_2)_4CH_2OH$	212)	C_6H_4-p-NO_2	198, 199)
$(CH_2)_4CH_2NH_2$	212)	C_6H_4-p-CN	199)
$(CH_2)_4CH(OH)CH_3$	212)	C_6H_4-p-COOH	199)
$(CH_2)_4CH(CH_2)_2C=O$	212)	C_6H_4-p-CH_2OH	199)
$COCH_2CH_2COOH$	212)	C_6H_4-p-CH_2Br	199)
$NHNH_2$	213)	C_6H_4-p-CH_2OEt	199)
$NHCH_2CN$	213)	C_6H_4-p-$CH_2CH_2C_6H_4$-p-Ad	199)
$NHCH_2COOH$	213)	$CH_2C_6H_5$	199)
$N(NO)CH_2COOH$	213)	$CH_2C_6H_4$-p-NO_2	199)
$CH_2CH_2CH_3$	203)	$CH_2C_6H_4$-p-NH_2	199)
$(CH_2)_3CH_3$	203, 211)	$CH_2C_6H_4$-p-Br	199)
$CH(CH_3)CH_2CH_3$	211)	$C(CH_3)CH_2CO_2Et$ | OH	218)
$NHCOOCH_2CCl_3$	214)		
C_6H_4-p-NH_2	198)	$C(CH_3)CH_2CH_2OH$ | OH	218)
C_6H_4-p-Br	198)		
C_6H_4-m-Br	198)		
C_6H_4-m-CH_3	198)	CH=C=CHCl	351)

Table 8 (continued)

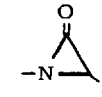
1-Substituent	Ref.	1-Substituent	Ref.
$NHCOC_6H_5$	352)	CH_2CCHCH_2Ad (O, OH)	221)
$NHCOCH_2C_6H_5$	352)		
$NHCSNHCH_2C_6H_5$	353)	$CH_2CCH_2CH_2Ad$ (O)	221)
$COC{=}N{-}C(Ad)(CH_3){=}CH{-}NH$	370)	$CH_2CH_2CH_2CH_2Ad$	221)
$N{-}C(CH_3){=}N{-}N{=}N$	371)	$CH{=}CH_2$	222)
$CH_3C(=CHCO_2Et)CH_3$	218)	SH	223)
$CH_3C(=CHCH_2OH)CH_3$	218)	OCH_2CO_2H	224)
$CH(CH_3)CH_2CH_2OH$	218)		225)
$CH(CH_3)CH_2CH_2Br$	218)	CHO	226, 227, 228)
$CBr(CH_3)CH_2CH_2Br$	218)	CH_2CHO	99, 227)
$COCH_2CH_2N(CH_3)_2$	218)	CH_2CH_2CHO	227)
OCH_3	51)	$POCl_2$	229)
$CH_2CH_2CH(CO_2Et)_2$	219)	$PO(OH)_2$	229)
$CH_2CH_2C(CO_2Et)_2(CH_2CH_3)$	219)	PH_2	229)
$CH_2CH_2CH(CO_2H)CH_2CH_3$	219)	N_3	230)
$CH_3C(=CHCH_2CHAc)CO_2Et$	220)	$OCH_2CH_2NH_2$	231)
$CH_3C(=CHCH_2CH_2Ac)$	220)	$CH_2CH_2CONHC_6H_5$	232)
$CH_3C(=CHCH_2C(CH_3)=CHCO_2Et)$	220)	CH_2NCO	232)
		CH_2CONH_2	232)
		$COCH_2Br$	233)
		CH_2COCH_2Br	233)
		SOCl	234)
		SO_2CH_3	234)
		SO_2OCH_3	234)
		$SON(CH_3)_2$	234)
		SCH_2CH_3	234)
		SO_2H	234)
		COCHO	235)
		$CH(OEt)_2$	236)
		$CH{=}C{=}O$	261)

Table 9. *1,3-Disubstituted adamantanes* (see also Ref. [4]).

1-Substituent	3-Substituent	Ref.
CH_3	CHClCOOH	193)
CH_2COOH	CHClCOOH	193)
OH	OCH_2CH_3	237)

Table 9 (continued)

1-Substituent	3-Substituent	Ref.
OH	SCH_2CH_3	237)
OH	Cl	237)
OH	$NHCOCH_3$	237)
OH	NH_2	237)
OH		237)
CH_2Br	Br	238)
CH_2HgOAc	OH	238)
CH_3	OCH_3	237, 238)
CH_3	Cl	238)
CH_3	C_6H_4-p-OCH_3	237, 238)
OH	CH_3	239)
OH	CH_2CH_3	239)
OH	$CH_2CH_2CH_3$	239)
OH	$CH(CH_3)_2$	239)
OH	$CH_2CH_2CH_2CH_3$	239)
Br	CH_2COOH	192)
OH	CH_2COOH	192)
CH_3	OAc	192)
CH_3	CH_2CH_3	240)
CH_2Br	Br	241)
CH_2Br	COOH	241)
CH_2Br	CH_2OH	241)
COOH	C_6H_4-p-NO_2	199)
CH_2OH	C_6H_4-p-NO_2	242)
CH_2Br	C_6H_4-p-NO_2	242)
CH_3	C_6H_5	242)
CH_3	C_6H_4-p-NO_2	242)
Br	C_6H_4-p-NO_2	199)
COOH	C_6H_4-p-NO_2	199)
CH_3	Cl	243)
CH_3	NHAc	243)
COOH	NHAc	243)
F	$NHCOOCH_3$	243)
F	$CONH_2$	243)
Cl	$CONH_2$	243)
Cl	$NHCOOCH_3$	243)
NH_2	Br	244)
$NHCH_3$	Br	244)
$N(CH_3)_2$	Br	244)
CH_3	$CH=CH_2$	222)
CH_3	CHO	226, 228)
OCH_3	CHO	228)
C_6H_5	CHO	228)
Cl	CHO	228)
Cl	CH_2CH_3	245)

Table 9 (continued)

1-Substituent	3-Substituent	Ref.
Br	Br	246)
F	CH_3	176)
Cl	Cl	234)
I	I	134)
C_6H_5	COOH	246a)
C_6H_5	CH_2OH	246a)
C_6H_5	CH_2Br	246a)
Br	CH_2Br	246a)
OH	CH_2Br	246a)
Cl	CH_2Br	246a)
CH_2COOH	CH_2Br	246a)

Table 10. *1,3,5-Trisubstituted adamantanes* (see also Ref. [4])

1-Substituent	3-Substituent	5-Substituent	Ref.
CH_3	CH_3	CHClCOOH	193)
CH_3	CH_3	CH_2COOH	192)
CH_3	CH_3	CH_2CH_3	13, 14)
CH_3	CH_2CH_3	COOH	241, 247)
CH_3	CH_2Br	COOH	247)
CH_3	Br	CH_2COOH	192)
CH_3	OH	CH_2COOH	192)
OH	OH	CH_3	253)
OH	OH	C_2H_5	253)
CH_3	CH_3	OH	239, 253)
CH_3	CH_2COOH	CH_2COOH	192)
CH_3	CH_2CH_3	Br	241)
CH_3	CH_2Br	Br	241)
CH_3	CH_2CH_3	CH_2OH	247)
CH_3	CH_2CH_3	CH_2Br	247)
CH_3	Br	CO_2H	248)
CH_3	NHAc	COOH	248)
CH_3	CH_3	$CH=CH_2$	222)
CH_3	CH_3	F	176)
Cl	Cl	Cl	234)

Table 11. *1,3,5,7-Tetrasubstituted adamantanes* (see also Ref. [4])

