ADAMANTANE: CONSEQUENCES OF THE DIAMONDOID STRUCTURE

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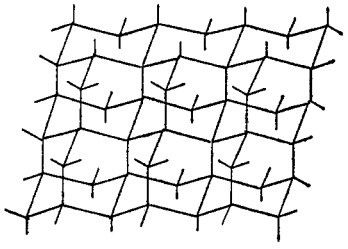
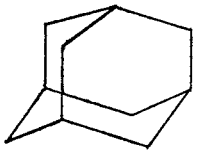
I. INTRODUCTION

The diamond has fascinated chemists (and their wives) for many years. Investigations of its structure and attempts at synthesis were a favorite research occupation at the turn of the century. As early as 1905 (80) and again, independently, in 1918 (75), the now familiar structure of fused chair cyclohexane rings (I) was postulated for its lattice.

It was only natural that attention also be devoted to the construction of hydrocarbon systems having the diamond structure. Decker (16), in 1924, proposed the synthesis of "dekaterpene," $C_{10}H_{16}$ (II), a tricyclic hydrocarbon which would have the same structure as



I

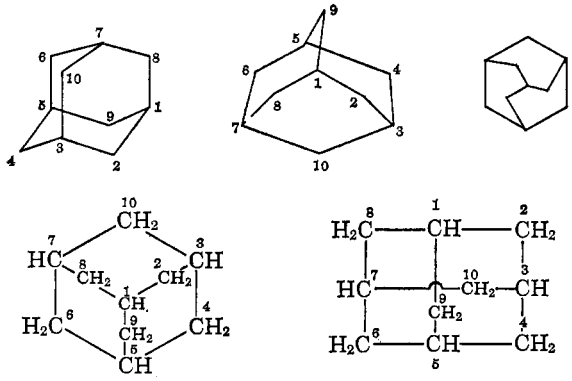


II

the diamond lattice and would be highly symmetrical and strain free.

In 1933, this substance was isolated from the petroleum of Hodinin, in Czechoslovakia, by Landa (63), and was named adamantane, from the Greek for diamond. The unique structure of adamantane (II) is reflected in highly unusual physical and chemical properties. So distinctive, in fact, are these properties that adamantane is one of the few compounds whose structure was effectively deduced from its melting point (269° in a sealed capillary)!

Representations of adamantane, tricyclo[3.3.1.1^{3,7}]-decane, and the numbering scheme are given below.



Several reviews of adamantane chemistry have appeared; all emphasize synthetic aspects (23, 52, 116, 117). This review will concern itself, in the main, with the interrelation of the chemical and physical properties of adamantane with the diamondoid structure. Heterocyclic analogs (23, 116, 117) of adamantane will not be considered except where they may serve as instructive comparisons. The literature, as far as possible, has been covered to Jan. 1, 1964.

II. SOURCES OF ADAMANTANE

A. ISOLATION FROM PETROLEUM

Landa, at length, and others have reported the isolation of adamantane from various petroleums (15, 47–51, 53, 54, 56, 61, 71) where it is present to the extent of about 0.0004%. It is accompanied by equally

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small amounts of alkylated adamantanes: 2-methyl-, 1-ethyl- (54), and probably also 1-methyl-, 1,3-dimethyl-, and others (136). The isolation of a single compound, adamantane, from such a complex mixture as is found in petroleum is a consequence of the uniquely high melting point. The cooling of fractionated petroleum steam distillates to low temperatures causes most of the adamantane to crystallize. An even more efficient separation can be achieved *via* the thiourea adduct (55, 56, 61).

The question of how adamantane comes to be present in petroleum is an interesting one. In view of the Lewis acid-catalyzed isomerization of tetrahydrodicyclopentadiene to adamantane (96, 99) discussed below, the most logical explanation is a similar transformation during petroleum biogenesis (54, 60, 92, 136). Some experimental support is available for this view. It has been shown (60) that, in addition to the various adamantanes, there is present in Hodinin petroleum some substance (or substances) which can be converted to adamantane upon treatment with a suitable catalyst. This was demonstrated by removing the adamantane from a sample of oil, fractionating the residue, and treating each fraction with various catalysts. Fractions boiling in the range 170–190° gave additional adamantane after such treatment (54, 60). Of the various catalysts tried, only $AlCl_3$ was found to be useful in this process; failure was experienced with such catalytic systems as oil-bearing stone from Hodinin (with or without added HF), aluminum silicate, aluminum oxide, concentrated sulfuric acid, zinc chloride, iron(III) chloride, tin(IV) chloride, and antimony(V) chloride (60). This observation, however, does not rule out the possibility that one or more of these catalyst systems, with the assistance of the pressures and temperatures possibly experienced by the petroleum during its formation, might bring about the isomerization. Indeed, it has been shown (85) that an aluminosilicate catalyst, ineffective at lower temperatures, is capable of causing the rearrangement of tetrahydrodicyclopentadiene to adamantane at 400–475°.

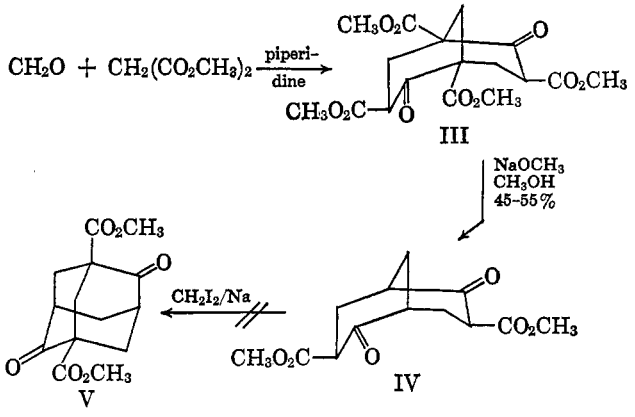
A variety of compounds, for example, decalin and octalin, mixtures of tetralin and decalin, and several bicyclic, monoolefinic, $C_{10}H_{16}$ isomers have been tested as possible adamantane precursors (40, 136). None of these, upon treatment with $AlCl_3$, yields quantities of adamantane detectable by capillary gas chromatography. For the present, the adamantane-forming substance in natural petroleum remains unknown.

An interesting sidelight of adamantane history is that for nearly 25 years, Landa had a practical, although not absolute, monopoly of the world's supply of adamantane. Convenient quantities of adamantane were obtained by the processing of enormous quantities of oil; for example, 66 kg. of petroleum steam distillate yielded 200 g. of adamantane. Yields of adamantane from synthesis (section B) were uniformly low; probably no other investigator had more than a few hundred milligrams at any one time.

B. SYNTHESIS BY RING CLOSURE

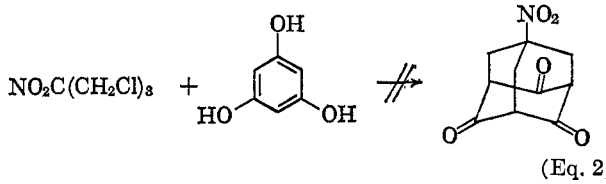
Although several synthetic schemes appear possible (116), all reported preparations of the adamantane skeleton by ring closure have proceeded from the bicyclo[3.3.1]nonane system by insertion of a methylene bridge.

The first attempted synthesis of an adamantane framework by this means (Eq. 1) was unsuccessful (74). The starting material (III) now called "Meerwein's ester," is readily prepared from formaldehyde and malonic ester; improved conditions (58) permit this interesting condensation to proceed in a yield of 85%. Meerwein's ester is a key intermediate in almost all of the adamantane syntheses which have subsequently been reported.



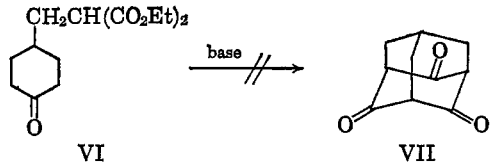
(Eq. 1)

Two entirely different approaches (Eq. 2 and 3) to the preparation of adamantane derivatives also failed (39). Compound VI was synthesized by a laborious



(Eq. 2)

route from *p*-aminobenzyl chloride. Its failure to give

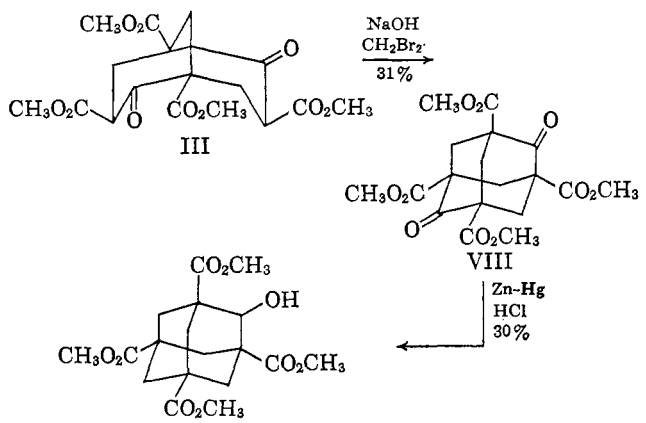


(Eq. 3)

adamantane-2,4,6-trione (VII) is not surprising, for with the bulky malonic ester substituent equatorial, reaction is forbidden by the sheer distance between the

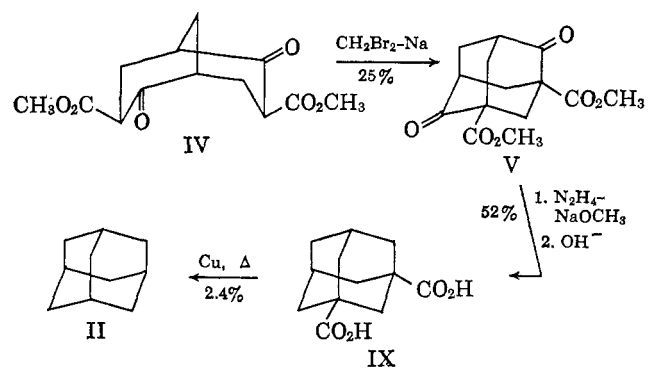
reacting groups; with it axial, models show that severe nonbonded interactions must be overcome.

Böttger (7) was the first to construct the tricyclo-[3.3.1.1^{3,7}]decane ring system (Eq. 4), although he did not synthesize adamantane itself.



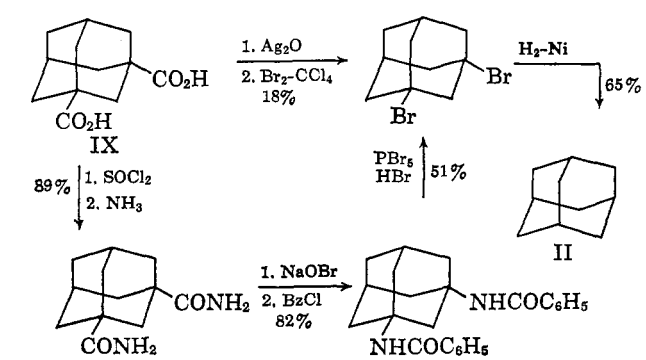
(Eq. 4)

The first successful synthesis of adamantane (87) began with the bicyclononanedione diester (IV) of Meerwein (74). One notes (Eq. 5) that the cyclization step, IV–V is virtually the same one which failed for Meerwein. The adamantane thus produced, in an over-all yield of 0.16% based on III, was identical with the



(Eq. 5)