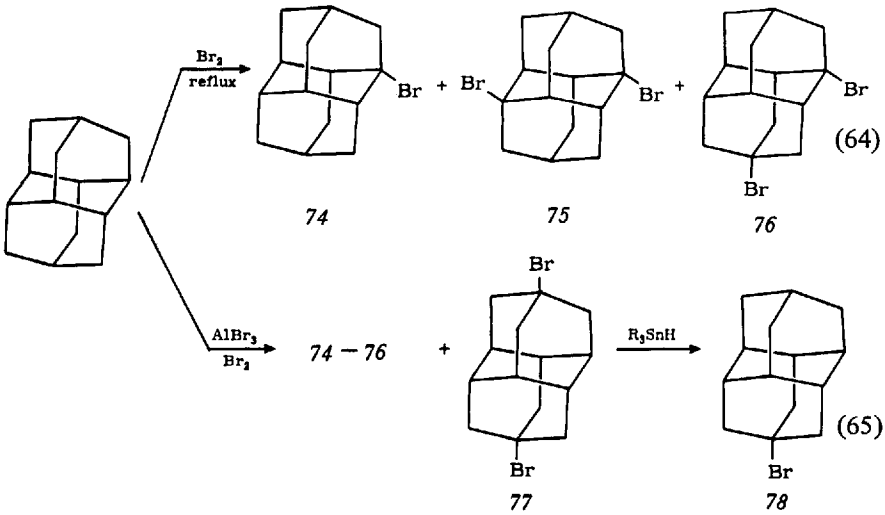
1-Substituent	3-Substituent	5-Substituent	7-Substituent	Ref.
CH_3	CH_3	CH_3	NH_2	249)
CH_3	CH_3	CH_3	OH	249)
CH_3	CH_3	CH_3	$OCONH_2$	249)
CH_3	CH_3	CH_3	SH	249)
CH_3	CH_3	CH_3	$CONH_2$	249)
CH_3	CH_3	CHClCOOH	CHClCOOH	193)
CH_3	CH_3	CH_3	CHClCOOH	193)
CH_3	CH_3	CH_2COOH	CHClCOOH	193)
CH_3	CH_3	CH_3	CH_2COOH	192)
CH_3	CH_3	CH_3	CH_2CH_3	25)
CH_3	CH_3	CH_3	OH	239,253)
OH	OH	OH	OH	250)
OAc	OAc	OAc	OAc	250)
OCOEt	OCOEt	OCOEt	OCOEt	250)
C_6H_5	C_6H_5	C_6H_5	C_6H_5	250)
C_6H_{11}	C_6H_{11}	C_6H_{11}	C_6H_{11}	250)
$CONH_2$	$CONH_2$	$CONH_2$	$CONH_2$	250)
NH_2	NH_2	NH_2	NH_2	250)
CH_3	CH_3	COOH	COOH	251)
CH_3	CH_2CH_3	CH_2Br	COOH	247)
CH_3	CH_3	OH	OH	251,253)
CH_3	CH_3	Br	Br	251)
CH_3	CH_3	Br	CH_2COOH	192)
CH_3	CH_3	OH	CH_2COOH	192)
CH_3	CH_3	CH_3	OAc	192)
CH_3	CH_3	CH_2COOH	CH_2COOH	192)
CH_3	CH_2CH_3	CH_2Br	Br	247)
CH_3	CH_3	Br	COOH	248)
CH_3	CH_3	NHAc	COOH	248)
CH_3	CH_3	CH_3	$CH=CH_2$	222)
D	D	D	D	252)
D	D	D	OH	40)
CH_3	CH_3	CH_3	CH_2CHO	99)
CH_3	CH_3	CH_2CHO	CH_2CHO	99)
CH_3	CH_3	CH_3	CHO	226)
CH_3	CH_3	NH_2	NH_2	254)
n-Pr	CH_3	CH_3	OH	253)
COOH	CH_3	CH_3	OH	253)
CH_3	CH_3	OH	OH	253)
CH_3	C_2H_5	OH	OH	253)

Table 12. *2-Substituted adamantanes* (see also Ref. [4])

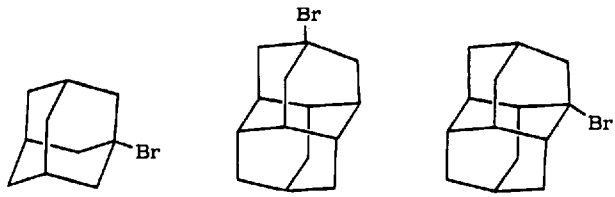
X-Substituent	Y-Substituent	Ref.
H	COOH	57, 70, 71)
H	$COOCH_3$	71, 206)
H	CH_2OH	71, 258)
H	Br	211, 255, 256)
H	I	255)
H	F	256)
H	Cl	255, 256)
H	OAc	255)
H	OCH_3	255)
H	C_6H_5	255)
H	C_6H_4-p-CH_3	255)
H	C_6H_4-p-OCH_3	255)
H	CH_2CH_3	257)
H	$CH_2CH_2CH_3$	257)
H	$(CH_2)_3CH_3$	211, 257)
H	$CH_2CH(CH_3)_2$	257)
H	$C(CH_3)_2OH$	71, 204)
H	$CH(CH_3)_2$	71)
H	$COCH_3$	71)
Br	Br	264)
Cl	Cl	264)
CH_3	COOH	57, 264)
OH	CH_2CH_3	208, 257)
OH	$(CH_2)_2CH_3$	257)
OH	$(CH_2)_3CH_3$	211, 257)
OH	$CH(CH_3)_2$	208)
OH	$C(CH_3)_3$	208)
OH	$CH_2CH(CH_3)_2$	257)
H	$CH(CH_3)CH_2CH_3$	211)
H	$C(CH_3)_3$	204)
CH_3	CH_3	204)
SH	OEt	259)
H	SH	259)
H	CH_2COOH	260)
H	CHO	260)
H	CH=C=O	260)
CH_2CN	CN	260a)
$CH_2CO_2CH_3$	CO_2CH_3	260a)
X = Y =	= 2–Ad	263)
X = Y =	= S	259)
X = Y =	= C = O	261)
X = Y =	= 2-Ad	262)
X = Y =	= C = 2-Ad	262)
X = Y =	$=CHCH_3$	257)
X = Y =	$=CHCH_2CH_3$	257)
X = Y =	$=CHCH(CH_3)_2$	257)

By analogy with adamantane, direct, ionic substitution reactions may be expected to be equally as effective for the synthesis of derivatives of other diamondoid hydrocarbons (*e.g.* diamantane and triamantane). In these cases, however, a larger number of isomers are possible. Diamantane has one methylene and two nonequivalent bridgehead positions while triamantane has four of each.

Preliminary results confirm the expected utility of direct ionic substitution reations for the preparation of *derivatives of diamantane.* In refluxing bromine, diamantane gives 1-bromodiamantane *(74)* [265] as well as a variety of disubstituted bridgehead bromides (Eq. (64)) [266]. If, on the other hand, the reaction is carried out in the presence of $AlBr_3$, significant amounts of 4,9-dibromodiamantane, *77*, are also observed (Eq. (65) [265]. Treatment of this dibromide with one equivalent of trialkyltin hydride yields the 4-monosubstituted diamantane, *78*.



The relative solvolysis rate constants of 1-bromoadamantane, *74*, and *76* explain this behavior [266]:



k_{rel} (solvolysis) 1 $1/_3$ 7

In the absence of $AlBr_3$, the kinetic product is the 1-bromide, *74*. Further bromination, if it occurs, takes place at the most remote bridgehead positions available to give *75* and *76*. When $AlBr_3$ is present in the reaction mixture, characteristically decreased selectivity is observed (see also Section II.B). Bromination at the 4-position is able to compete effectively and *77* is obtained as one of the bromination products.

Methylene substituted diamantanes are also obtained in a manner analogous to that employed for adamantane. Treatment of diamantane with concentrated sulfuric acid gives good yields of diamantanone [265].

As with adamantane itself, once functionalization has been achieved at a given position, other derivatives may be readily prepared by conventional procedures [265].

Direct substitution reactions of other diamonoid hydrocarbons have not been studied extensively. Triamantane, for example, remains relatively unavailable at this time. Moreover, the low symmetry of this molecule discourages attempts to prepare triamantane derivatives by direct substitution. The highly selective ionic reactions would most certainly not give all possible isomers. Less selective substitutions (*e.g.* free radical, see below), on the other hand, might enable the preparation of most isomers but separation of the product mixtures would undoubtedly be extremely tedious.

Similar symmetry problems confront the substitution reactions of other systems, *e.g.* noradamantane, homoadamantane and ethanoadamantane. Noradamantane, for example, may be brominated when treated with bromine under vigorous conditions but a difficult to separate mixture of bromides results [72]. At the present time, derivatives of noradamantane (see also Scheme 8), homoadamantane, and related systems are most readily obtained by more indirect methods as discussed in Section III. Bromination of ethanoadamantane *(25)* gives a single monobromide, however [38b].

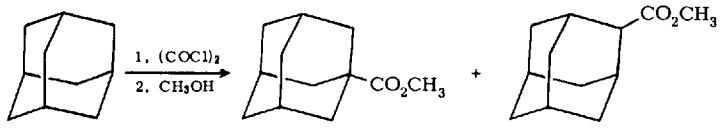
2. Free Radical Reactions

In contrast to the highly 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. The complex product mixtures which result, however, are generally difficult to separate. Consequently, there are few examples of the synthesis of specific derivatives of diamonoid hydrocarbons by this method.