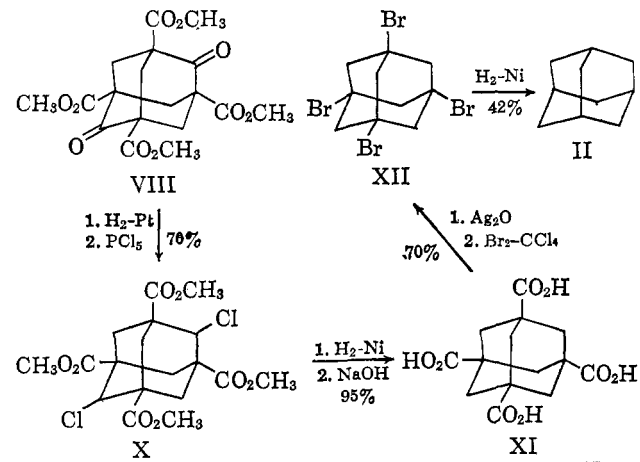
material isolated by Landa. Particularly unsatisfactory in this synthesis was the method of removing the carboxyl groups from IX. Equation 6 illustrates



(Eq. 6)

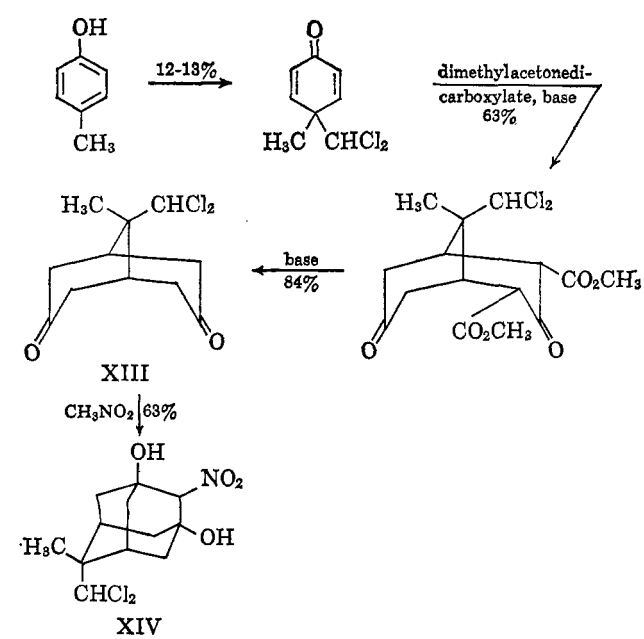
two improved methods of decarboxylation; the Hunsdiecker pathway gave an 11% yield, based on the diacid IX, while the sequence involving the Hofmann reaction gave 24% from the same precursor (88). This improvement raised to 1.5% the over-all yield of adamantane from III.

Stetter, Bander, and Neumann (119) also obtained adamantane in a similar fashion (Eq. 7), but their modifications increased the over-all yield to 6.5% from III. Wolff–Kischner reduction can also convert VIII to XI directly (59).



(Eq. 7)

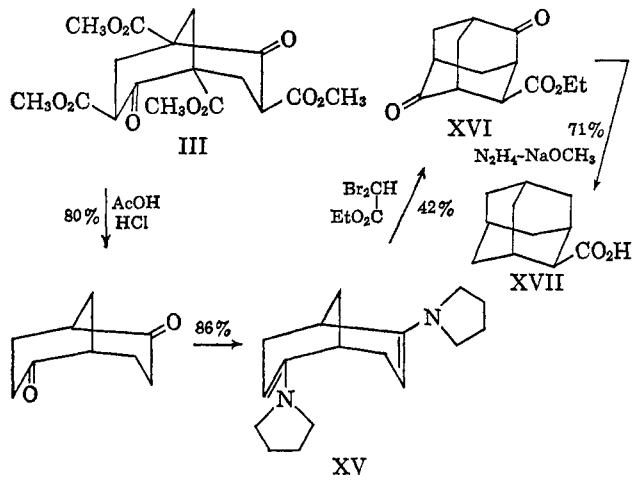
Recently, this same type of ring closure has been utilized for preparation of 2-substituted adamantanes (122, 123). Equations 8 and 9 present the general synthetic schemes. The polyfunctional derivative XIV is chiefly a curiosity, but the preparation in four steps of adamantane-2-carboxylic acid (XVII) in 11.6% over-all yield from Meerwein's ester (III) is



(Eq. 8)

important, since XVII is a useful intermediate for conversion to other 2-substituted adamantanes which are difficult to obtain by other methods.

All of the syntheses in this section suffer from a common disadvantage: the step which converts the bi-



(Eq. 9)

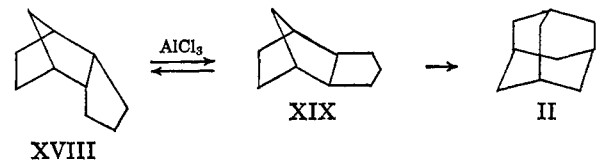
cyclo[3.3.1]nonane precursor into the adamantane skeleton in each case proceeds in poor yield: IV → V, 25%; III → VIII, 31%; XIII → XIV, 63%; XV → XVI, 42%. This restriction necessarily limits the over-all yields possible even if all other steps are favorable. To obtain adamantane, once the basic skeleton has been constructed, many unwanted functional groups must be removed; this complicates the syntheses and increases the number of steps involved.

Since adamantane can now be obtained easily by another method (see below), these sequences have been abandoned for the practical preparation of the parent hydrocarbon. However, several of these intermediates, notably adamantane-1,3,5,7-tetracarboxylic acid (XI), adamantane-1,3-dicarboxylic acid (IX), and adamantane-2-carboxylic acid (XVII), have been used to prepare other adamantane derivatives. Many of these conversions follow classical synthetic lines and will not be discussed here; compounds so prepared have been included in appropriate tables. However, it has proven easier and more profitable, when a mono- or dibridgehead-substituted adamantane is desired, to prepare the "bare" hydrocarbon and *then* functionalize.