For adamantane itself, statistically corrected tertiary/secondary ratios of 2-6 are commonly observed for free radical initiated hydrogen abstractions [206,268-272]. For example, *photochlorination* of adamantane in CCl_4 gives 37 % 1-chloroadamantane and 73 % of the secondary isomer [268]. Due to the decreased

symmetry of substituted adamantanes, free radical substitutions of these substrates gives rise to even more complex product mixtures [270–272].

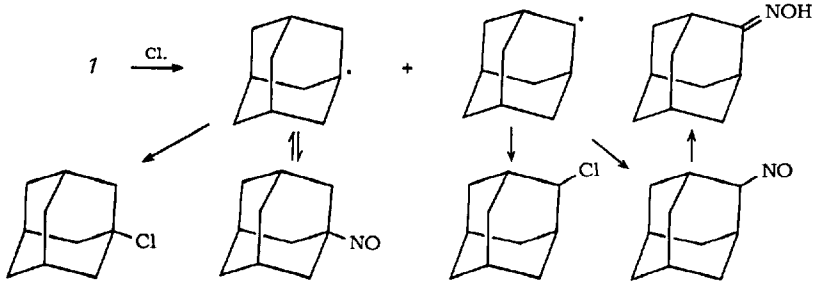
Occasionally, special circumstances permit a simple separation of the products which result from such free radical substitutions. Thus, *chlorocarbonylation* of adamantane followed by a methanolic work-up (Eq. (66)) results in a nearly 1 : 1 ratio of 1- and 2-methyl adamantane carboxylates which may be separated readily by fractional distillation [206].



(66)

Adamantanone oxime may also be isolated easily from the *photooximation* of adamantane [273]. The reaction involves the photolysis of a solution of adamantane in CCl_4 through which is bubbled Cl_2, NO and HCl gases. Scheme 18 summarizes the basic course of the reaction [275]. The adamantanone oxime, which is protonated in the acid solution, precipitates from the reaction mixture.

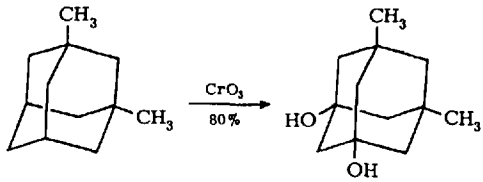
Scheme 18



The reported [273] yield of adamantanone oxime from this reaction (63 %) is misleading since it is based on Cl_2 as the limiting reagent. Careful product analyses have shown that the overall ratio of tertiary to secondary substitution products (~2) is quite normal [275]. While this reaction is clearly much less useful for the preparation of methylene substituted adamantanes than the ionic processes discussed above, it may be applicable in more specialized cases such as, for example, the synthesis of polyalkylsubstituted adamantanones where the ionic processes work poorly.

Chromic acid oxidation is a third synthetically useful free radical or, at least, free radical-like reaction for the substitution of diamonoid hydrocarbons. While

the transition state of chromic acid-alkane oxidation is believed to be closest to free radical in character [276], bridgehead oxidation of adamantane and alkyl-substituted adamantanes predominates to a much greater extent than is observed for typical free radical processes. Thus, reaction of adamantane with CrO_3 in acetic acid-acetic anhydride solvent gives mainly 1-adamantanol (71 %). Only a 9 % yield of adamantanone is obtained [277]. More recent studies confirm this result [253]. In addition, if excess oxidant is employed, good yields of 1,3-diols can be obtained (*e.g.* Eq. (67)) [253]. The greater selectivity of these



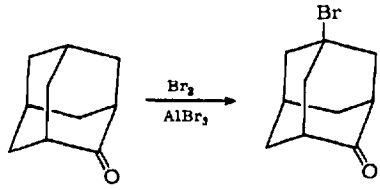
(67)

oxidations relative to typical free radical processes may be due to significant ionic character in the oxidation transition states [277].

3. Special Techniques: 1,2-, 1,4-, 2,4- and 2,6-Disubstituted Adamantanes

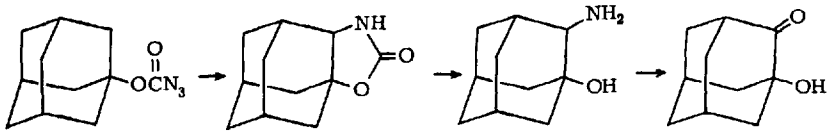
While the preparation of bridgehead (mono-, di-, etc.) and methylene substituted adamantanes is extremely easy, polysubstituted adamantanes in which one of the substituents is at a methylene position are much less readily prepared. In general, special techniques must be developed for each specific substitution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

2-Substituted adamantanes 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 $AlBr_3$ for 10 days gives 5-bromo-2-adamantanone in 90 % yield (Eq. (68)) [278]. As indicated preciously, the sulfuric acid reaction of 2-adamantanol gives analogous results (see Eq. (59)) [197].



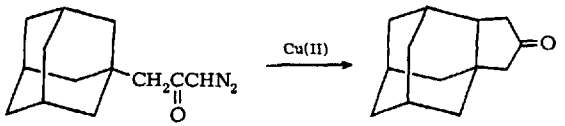
(68)

1,2-Disubstituted adamantanes are most frequently obtained from internal cyclization reactions of a bridgehead substituent. Thus, photolysis of the azidoformate *79* gives *80* by nitrene insertion [279]. *80* may be readily hydrolyzed to 2-amino-1-adamantanol *(81)* [75]. Subsequent oxidation gives 1-hydroxy-2-adamantanone *(82)* from which other derivatives may be prepared [280, 281]. An analogous carbene insertion is initiated by the thermal decomposition of the



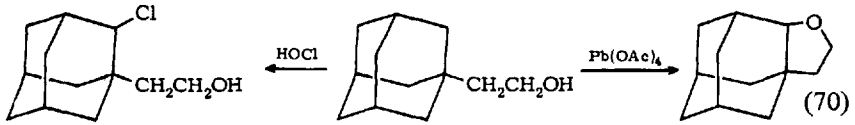
79 *80* *81* *82*

diazo-ketone, *83* (Eq. (69)) [282].



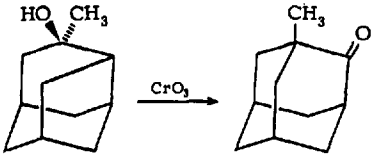
(69)

Similar internal cyclizations occur when 2- (1-adamantyl)-ethanol is treated with lead tetraacetate to give the cyclic ether *83* [217, 283] or with HOCl to give *84* (Eq. (70)) [283]. These reactions apparently involve hydrogen abstractions by the initially formed alkoxy radical.



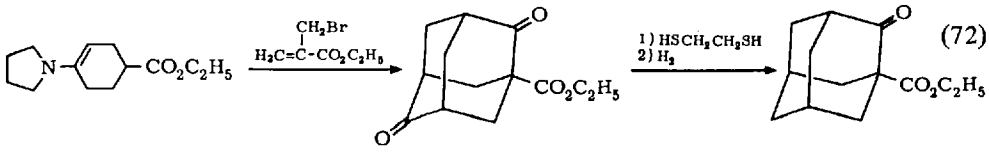
84 *83* (70)

Rearrangements of substituted protoadamantyl derivatives (see Section III.A) also appear to provide attractive routes to 1,2-disubstituted adamantanes. This is illustrated by the acid catalyzed rearrangement of the isomeric 4-methyl-4-protoadamantanols to 1-methyl-2-adamantanone in near quantitative yield (Eq. (71)) [42, 76].



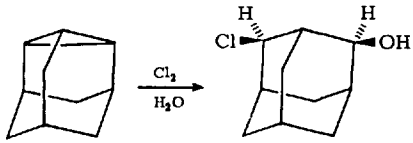
(71)

Direct synthesis of the adamantane skeleton itself also provides a route to 1,2-disubstituted adamantanes. This approach is illustrated in Eq. (72) [284].



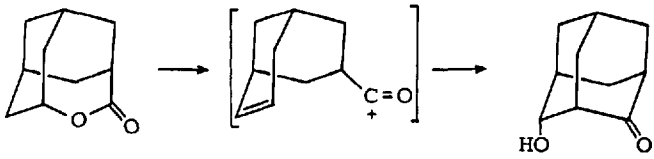
(72)

2,4-disubstituted adamantanes may be prepared by three general methods. The first involves electrophilic additions to 2,4-dehydroadamantane [255] and to protoadamantene [267]. Although, in principle, several different stereoisomers for each different 2,4-disubstituted adamantane are possible from these reactions stereospecific addition is observed in many cases. Eq. (73) provides an illustrative example [255].