C. SYNTHESIS BY ISOMERIZATION

It was early recognized that if the diamondoid arrangement of carbons did indeed represent an exceptionally stable system, it should be possible to produce this structure by isomerization of other saturated hydrocarbons (95). Following a parallel line of thought, it was reasoned that unsaturated compounds should give graphite or graphite-like polymers. However, when a number of phenylethylenes and phenylbenzenes gave only tars and no graphite upon treatment with $AlCl_3$, this promising line of attack was abandoned and no attempt was made to investigate the saturated series.

In 1956, the first instance of an adamantane preparation by rearrangement of a $C_{10}H_{16}$ hydrocarbon was discovered. Schleyer and Donaldson (96, 99), who were studying the facile $AlCl_3$-catalyzed isomerization of *endo*-tetrahydrodicyclopentadiene (XVIII) to its *exo* isomer (XIX) (Eq. 10), observed a small amount of adamantane as a white crystalline substance collecting in the head of a fractionating column at the end of a distillation of an isomerization mixture. At that time,



(Eq. 10)

this substance, at first believed to be an undescribed rearrangement product, was scraped out and set aside. Later, a melting point suggested the adamantane structure, and this was confirmed by infrared analysis (10), mass spectroscopy (11), and other methods (96, 99).

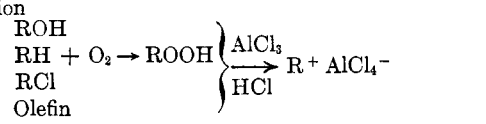
Since dicyclopentadiene is available commercially and can easily be hydrogenated, adamantane has become conveniently available through this isomerization. A yield of 15–20% may readily be obtained (100). Two modifications of the simple $AlCl_3$-catalyzed reaction have been developed. The first (40) uses as catalyst $AlCl_3$ + HCl, and the reaction is carried out in a hydrogen atmosphere at 40 atm. pressure. Adamantane is obtained in about 40% yield; *trans*-decalin (10%) is a major by-product. The other modification (70) substitutes HF–BF_3 for $AlCl_3$, and gives 30% yields of adamantane. A few per cent of *trans*-decalin is also obtained in this reaction. The advantage of less tar formation is claimed, but inert nonglass apparatus must be used.

Yields in these rearrangements are not quantitative because fragmentation and other side reactions can compete successfully with isomerization. The capillary gas chromatogram of the mother liquor from an $AlCl_3$-catalyzed adamantane preparation shows the presence of hundreds of compounds (136). With an aluminosilicate catalyst, in the gas phase at 450–475°, *endo*-tetrahydrodicyclopentadiene (XVIII) gave 6–13% adamantane and numerous acyclic, monocyclic, and bicyclic aliphatic and aromatic by-products. Some 40 of these were identified and quantitatively determined (85). The driving force for the Lewis acid-catalyzed rearrangements is relief of strain (see following discussion), and this is as easily accomplished by the destruction of the molecule as by its isomerization. Use of hydrogen, or of the milder catalyst, HF–BF_3, apparently serves to damp the fragmentation reactions.

Still milder catalysts, such as concentrated H_2SO_4, although capable of giving the isomerization XVIII → XIX, give no adamantane (60, 99).

The adamantane rearrangement certainly is one of the more profound skeletal transformations known to organic chemists and merits some discussion. The aluminum chloride-catalyzed rearrangement of alkanes, proceeding through carbonium ions, differs from ordinary carbonium ion rearrangements in that the ions are formed *reversibly* and *repeatedly*, as shown in the following mechanism of alkane isomerization (106).

Initiation



(Eq. 11)

Propagation

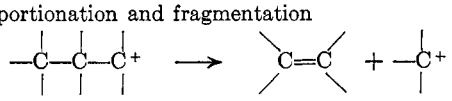
$$R^+ AlCl_4^- + R'H \leftrightarrows R'^+ AlCl_4^- + RH \quad \text{(Eq. 12)}$$

$$R'^+ AlCl_4^- \leftrightarrows R''^+ AlCl_4^- \quad \text{(Eq. 13)}$$

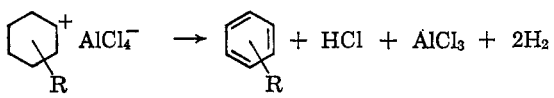
$$R''^+ AlCl_4^- + R'H \leftrightarrows R'^+ AlCl_4^- + R''H \quad \text{(Eq. 14)}$$

Side reactions

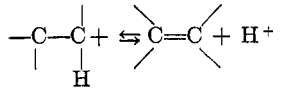
Disproportionation and fragmentation



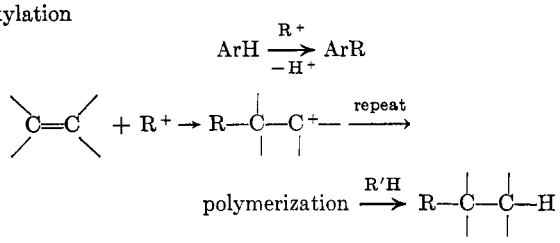
Aromatization



Olefin formation



Alkylation



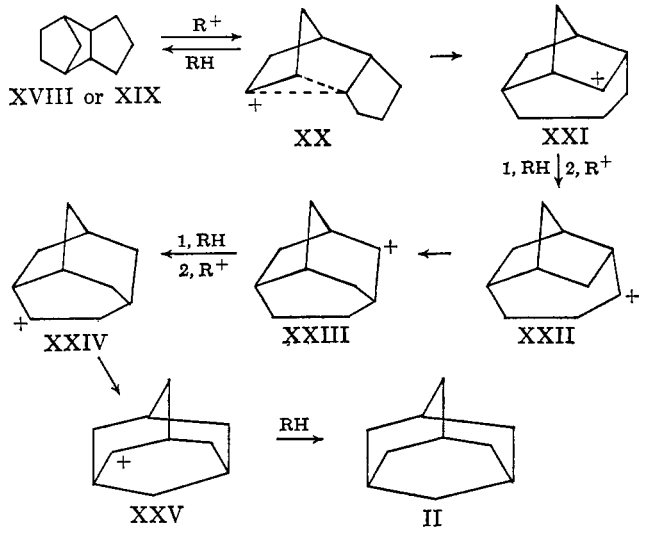
Reaction is initiated by the generation of a carbonium ion in any of several ways (Eq. 11). The initiating species are usually present as trace impurities; rigorously purified alkanes do not react with freshly sublimed $AlCl_3$, and in such cases initiators must be added deliberately (106).

The propagation step involves attack of the initial ion, R^+, on an alkane molecule, R'H, producing a new ion, R'^+, by hydride transfer (Eq. 12). The new ion, R'^+, may attack another alkane molecule and be quenched, or it may rearrange to R''^+ (Eq. 13) before hydride abstraction, to give a new hydrocarbon, R''H (Eq. 14). Any new, isomerized alkane formed in this manner may again be attacked by a carbonium ion, and still another isomer produced. That is, a positive charge may be generated anywhere in the alkane molecule, quenched, and regenerated elsewhere. Complex rearrangements are facilitated greatly by this kind of an intermolecular process, so that very extensive rearrangements are normally observed under these conditions. Products are usually those of thermodynamic control (106, 136).

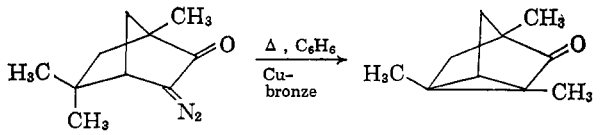
Side reactions are disproportionation and fragmentation, either of the ion itself or of the aluminum halide complex, aromatization and subsequent alkylation, and tar formation. These processes account for the fantastic number of side products observed in the adamantane rearrangement.

The driving force for the adamantane rearrangement may be found in the relief of the considerable strain inherent in the bicyclo[2.2.1]heptane system (4). However, no entirely satisfactory mechanism for the transformation is presently available. Schleyer and Donaldson (99) have proposed a mechanism for the adamantane rearrangement (Scheme I), merely as an illustration. The 2,6-alkyl migration, XX → XXI, has no direct precedent and is therefore subject to some suspicion. Analogous 2,6-hydride shifts are well documented (*inter alia*, 5, 94), however, and a 2,6-

SCHEME I



methyl migration (Eq. 15) has been observed in a carbenoid reaction (148). The postulated alkyl migration in the adamantane rearrangement therefore is not altogether unreasonable.

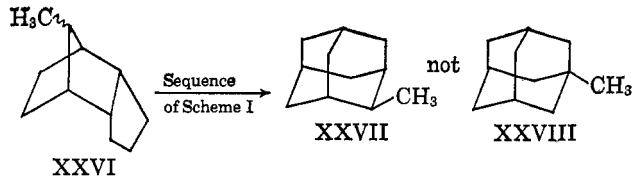


(Eq. 15)

The other rearrangement steps, XXII → XXIII and XXIV → XXV, should be quite favorable, since they would proceed with relief of strain. Whatever the detailed mechanism may actually be, it is clear that a

very large number of carbonium ions and rearrangement steps are possible. Some of these may be nonproductive, but there may also be more than one pathway leading to adamantane.

The isomerization of several methyl-substituted trimethylenenorbornanes has been investigated (79, 104) in an attempt to illuminate the intricacies of the hypothesized mechanism. It was hoped that a methyl group might act as a label; for example, if the mechanism in Scheme I is valid, 7-methyl-*endo*-trimethylenenorbornane (XXVI) should lead to 2-methyladamantane (XXVII) as in Eq. 16. Experimentally, it was found that XXVI and every other methyltrimethylene-

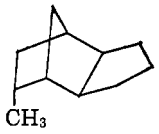
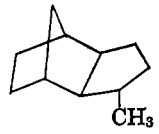
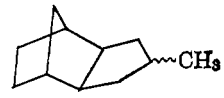
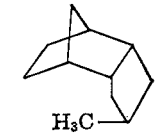
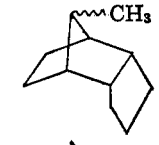
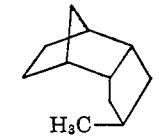


XXVI XXVII XXVIII

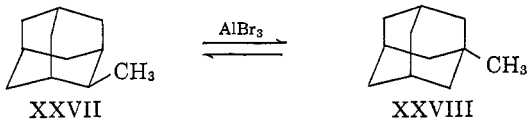
(Eq. 16)

norbornane examined gave a mixture of 1- and 2-methyladamantane, and that the ratio of the two isomers varied relatively little with starting material (Table I).

TABLE I
COMPOSITION OF METHYLADAMANTANE PRODUCT FROM METHYLTRIMETHYLENENORBORNANES

Starting material	Temp.	Yield of methyladamantanes	Product composition, % 1-Methyl-	2-Methyl-
	Room	40	99.7	0.3
	Room	77	92.3	7.7
	Room	47	87.3	12.7
	Room	49	84.5	15.5
	Reflux	65	98.6	1.4
	Reflux	*ca.* 100	Main	

The product ratios are explicable if, under the reaction conditions, the starting materials, the intermediates, or the two methyladamantanes equilibrate. The latter equilibration has been demonstrated (79), and preliminary quantitative measurements have been made on the position of the equilibrium (6). The thermodynamics of the monomethyladamantane equilibrium, XXVII → XXVIII, are $\Delta F°_{298} = -2.4 \pm$

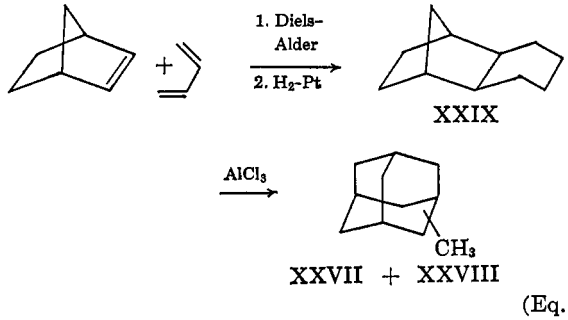


XXVII XXVIII

0.2 kcal./mole, $\Delta H° = -2.5 \pm 0.2$ kcal./mole, and $\Delta S° = -0.2 \pm 0.2$ e.u.