(73)

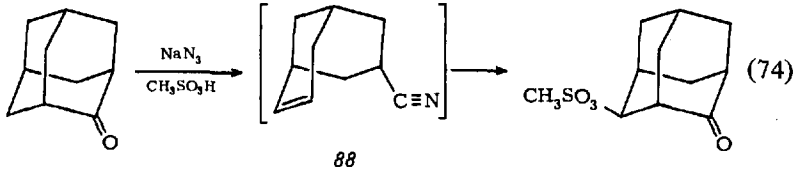
The second route to 2,4-disubstituted adamantanes involves a π-route ring closure of substituted bicyclo[3.3.1]nonenes. Thus, lactone *85* [285] rearranges in 50 % sulfuric acid to 4-hydroxy-2-adamantanone *(86) via* the acylium ion *87* [278]. Adamantanone oxime rearranges in 96 % sulfuric acid to *86* (mixture of isomers) in an analogous manner [109]. Similarly, the Schmidt reaction of



85 *87* *86*

adamantanone results in the overall formation of 4-methanesulfonyl-2-adamantanone [110] presumably *via* the unsaturated nitrile *88* (Eq. (74)) [109, 278]. It is interesting to note that the stereochemistry of the mesylate product is opposite to that observed for *86* [278]. The reason for this conflicting behavior is not clear.

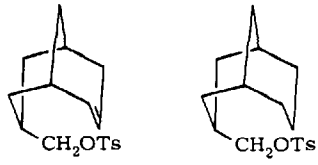
The driving force for these π-route ring closures is large. In 80 % acetone, the solvolysis of the unsaturated tosylate *89* is 10^4 times faster than that of the sa-



(74)

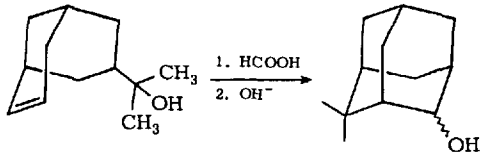
88

turated analogue *90*. Only 2-adamantyl products are observed from the solvolysis of *89* [287].



89 *90*

Clearly, many extensions of these π-route cyclizations should be possible for the convenient synthesis of a variety of 2,4-disubstituted adamantanes. An illustrative example is provided by the rearrangement of the alcohol *91* to 2,2-dimethyl-4-adamantanol (Eq. (75))[278].

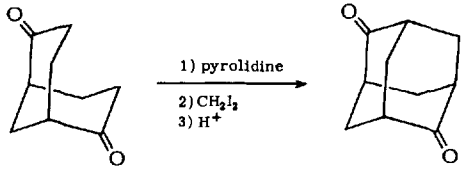


(75)

91

Direct synthesis provides a third route for the preparation of 2,4-disubstituted adamantanes. A wide variety of optically active β-substituted adamantanones have been prepared in this manner [180–185].

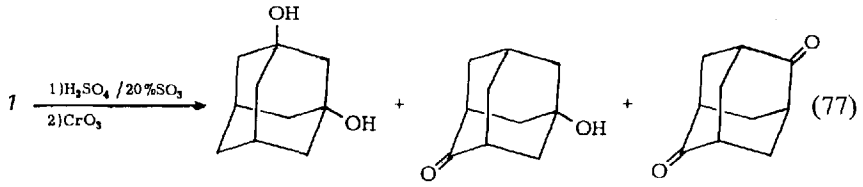
Finally, *2,6-disubstituted adamantanes* may be obtained either by direct synthesis or as minor components of specific ionic substitution reactions. Treatment of 2,6-bicyclo[3.3.1]nonanedione with pyrolidine and methylene iodide followed by acid hydrolysis provides pure 2,6-adamantanedione *(42)* in an overall yield of approximately 20 % (Eq. (76)) [288].



(76)

92

The fuming sulfuric acid reaction of adamantane followed by chromic acid oxidation has also been found to produce small amounts of *92* (Eq. (77)) which may be isolated by column chromatography [289].



(77)

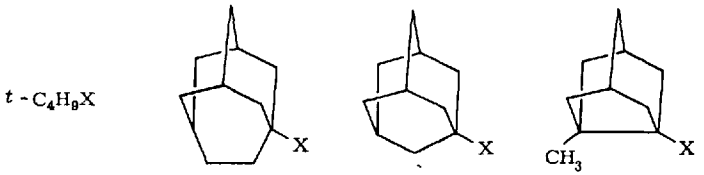
92

B. Physical Organic Chemical Applications

1. Carbonium Ion Chemistry

Derivatives of polycyclic hydrocarbons have played a central role in the development of physical organic chemistry [290]. Polycyclic substrates have been found to be ideal models for numerous quantitative investigatious since their conformations are generally rigid and fixed and since they provide a large variation in structural types. Recent, comprehensive reviews of bridgehead reactivity are available [187, 291].

Early work in the area of physical organic chemistry revealed that the *bridgehead positions* of many polycyclic hydrocarbons are unusually inert to solvolysis and to nucleophilic attack [187]. It is now realized that the solvolytic reactivities of bridgehead derivatives of a variety of polycyclic hydrocarbons vary widely. This is illustrated below for the adamantane family. The reactivities range from 3-homoadamantyl *(93)*, the reactivity of which is nearly the same as that found for typical tertiary acyclic analogues (*e.g.* *t*-butyl), to 7-methyl-3-noradamantyl *(94)* [36, 95, 105, 187].



93 *94*

Approximate rel. rates[36]	1.0	0.5	10^{-3}	10^{-11}

These variations in the ease of formation of bridgehead cations are attributed to steric effects [95, 105, 187]. Carbonium ions prefer planarity strongly [187, 292].

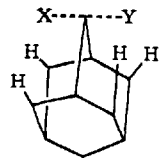
The bridgehead positions of polycyclic substrates inhibit cation planarity to varying degrees. Employing computer conformational analysis to estimate enthalpy differences between ground states and transition states (the strain energy differences between hydrocarbons and the corresponding carbonium ions are actually calculated), bridgehead solvolytic reactivities which vary by nearly eighteen powers of ten are correlated satisfactorily [95, 105, 293].

Since the solvolysis reactions of bridgehead substrates are mechanistically uncomplicated (*i.e.* competing elimination is highly unlikely [187, 115-119] and backside solvent participation is impossible), they provide ideal models for limiting *carbonium ion behavior*. Adamantyl derivatives have become the substrates of choice for this purpose due to their availability and convenient reactivity.

In order to access the role of solvent in solvolyses of *t*-butyl chloride, the reference compound originally chosen for the evalution of *solvent ionizing power* in the absence of solvent nucleophilicity [294], rate constants for solvolysis of 1-adamantyl bromide [62] and 1-adamantyl tosylate [295] in a variety of solvents have been determined. In general, an excellent correlation between data for *t*-butyl chloride and the 1-adamantyl derivatives is found suggesting that both compounds solvolyze by highly similar mechanisms in most solvents. Conclusive evidence indicating that t-butyl chloride solvolyzes by a limiting mechanism, free from nucleophilic solvent participation and from rate determining elimination is therefore provided. As a corollary, nothing intrinsically "unusual" is indicated for the solvolysis of bridgehead compounds [62, 295].

In contrast to typical mono- or acyclic substrates (*e. g.*,isopropyl), 2-adamantyl derivatives are also found to be insensitive to changes in solvent nucleophilicity. A variety of criteria, summarized in Table 13, establish this point. In all cases, the behavior of 2-adamantyl tosylate is comparable to that observed for its tertiary isomer but quite unlike that observed for the isopropyl derivative. Significant nucleophilic solvent participation is indicated in the solvolysis reactions of the isopropyl system. The 2-adamantyl system, on the other hand, appears to be a unique case of limiting solvolysis in a secondary substrate [296]. The ^{k}2-adamantyl/^{k} isopropyl ratios in various solvents therefore provide a measure of the minimum rate enhancement due to nucleophilic solvent assistance in the isopropyl system [297].

The limiting nature of the solvolysis reactions of 2-adamantyl solvolyses apparently arises as a result of steric inhibition of rearside nucleophilic solvent participation by the axial hydrogens shown in *95*. Such steric effects are absent



95

Table 13. *Summary of mechanistic criteria for solvolysis* [a].

Compound	m [b] aq. EtOH	$(k_{EtOH}/k_{AcOH})Y$ [b]	k_{OTs}/k_{Br} [c] 80 % EtOH	k_{CH_3}/k_H [d] Bromides 80 % EtOH	Retention [e] Inversion Ratios	Azide Rate-Product Correlation [h]
1-Adamantyl tosylate	0.99	0.16	9750		(0.8-1.2) [f]	no [i]
2-Adamantyl tosylate	0.91	0.13	231	$10^{7.5}$	2 – 5	no
Isopropyl tosylate	0.42	7.8	40	$10^{3.7}$	<0.05 [g]	yes

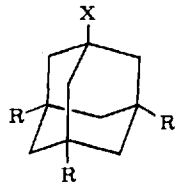
a) Unless otherweise noted all data taken from Ref. [296].
b) See Ref. [294] and [296].
c) See Hoffmann, H. M. R.: J. Chem. Soc. 6748, 6753, 6762 (1965).
We are of the opinion that the mechanistic significance of these ratios is limited (see Ref. [95]). We attribute the very high tertiary value to relief of ground-state tosylate nonbonded strain which is not present when bromide is used as the leaving group.
d) Ref. [55] and references cited therein.
e) Bone, J. A., Whiting, M. C.: Chem. Commun. 115 (1970) and references cited therein.
f) Typical values for tertiary substrates.
g) Typical values for secondary acyclic substrates.
h) Harris, J. M., Raber, D. J., Hall, R. E., Schleyer, P. v. R.: J. Am. Chem. Soc. *92*, 5729 (1970).
i) Determined for 1-adamantyl bromide.

in typical acyclic secondary substrates. Significant rate enhancement due to nucleophilic solvent participation is possible in these cases [296].

The rigid, fixed conformation of the adamantane nucleus also makes investigations of *substituent effects* on 1-adamantyl solvolyses particularly instructive. The most intriguing effect produced by substituents at the remaining bridgehead positions of the 1-adamantyl system is the unexpected decrease in reactivity of 3-methyl-1-bromoadamantane relative to the parent compound. This effect appears to be general. Each successive methyl group added to the bridgehead positions of 1-bromoadamantane reduces the rate by approximately two-thirds. Other alkyl groups, however, display the normal inductive order (*i.e.*, methyl < ethyl < *i*-propyl < *t*-butyl) [56, 164, 298, 299].

Qualitatively, the methyl substituent appears to be electron withdrawing with respect to hydrogen in 1-adamantyl solvolyses. This interpretation is also encouraged by the measured dipole moments of various adamantane derivatives [300] presented in Table 14 (*cf.* the dipole moment of propane) [301] and by the methyl

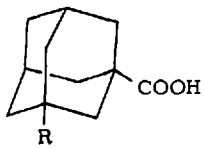
Table 14. *Dipole moments of adamantane derivatives* [300]



X	R	μ(D)
Br	H	2.61
Br	CH_3	2.55
CN	H	3.99
CN	CH_3	3.94

induced substituent chemical shift in the ^{19}F nmr of 3-methyl-1-fluoroadamantane (see Section IV.C) [176–177]. On the other hand, the acidities of alkyl substituted adamantane carboxylic acids (Table 15) suggest that in this case methyl is more electropositive than hydrogen [302]. A variety of other cases of the divergent inductive effect of remote methyl substituents in saturated systems are known [298, 299].

Table 15. *Acidities of alkyl substituted adamantane carboxylic acids* (see also Ref.[4])



R	pKa
H	6.78
CH_3	6.88
CH_2CH_3	6.95
$CH(CH_3)_2$	7.02

If one extends the series of 3-substituted adamantanes to include several more polar substituents a possible explanation for the apparent inconsistent behavior of the methyl substituent, at least in the adamantyl system, is suggested. Fig. 4 illustrates the decrease in the solvolytic reactivity of 3-substituted-1-adamantyl

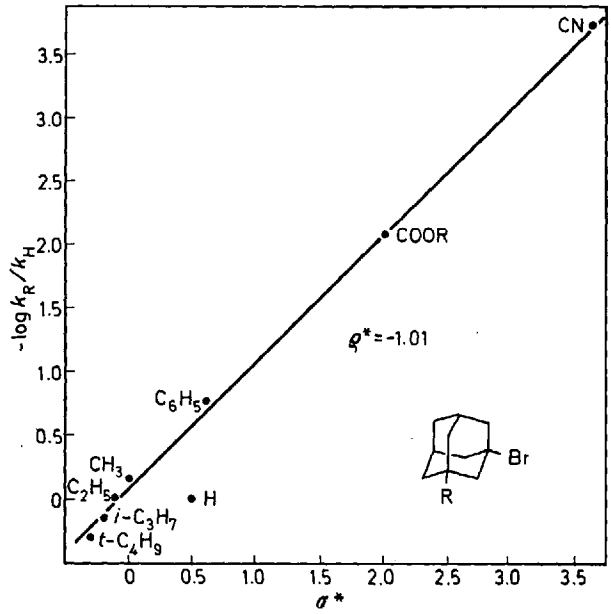
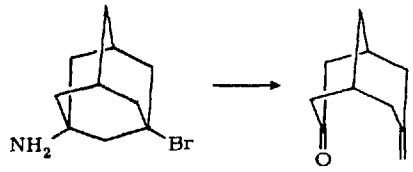


Fig. 4. Negative log of the relative solvolysis rate constants of 3-substituted adamantyl bromides in 80 % ethanol at 75 °C plotted against σ^*. (Reproduced from Ref. [299]).

bromides with an increase in substituent electronegativity as measured by σ^* [298, 299]. The electronic effect of the methyl substituent is found to be normal when treated in this manner. The parent compound is the one which deviates from the expected inductive order.

A substituent induced structural perturbation may be the source of this deviation. Replacement of hydrogen by methyl may produce a small but significant change in geometry which is reflected in the solvolysis rates, by the ^{19}F chemical shifts [176] and by the dipole moments of adamantyl derivatives. The effect is less pronounced in the case of the carboxylic acid pKa's where the reaction site is farther removed from the adamantyl nucleus. In this case, electronic effects may dominate [298, 299]. Perhaps it would be best to consider alkyl groups as being polarizable substituents rather than having a fixed electron withdrawing or releasing character relative to hydrogen.

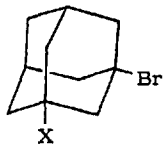
Other substituents, *e. g.* amino, have been found to induce *fragmentation of the adamantyl nucleus.* Quantitative studies of the solvolysis of aminosubstituted adamantyl bromides (Table16) suggest that fragmentation occurs simultaneously with ionization. The common product from each of the aminobromoadamantanes in Table 16 is 3-keto-7-methylenebicyclo[3.3.1]nonane (*e.g.* Eq. (78)) [303].



(78)

As indicated in Table 16, the amino substituted adamantyl bromide solvolyses are significantly enhanced relative to the corresponding alkyl substituted adamantyl bromides. The effect is even more dramatic when one recalls that the σ_I substituent paramter for -N $(CH_3)_2$ and -C_6H_5 are nearly identical [304]. The solvolysis rate of 3-phenyl-1-bromoadamantane [298] is nearly 10^4 times slower than that of 3-dimethylamino-1-bromoadamantane [303] at 50 °C, however.

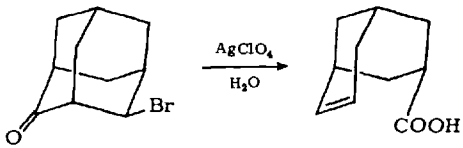
Table 16. *Solvolysis of aminobromoadamantanes* [303]



X =	k, sec $^{-1}$ 80 % EtOH 50 °C	k_{amino}/k_{alkyl}
NH_2	3.14×10^{-4}	30
CH_3	1.04×10^{-5}	
$NHCH_3$	3.22×10^{-3}	222
CH_2CH_3	1.45×10^{-5}	
$N(CH_3)_2$	1.13×10^{-2}	520
$CH(CH_3)_2$	2.17×10^{-5}	

Similar fragmentation reactions are observed when the stereoelectronically favorable *W* conformation is present in 2,4-disubstituted adamantanes. Thus,

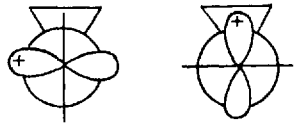
treatment of equatorial-4-bromo-2-adamantanone with aqueous $AgClO_4$ (Eq. (79)) results in the formation of *96* [285].