At equilibrium, at 25°, there is present about 98% of the 1-methyl isomer, which is the more stable by virtue of having no repulsive interactions. A methyl group in the 2-position of adamantane is equatorial to one of the fused cyclohexane rings, but axial to another, and so is destabilized. In the 1-position, on the other hand, the methyl is equatorial to three rings and is attached to a quaternary carbon (18). All of the methyltrimethylenenorbornanes in Table I, then, given sufficient time to attain equilibrium, would yield the same mixture of 1- and 2-methyladamantanes.

exo-Tetramethylenenorbornane (XXIX) also gives a mixture of methyladamantanes when treated with $AlCl_3$; this hydrocarbon is the most convenient source of 1-methyladamantane, since XXIX is readily obtained from norbornene and butadiene (Eq. 17). The yield of adamantanes is nearly quantitative at room temperature, and 1-methyladamantane (XXVIII) predominates, although the ratio of 1-methyl- to 2-methyl- has been observed to vary in different runs (79, 136).

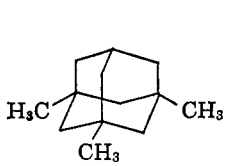


XXIX

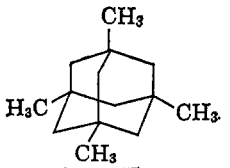
XXVII + XXVIII

(Eq. 17)

The above thermodynamic results are capable of further generalization. A substituent will normally be more stable at the 1- rather than the 2-position, and additional groups will also prefer attachment at other available bridgehead positions. For example, the most stable dimethyladamantane is the 1,3 derivative (XXX), and 1,3,5-trimethyladamantane (XXXI), and 1,3,5,7-tetramethyladamantane (XXXII) should also be preferred. Thus, 1,3-dimethyladamantane is pro-

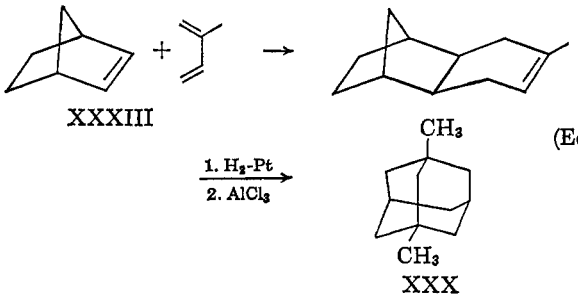


XXXI



XXXII

duced by isomerization of the appropriate norbornane derivative (104) (Eq. 18). The hydrogenation product of commercially available methylcyclopentadiene

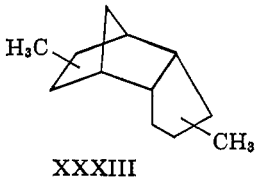


XXXIII

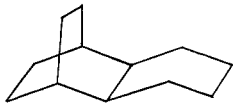
XXX

(Eq. 18)

dimer (XXXIII), when isomerized under the usual conditions, gave dimethyladamantane as one component of a mixture (39% by gas chromatographic analysis). Koch and Franken (41) obtained dimethyladamantane 95% pure from this same progenitor



XXXIII


XXXIV

(XXXIII) by using HCl–$AlCl_3$ in a hydrogen atmosphere. Tetrahydrodicyclohexadiene (XXXIV) likewise yielded a mixture containing 60% of dimethyladamantane (104).

It is clear that the adamantane isomerization process is capable of considerable extension. In fact, all strained, tricyclic, saturated hydrocarbons having ten or more carbon atoms thus far investigated have rearranged at least in part to adamantane derivatives. C_{11} tricyclics give methyladamantanes, C_{12} tricyclics give dimethyladamantanes, and C_{13} and higher tricyclics also give adamantane products (136). The yields of adamantane are dramatically increased by additional carbons in the precursors; in some instances, nearly quantitative conversions are observed, in contrast to the 15–20% yields found for adamantane itself (which requires higher temperatures for formation). These higher homologs are also formed quite cleanly; the gas chromatograms of the products show the presence of only traces of fragmentation and other side products. Interestingly, if some of these isomerization reactions are interrupted when partially complete, the presence of rearrangement intermediates can be detected by gas chromatography (136). The identification of these materials may give some information concerning the mechanism of the reactions.

With the higher homologs, it is clear that the rearrangement process is facilitated, and it competes successfully with the side reactions. The reason for this is nebulous. Perhaps a different or modified mechanism is operative, or some key mechanistic step is favored, possibly because of the larger, less strained rings which can now be formed.

The most convenient preparation, then, of adamantane (II), 1-methyladamatnane (XXVIII), 1,3-dimethyladamantane (XXX), and possibly of other adamantane hydrocarbons (136), is by isomerization. Since efficient methods have been developed for introducing functional groups onto the adamantane skeleton, the rearrangement route is often the best for the synthesis of numerous adamantane derivatives.