(79)

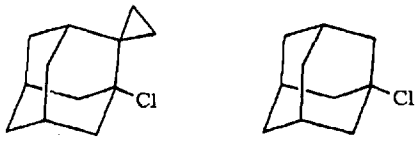
96

The rigid geometry of the adamantyl nucleus has also been utilized to quantitatively evaluate the stereoelectronic requirements of *cyclopropylcarbinyl cations*. The bisected conformation of the cyclopropyl cation, *97*, is known to be preferred strongly relative to the perpendicular conformation, *98* [280]. The adamantyl derivate *99* incorporates a cyclopropyl carbinyl system locked in the



97 *98*

unfavorable perpendicular *(98)* conformation. The solvolysis rate constant of *99* is found to be 10^3 times shower than 1-adamantyl chloride *(100)* itself [280].

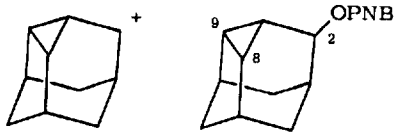


99 *100*

Similar results are obtained for the corresponding tosylates [281]. In conformationally nonrigid systems, on the other hand, where the preferred bisected *(97)* conformation may be adopted, cyclopropyl substituents enhance solvolysis rates by a factor of approximately 10^4 [305]. Therefore, a free energy difference between *97* and *98* of about 10 kcal/mole (1.36 log 10^7) may be estimated for tertiary cyclopropylcarbinyl cations at 25 °C [280].

The 8,9-dehydro-2-adamantyl cation *(101)* incorporates a cyclopropylcarbinyl system in the preferred bisected *(97)* conformation. As would be expected, then, 8,9-dehydro-2-adamantyl derivatives (*e.g. 102*) are highly

reactive solvolytically; *102* is estimated to be approximately 10^8 times more reactive than the corresponding 2-adamantyl derivative. During the solvolysis

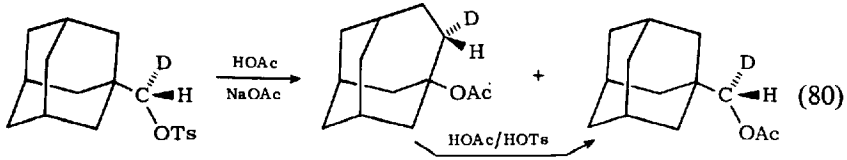


101 *102*

of *102*, carbons 2,8 and 9 become nearly equivalent by rapid equilibration, as indicated by deuterium scrambling results [82].

A final example of the utility of adamantyl substrates as model systems in mechanistic investigations is provided by 1-adamantylcarbinyl derivatives. Detailed product and rate constant determinations of 1-adamantylcarbinyl solvolyses have been interpreted relative to the mechanism of the solvolysis reactions of neopentyl systems in general.

As indicated previously (see Eq. (31)), 1-adamantylcarbinyl tosylate solvolyzes in buffered anhydrous acetic acid to give 3-homoadamantyl acetate (93 %) and 1-adamantylcarbinyl acetate (7 %) [96]. The acetolysis of chiral 1-adamantyl-1'-d tosylate *(103)* has been found to occur with complete retention of configuration in both products (Eq. (80)) [97]. This result suggests



103 (80)

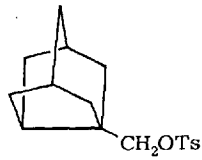
that free, primary carbonium ions are not involved in neopentyl solvolyses; a bridged ion intermediate is strongly implicated [97].

Surprisingly, a first order analysis of the solvolysis rate constants of 1-adamantylcarbinyl derivatives fails to reveal the involvement of a bridged ion intermediate. In terms of ring strain factors, the rearrangement of an adamantyl to a homoadamantyl system is an energetically unfavorable process. Therefore, a diminished driving force for the rearrangement of the 1-adamantylcarbinyl system relative to neopentyl itself might be anticipated. Experimentally, the 1-adamantalcarbinyl substrates are found to solvolyze slightly faster, not slower, than the corresponding neopentyl derivatives [96].

One possible explanation for this apparent discrepancy has been proposed [306]. While electrons in the C-C bonds adjacent to the developing electron

deficient center in both the adamantyl carbinyl and the neopentyl system drift toward the developing vacant orbital in their solvolysis transition states, movement of nuclei may be only slight. In other words, the stabilization of the neopentyl solvolysis transition states by the neighboring C-C bonds may be essentially hyperconjugative in nature [306, 307].

Attempts to correlate alicyclic neopentyl-like solvolysis rates with differences in strain energy between either starting material and product [308] or starting material and rearranged carbonium ion [309] have been moderately successful. In general, the rates of systems which solvolyze with overall strain relief are correlated well; others correlate poorly. The above arguments rationalize these results. Strain relief may not be the actual mechanism by which neopentyl solvolysis rates are enhanced. Instead, transition state energies may be controlled by the effectiveness of the overlap between the developing vacant orbital with the adjacent C-C σ-bonds. This overlap is better for the more highly strained systems since the p character of the C-C bonds in these systems is greater [307]. Thus, the hybridization of the "participating" C-C bonds may be the controlling factor. On this basis, since the p character of the C-C bonds in both neopentane and 1-methyladamantane should be nearly the same, similar solvolysis rates for the corresponding neopentyl and 1-adamantyl carbinyl derivatives would be expected. On the other hand, the more highly strained 3-noradamantylcarbinyl system *(104)*, with greater p character in the endocyclic C-C bonds relative to adamantane, should be expected to solvolyze at a faster rate, consistent with observations [36]. In actual fact, the seeming diffences between these "participation" and "hyperconjugation" explanations may be more apparent than real.



104

2. Free Radical Chemistry [309a]

Following the extensive investigation of bridgehead carbonium ion reactivities, which provides the most conclusive experimental evidence available for the preferred planarity of carbonium ions [187], similar studies of bridgehead free radical reactivity have been initiated. The results are equally instructive.

A variety of bridgehead free radical reactions, including aldehyde decarbonylations [310] and *t*-butyl perester [311] and diazo decompositions [312] of ada-

mantane and other cyclic and acyclic systems all lead to essentially the same conclusion: Free radical reactions are inhibited at carbocyclic bridgehead positions (*i.e.* free radicals prefer planarity), but to a lesser degree than carbonium ion processes [312, 313]. This is illustrated in Table 17 by the relative rates of *t*-butyl perester and azo decompositions.

Table 17. *Relative rates of t-butyl perester and azo decompositions*

R	k_{rel} [311] RCO_3-*t*-C_4H_9 cumeme, 65 °C	k_{rel} [312] R-N=N-R benzene, 300 °C
$(CH_3)_3C$	1.0	1.0
$(CH_3CH_2)_3C$	3.2	
1-adamantyl	1.2	4.0×10^{-4}
1-bicyclo[2.2.2]octyl	0.16	5.0×10^{-5}
1-norbornyl	1.3×10^{-3}	3.2×10^{-6}

In general, bridgehead free radical reactivities parallel those for the corresponding carbonium ions [311, 312]. The position of *t*-butyl in this scale is different for the *t*-butyl perester decompositions than it is for the corresponding azo reactions, however. On the basis of the rates of the *t*-butyl perester decompositions, the 1-adamantyl radical is slightly more stable than the *t*-butyl and only slightly destabilized relative to the triethylmethyl radicals [311]. The rates of the azo decompositions, on the other hand, suggest that the 1-adamantyl radical is much less stable than the *t*-butyl [312, 314]. This conflicting behavior has been attributed to a greater degree of bond breaking in the azo decompositions [312]. They would, therefore, be much more sensitive to ring strain than the *t*-butyl perester reactions.

Comparison of the cyclic systems in Table 17 leads to the opposite conclusion, however; the destabilization of the 1-norbornyl radical relative to the 1-adamantyl is less for the azo decompositions. Perhaps the mechanism of the azo decompositions of the more unreactive systems is different from that of, for example, the *t*-butyl azo compound (*i.e.* the rate determining step of the 1-norbornyl azo compound may be a one bond homolysis rather than the synchronous two bond fission of the *t*-butyl system [312, 315]). Also, the smaller 1-norbornyl/1-adamantyl rate ratio for the *t*-butyl perester decompositions may be due to a greater influence of polar effects in these reactions [309a]. This problem is under active investigation [309a].

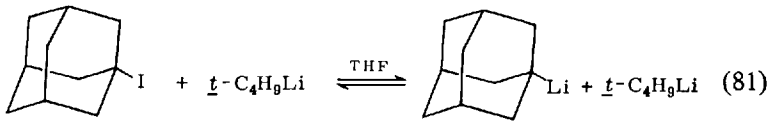
The relative selectivities of the 1- and 2-adamantyl radicals also suggest the preferred planarity of simple aliphatic radicals. While hydrogen abstraction from adamantane occurs preferrentially at the bridgehead position (see Sec-

tion V.A.2), the 2-adamantyl radical, once formed, is found to be more selective in product formation than is its tertiary isomer. Similar selectivity differences are observed for the Hunsdiecker reactions of 1- and 2-adamantane carboxylic acids. Thus, in contrast to the observed reactivity ratios for radical formation, relative selectivities in product formation suggest that the secondary and not the tertiary radical is more stable. The 2-adamantyl radical is free to become planar; a large structural change and energy difference between this radical and the transition state leading to it is possible. The 1-adamantyl radical, on the other hand, has a fixed nonplanar conformation; there is probably little difference in the structure and energy of this radical and the transition state leading to it. Apparently, the ability of the secondary radical to achieve a planar configuration allows it to be more stable, therefore more selective than its nonplanar tertiary isomer [269, 317].

Substituent effects on bridgehead hydrogen abstraction in adamantane [270] generally parallel those observed in the corresponding carbonium ion reactions [298] although the effect, as expected, is less pronounced. Thus p^* (using σ^* CH_2 parameters) for solvolysis of 3-substituted adamantyl bromides [298] is -2.70 compared with the value of -0.40 and -0.59 obtained for bridgehead adamantane hydrogen abstractions by the trichloromethyl radical [270] and bromine atom [271], respectively. It is interesting to note that the effect of methyl substitution on the free radical reactions is opposite to that observed in the carbonium ion process. In the free radical case, the expected electron donating effect of the methyl is observed suggesting that free radical reactions may be less sensitive to substituent induced structural perturbations (see Section V.B.1).

3. Carbanion Chemistry

Bridgehead adamantyl carbanions have been found to be quite elusive. Attempts to generate bridgehead organometallic derivatives of adamantane frequently result instead in the preparation of 1,1-biadamantane [318, 319]. 1-Adamantyl lithium may be obtained, however, by the exchange reaction illustrated in Eq. (81).

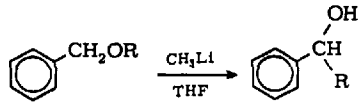


(81)

The position of the equilibrium of similar exchange reactions has been studied for a number of cyclic and acyclic systems [318, 320]. Although the

inherent stability of the carbanions involved in such reactions is somewhat difficult to extract from the data obtained due to solvation and metal organic association problems, the results suggest that 1-adamantyl and *t*-butyl lithium are of comparable stability and are somewhat less stable than 1-bicyclo[2.2.2]-octyl and 1-norbornyl lithium [187, 320].

This stability order has been used in a reevaluation of the mechanism of the Wittig rearrangement of alkyl benzyl ethers (Eq. (82)). The migration



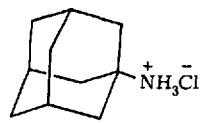
(82)

tendency of the R group has no relation to the stability of the corresponding alkyl lithium. For example, although 1-norbornyl lithium appears to be significantly more stable than the 1-adamantyl derivative, the norbornyl ether does not rearrange while the adamantyl ether gives 54 % of the rearranged carbinol. A cleavage-recombination mechanism involving radical pairs is proposed [320].

VI. 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* whereas the efficacy of other known drugs has been found to be significantly enhanced or modified in useful ways by the incorporation of an adamantane moiety.

Since the original discovery [321] that 1-adamantanamine-HCl *(105)* inhibits



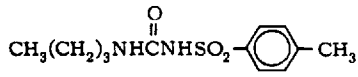
105

specific strains or influenza A, Al, A2 and C in tissue culture, chick embryos, and mice, the range of effectiveness of this drug has been considerably extended [322-324]. Similar antiviral activity has been found in man [324-327]. In addition to the A, Al, A2 and C strains of influenza which are most consistently affected [321, 328-333], other viruses such as rubella[334, 335], Rous[336, 337] and Esh[336], Sarcoma and parainfluenza [321, 328, 333] have also been reported to be sensitive in one or more test systems.

The effectivenes of *105* in the prevention of illness in man caused by *influenza A2 virus* led to its introduction as a prescription drug (Symmetrel, DuPont). A clinical test made on 850 human volunteers during an A2 (Asian) influenza epidemic found that the administration of the drug before detectable infection had occured resulted in an approximately fourfold decrease in the incidence of the disease relative to subjects receiving placebos [325, 327]. The symptomatic manifestations in those who were treated with the drug but did contract the illness were sharply decreased. More recent studies have found a similar decrease in the number and severity of cases [338-340], although a conflicting report has been published [341]. The drug, at least in mice, does not appear to affect antibody response to a great extent [330]. Hence, development of natural immunity should not be impaired [323].

The *mode of action* of this drug is not completely clear. It has been shown that virus absorbed to cells *in vitro* in the presence of *105* was susceptible to antibody inactivation several hours after infection whereas virus in a corresponding system free of *105* was not. This suggested that perhaps the drug did not inactivate the virus itself but prevented the penetration of the virus into the host cell [321]. Subsequent studies have supported this conclusion [342]. The manner in which cell penetration is prevented is not known. Perhaps *105* selectively binds to or in some way inhibits an enzyme essential for cell penetration or perhaps it acts by selectively binding the virus to areas of the cell wall which are not susceptible to penetration [342]. Other studies have also demonstrated a therapeutic effect of this drug [343].

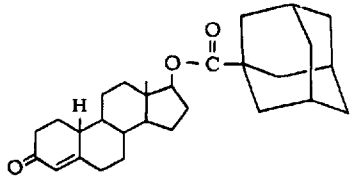
The enhanced efficacy of known drugs resulting from the introduction of an adamantyl moiety [344] is exemplified by the replacement of the butyl group of N-p-tolysulfonyl N-n-butylurea *(106)* by 1-adamantyl which results in a 15 fold increase in the *hypoglycemic activity* of the drug [345]. On the



106

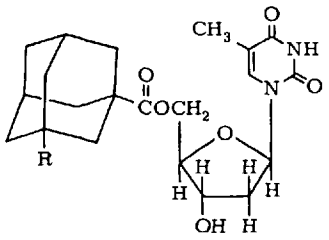
other hand, replacement of the butyl group by 3-methyl-, 3,5-dimethyl-, or 3,5,7-trimethyl-1-adamantyl reduces the usefulness of the drug.

Similar results are obtained when 19-nortestosterone and related androgens [346] as well as various nucleosides [347] are esterified with adamantane carboxylic acids. Whereas *107* exhibits a long duration of *myotropic activity* coupled with significantly reduced androgenicity, the 3-methyl and 3,5-di-



107

methyl-1-adamantyl analogues are much less potent [346]. Similarly, the *inhibition of antibody growth* by several nucleoside 5'-adamantoates (*e.g. 108* and *109*) is found to be markedly decreased when R=CH_3 relative to the parent compound (R=H).



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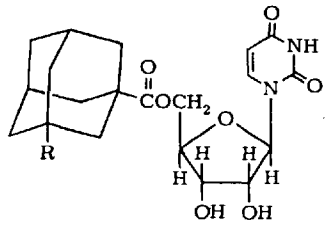
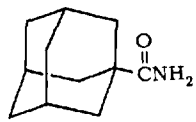


109

The pharmacological efficacy of adamantane derivatives may be attributed to several factors. The high *lipophilic character* associated with high molecular weight hydrocarbons appears to be coupled with a highly precise and specific donor-receptor interaction between adamantane and the receptor proteins. Addition of methyl groups to the adamantane nucleus apparently destroys the precision with which the adamantyl group fits into the receptor site [346, 347].

The structure-activity relationship is 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 *(110)* does result in a progressive increase in the sedative activity of the drug in mice [249].



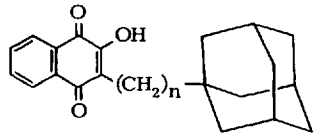
110

A second factor contributing to the pharmacological efficacy of adamantane derivatives may be the high resistance of the adamantane substrates toward *metabolic attack.* The prophylatic activity of *105* toward the A2 influenza virus is affected without metabolic degradation [349]. In man, 90 % of the drug has been recovered in the urine unchanged; 50 % is recovered in 24 hours. The long duration of the myotropic activity of *107* is attributed to the enhanced resistance of the adamantyl ester toward hydrolysis [346].

The resistance of adamantane derivatives toward metabolic degradation is apparently due to three factors. First, adamantane is an unnatural biological substrate. For this reason, enzymes have not been developed in man to specifically attack it. Second, common degradative routes such as elimination are blocked in the adamantane nucleus. Adamantene or the enol of adamanta-

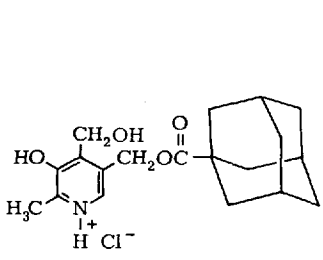
none should form only with extreme difficulty. Third, the adamantane moiety affords a high degree of steric hindrance.