III. Structure and Physical Properties

A. General

Adamantane possesses a unique rigid but strain-free ring system, composed of three fused chair cyclohexane rings. X-Ray and electron diffraction studies (25, 26, 82, 83), while not of particularly high precision, have shown that adamantane crystallizes in a face-centered cubic lattice (extremely unusual for an organic compound) of space group $T_d^2F\bar{4}3m$, with $a = 9.426 \pm 0.008$ Å., and four molecules per unit cell. All carbon–carbon bond lengths are 1.54 ± 0.01 Å. and all C–C–C angles $109.5 \pm 1.5°$. The molecule therefore should be completely free from both angle and torsional strain.

At the beginning of growth, crystals of adamantane show only cubic and octahedral faces, as expected for a face-centered cubic lattice with only forces between nearest neighbors effective (36).

The effects of this unusual structure upon physical properties are striking. As has been previously remarked, adamantane is one of the highest melting hydrocarbons known, m.p. 269°, yet it sublimes readily, even at atmospheric pressure and room temperature. The boiling point, of course, is undeterminable directly. However, adamantane, present in a mixture of hydrocarbons being fractionally distilled, is found in the cuts of b.p. near 190° (63, 71).

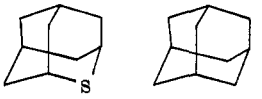
Unfortunately, thermochemical data currently available do not permit a check on the theoretical assumption that adamantane is strain free. An early value for the molar heat of combustion of solid adamantane, $-\Delta H_c°$, = 1451.7 kcal., at constant volume (63), is obviously in error, since virtually the same value (1451.8 kcal./mole at constant volume) was reported (3) for *endo*-tetrahydrodicyclopentadiene (XVIII) which must be strained considerably. The latter has both a norbornane ring [18–19 kcal. strain (4)], and a five-membered ring [3 kcal. extra strain (18)] in the unfavor-

able *endo* configuration [3 kcal. strain (3, 99)], and thus should be less stable than adamantane by about 25 kcal. A recent redetermination of the heat of combustion of solid adamantane gave a value of 1440 kcal./mole, said to compare with a calculated value of 1442 kcal./mole (145). This value is confirmed by heat of combustion studies on thiaadamantane (XXXV) from which thermodynamic data for adamantane can be estimated (Table II).

TABLE II

ESTIMATION OF HEATS OF COMBUSTION AND FORMATION OF SOLID ADAMANTANE

			Difference
$-\Delta H_f°$ (25°, liquid), kcal./mole	25.41[a]	37.34[b]	11.93
$-\Delta H_c°$ (25°, liquid), kcal./mole	930.34[a]	936.88[b]	6.54



XXXV

$-\Delta H_f°$ (25°, solid), kcal./mole	34.29[c]	46.22 (calcd.) 47.0 (exptl.)
$-\Delta H_c°$ (25°, solid) kcal./mole	1434.24[c]	1440.78 (calcd.) 1440 (exptl.)

[a] Ref. 134. [b] Ref. 93. [c] Ref. 45.

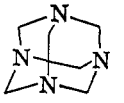
No value for the heat of sublimation of adamantane or thiaadamantane is yet available, and therefore no estimation of the heats of combustion and formation in the gas phase is possible for these substances. Gas phase values are needed for more meaningful comparisons with other data, such as those which can be calculated for an assumed strain-free adamantane or thiaadamantane by using appropriate bond energy schemes (112). A precise, modern thermochemical investigation of adamantane and some of its derivatives and their precursors is most desirable.

Measurements of the heat capacity of adamantane (12, 142) reveal a pronounced transition at 208.62°K. to a body-centered tetragonal lattice having $a = 6.641$ Å. and $c = 8.875$ Å. The transition presumably involves an increase in molecular freedom; the adamantane molecules are able to rotate more freely, or to assume different, random orientations on the lattice sites of the high temperature form (12): $-\Delta H°$ for the transition is 0.807 kcal./mole; $\Delta S°$ is 3.27 e.u. Table III gives some thermodynamic properties of adamantane. Those of hexamethylenetetramine (XXXVI) are included for comparison. This latter substance, despite similarity of shape, apparently does not undergo a transition similar to that experienced by adamantane. It was concluded from these data that the face-centered cubic lattice characteristic of adamantane at room temperature is actually a disordered phase.

TABLE III

THERMODYNAMIC PROPERTIES OF ADAMANTANE AT 25° (12, 142)

Compound	C_p, cal./mole deg.	$S°$, cal./mole deg.	$(H° - H_0°)/T$	$-(F° - F_0°)/T$
Adamantane	45.35	46.80	24.38	22.42
Hexamethylenetetramine	36.42	39.05	18.26	19.65



XXXVI

An n.m.r. study of solid adamantane (72) suggests a rotational transition at about 143°K. Just what relation this transition bears to that found by heat capacity measurements is not clear. Smith (115) has demonstrated an error in the calculation of the theoretical second moment of adamantane in this work and cites a private communication from the authors describing an error in their experimental work (see also ref. 12). No revised report on the work has appeared, so that the status of this second transition remains vague.

Adamantane displays an exaltation of its molecular diamagnetism (30–32) beyond that calculated from Pascal's atomic increments (Table IV). The deviation is attributed to the high symmetry of the adamantane system, but no detailed explanation is offered. By way of comparison, most nonaromatic molecules deviate no more than five units ($\lambda = \pm 5$), while aromatic molecules often have λ values ranging from -5 to -150.

TABLE IV

THE DIAMAGNETISM OF ADAMANTANE

Compound	$\chi_g \times 10^6$	χ_M measd. $\times 10^6$	χ_M calcd. $\times 10^6$	λ
Adamantane	−0.692	−94.3	−106.0	11.7
Hexamethylenetetramine	−0.493	−69.1	−89.6	20.5
Diamond (11)[a]	−0.49	−58.8	−74.0	15.2

[a] Calculated assuming diamond to be composed of ten atom molecules.