It should be pointed out, however, that the pharmacological effects of adamantyl moieties are not general. The adamantyl substituted naphthoquinones, *111*, for example, are found to be slightly less effective antimalarials than the



111

corresponding cyclohexyl substituted compound [202]. Similarly, the adamantyl esters of pyridoxyl (*112* and *113*) are found to be "comparitively weak growth inhibitors" [350].



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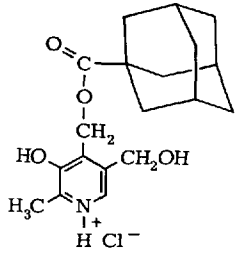
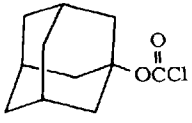


113

Both 1-adamantyl chloroformate [209] *(114)* and 1-adamantoyl chloride [347] *(115)* have been found to be useful *blocking agents in biochemical syntheses.*



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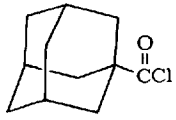
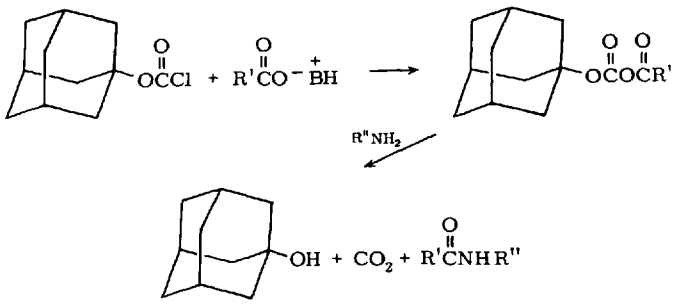


115

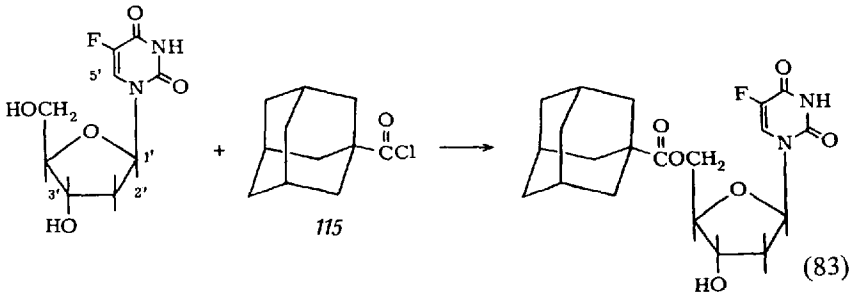
114 is found to be a better amino acid blocking group than the analogous t-butyl chloroformate in many cases [209]. Not only is *114* more stable than the t-butyl derivative thereby allowing the protection of more unreactive amino functions, but also the adamantyloxycarbonyl amino acids shows a greater tendency to be crystalline. The amino acids may be readily regenerated by the treatment of the derivatives in trifluoroacetic acid at room temperature for 15 min. [209].

The adamantyloxycarbonyl function has also been found to be a useful *protecting group in peptide synthesis* [209]. The general reaction sequence is summarized in Scheme 19. The success of this peptide synthesis perhaps results from the bulk of the adamantyl group which directs attack to the desired carbonyl group.

Scheme 19



Adamantoyl chloride *(115)* serves as a protecting group for the 5′ position of deoxynucleosides (Eq. (83)) [347]. The adamantoyl group may be readily removed by mild base.



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(83)

VII. Addendum

Since submission of this article for publication [5], additional references have become available. These are included here. Particular attention is called to other recent reviews [6].

Treatment of adamantane with aluminum halide catalysts in the presence of nonane or 2,3,5-trimethylhexane results in the formation of a mixture of methylated adamantanes [354]. Apparently, the 1-adamantyl cation generated by Lewis acid catalysts can initiate intermolecular alkyl shifts (presumably *via* attack on olefinic intermediates).

The mass spectra of a variety of 1- and 3-substituted homoadamantanes have been analyzed and compared [355]. Analyses of the infrared spectra of alkyl substituted adamantanes [356] and analyses of the microwave spectra of 1-halogen substituted adamantanes [357] are also available.

The "liquid crystal" properties of adamantane at room temperature [358] have led to the use of the adamantane crystal lattice in ESR spectroscopy. The ESR spectra of a wide variety of free radicals formed by the radiation of appropriate precursors trapped in the adamantane crystal lattice show greatly improved resolution [359]. It should also be noted that radiation damage of the matrix itself may occur. Irradiation of "pure" adamantane gives rise to free radicals whose ESR spectra are said to be consistent with those anticipated for the 1- and 2-adamantyl radicals [360]. The reported exclusive formation of the secondary radical at 77 °K is quite unexpected, however. Furthermore, 1-adamantyl radical has been generated by low temperature photolysis of a cyclopropane solution of *t*-butyl 1-peroxyadamantanecarboxylate [372]. The ESR spectrum, quite different from that reported [360], shows unusually large hyperfine couplings to the γ (bridgehead) and to one type of δ hydrogens [372].

Two additional substitution reactions of the adamantane nucleus have been studied. Dichlorocarbene is found to insert exclusively and in high yield at the bridgehead position of adamantane. The insertion reaction is strongly inhibited by the presence of electronegative substituents on the substantial positive charge in the transition state of this insertion reaction [361].

The chlorination of adamantane by either antimony pentachloride or ferric chloride in carbon tetrachloride gives low (approximately 4) initial tertiary: secondary product ratios. Attention was called to the similarity of these ratios to those of known radical processes [360].

Treatment of 1,3-dibromo-3,5-dibromomethyladamantane with zinc results in a double fragmentation of the adamantane ring: 1,3,5,7-tetramethylenecyclooctane is formed in high yield. Bromination of the product with bromine in carbon tetrachloride regenerates the starting material [363].

The chemistry of adamantylidene adamantane has been found to be quite unusual, due primarily to the highly hindered character of the double bond in this system. Bromination of adamantylidene adamantane gave the first isolated bromonium ion [263]. Chlorination gives similar results at low temperatures while at higher temperatures chlorine is found to enter the methylene positions of the adamantyl nucleus, presumably *via* a protoadamantene-like intermediate [364].

The sterically hindered character of the double bond in adamantylidene adamantane is also reflected by the fact that it is inert to oxidation by potassium permanganate and that although the corresponding epoxide may be formed, the epoxide is inert to hydrolysis conditioning. Adamantylidene adamantane glycol may be prepared, however, by treating adamantanone with sodium metal in xylene [365].

Substituted adamantanes have been employed in the study of several reaction mechanisms. The Kolbe electrolyses of 1- and 2-adamantane carboxylic acids and 1- and 2-adamantyl acetic acids have been compared in detail. Carbonium ion-derived products are observed from the electrolyses of both 1-adamantyl carboxylic acid and 1-adamantyl acetic acid. A mixture of radical and carbonium ion-derived products are obtained from 2-adamantyl carboxylic acid and mainly radical-derived products are obtained from 2-adamantyl acetic acid. These results parallel the known or expected stabilities of the intermediate carbonium ions [366].

The rates of nucleophilic additions to adamantanone have been studied in an attempt to determine the structure of the transition states of nucleophilic additions to carbonyl compounds in general. The kinetic analysis suggests that the transition states of borohydride reductions of ketones are product-like while for bisulfite additions the transition states are reactant-like [367]. A similar analysis [367] of data obtained for photo-initiated oxetane formation (*trans*-dicyanoethylene + carbonyl compound) [368] indicates a reactant-like transition state.

Finally, microbiological hydroxylation has been shown to be highly stereoselective and stereospecific using adamantyl substrates [369].

VIII. Summary

The chemistry of adamantane and related "cage-like" hydrocarbons has developed rapidly in recent years. These developments, encompassing a broad spectrum of the chemical world, have not been stimulated by any unique properties associated with the cage strutures of these molecules; the chemistry of such systems is typically hydrocarbon in nature. The particular utility of "cage-like" substrates in a variety of chemical investigations arises, for the most part, from their conformational rigidity; variables (*e.g.* those associated with structure) appropriate to more mobile compounds are often eliminated by the use of "cage-like" systems. The availability, ease of functionalization, and the near ideal structure of adamantane make it extremely useful for this purpose.

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