Ring currents have occasionally been postulated in saturated carbocyclic systems, for example, to account for the difference in nuclear magnetic resonance chemical shift between the axial and equatorial protons in cyclohexane (86). The average values of λ given by Havemann (32) suggest that a ring current should not be invoked to explain the exaltation in adamantane, for such a current would be expected to lead to a λ of negative sign, contrary to what is observed.

The dipole moments of two adamantyl halides, 1-chloroadamantane and 1-bromoadamantane, have been measured (137). Again the "strangeness" of adamantanes is evident (Table V). The moments calculated from the refraction at the sodium D-line ($P_\infty - R_D$) in the usual manner are considerably larger than any ob-

TABLE V

DIPOLE MOMENTS OF 1-ADAMANTYL HALIDES

Halide	μ (D.), calcd. from $(P_\infty - R_D)$	$(P_\infty - P_{E+A})$	Total induced polarization
1-Chloroadamantane	2.51	2.18	78.9
1-Bromoadamantane	2.54	2.21	81.8

served for acyclic or alicyclic halides: *e.g.*, *t*-butyl chloride, μ = 2.13 D.; 1-chlorobicyclo[2.2.1]heptane, μ = 2.17 D. (144); cyclohexyl bromide, μ = 2.2 D. If an estimated value for the total induced polarization, *including an atomic polarization term* (137, 138) is used in the calculations ($P_\infty - P_{E+A}$), the moments have the expected values (Table V). Why these compounds should display an unusually high atomic polarization is not known at present.

Adamantane has a somewhat higher adhesion to water than does norbornane, as indicated by the contact angles of water against the hydrocarbons (1): 98 and 102°, respectively. The contact angle for hydrocarbons is thought (1) to vary with the nature of the group exposed by the molecule, methyl groups having the least attraction for water and methine groups the highest attraction. Paraffin wax has a contact angle of 114° (1), suggested to reflect a surface composed entirely of methyl groups, while polyethylene, with a surface of methylene groups, has a contact angle of 93°.

B. SPECTRAL PROPERTIES

As expected, the high symmetry of adamantane (symmetry number 12!) has significant consequences in the spectral characteristics of the parent hydrocarbon and its simple derivatives.

The infrared spectrum of adamantane itself is nearly featureless, consisting of only nine significant lines in the 2 to 14 μ region (10, 71); it has been analyzed by Mecke and Spiesecke (73), who made the assignments in Table VI. The Raman spectrum of solid adamantane (136) shows bands at 2944, 2917, 2895, 2849, 1437, 1315, 1223, 1099, 972, 951, 760, and 443 cm.$^{-1}$.

TABLE VI

THE INFRARED SPECTRUM OF ADAMANTANE

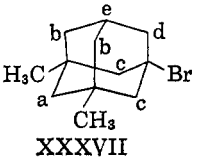
Assignment	Frequencies, cm.$^{-1}$
CH, CH_2 bond stretching	2907, 2933, 2857
CH_2 scissoring and wagging	1453, 1357
CH deformation	1155
CH_2 rocking	799
Skeletal vibrations	966, 714

Those infrared spectra of 1-substituted adamantanes which have been reported show the same basic simplicity (55, 57, 62, 79). It has been remarked (55) that all simple adamantane derivatives examined in the infrared show an absorption in the region 1017–1038 cm.$^{-1}$ which is not present in the spectrum of adamantane itself. However, the suitability of this band as a diagnostic test for the presence of an adamantane skeleton is impaired by its occasional extremely low intensity. In adamantane-1-carboxylic acid, for example, this band cannot be seen (79). Spectra of 2-substituted compounds, which are of lower symmetry than their 1-substituted counterparts, are more complex (79); spectra of disubstituted adamantanes (58, 79) likewise are "normally" complex.

Nuclear magnetic resonance spectra of adamantanes are of considerably more value. These have quite characteristic features (101) and structures are easily assigned from the chemical shifts and integrated intensities. Analysis is facilitated by the absence of strong coupling. The spectrum of 1,3-dimethyl-5-bromoadamantane (XXXVII) (Table VII) is representative.

TABLE VII

N.M.R. SPECTRUM OF 1,3-DIMETHYL-5-BROMOADAMANTANE



XXXVII

Peak, τ	Multiplicity	Area, protons	Assignment
9.12	Singlet	6	CH_3's
8.79	Singlet	2	H_a's
8.61	Singlet	4	H_b's
8.02	Singlet	4	H_c's
7.88	Singlet	2	H_d's
7.70	Singlet	1	H_e

Adamantane itself appears as a sharp doublet at 8.22 τ, spacing 1.7 c.p.s. Evidently the methine and methylene resonances fortuitously have nearly the same chemical shift. The coupling constant J_{vic} between the bridgehead and methylene protons has been estimated by examination of the ^{13}C satellite pattern (66, 67). Although the peaks are complicated by virtual (78) or long range coupling, it can be shown that $J_{^{13}CH} = 120 \pm 1$ c.p.s. and $J_{vic} \leq 2.65$ c.p.s. For comparison, cyclohexane resonates at τ 8.56, *cis*-decalin at τ 8.59 (135); in the former, $J_{^{13}CH} = 124 \pm 1$ c.p.s. (67).

The spectra of adamantane derivatives are distinguished by strong dependence of the resonance of *all* protons in the molecule upon the nature of the substituent(s) and by the absence of any strong coupling. Where measurable, J values between protons on the adamantane nucleus are 2.6 ± 0.1 c.p.s. (101), in accord with the result for adamantane and with the Karplus curve (37), and at variance with proposals to displace the curve toward higher coupling constants (*inter alia*, 68). The rigidity of adamantane makes particularly valuable the examination of its coupling constants, for there is no possibility of appreciable distortion from the expected 60° angle between vicinal protons; furthermore, the substituents are separated

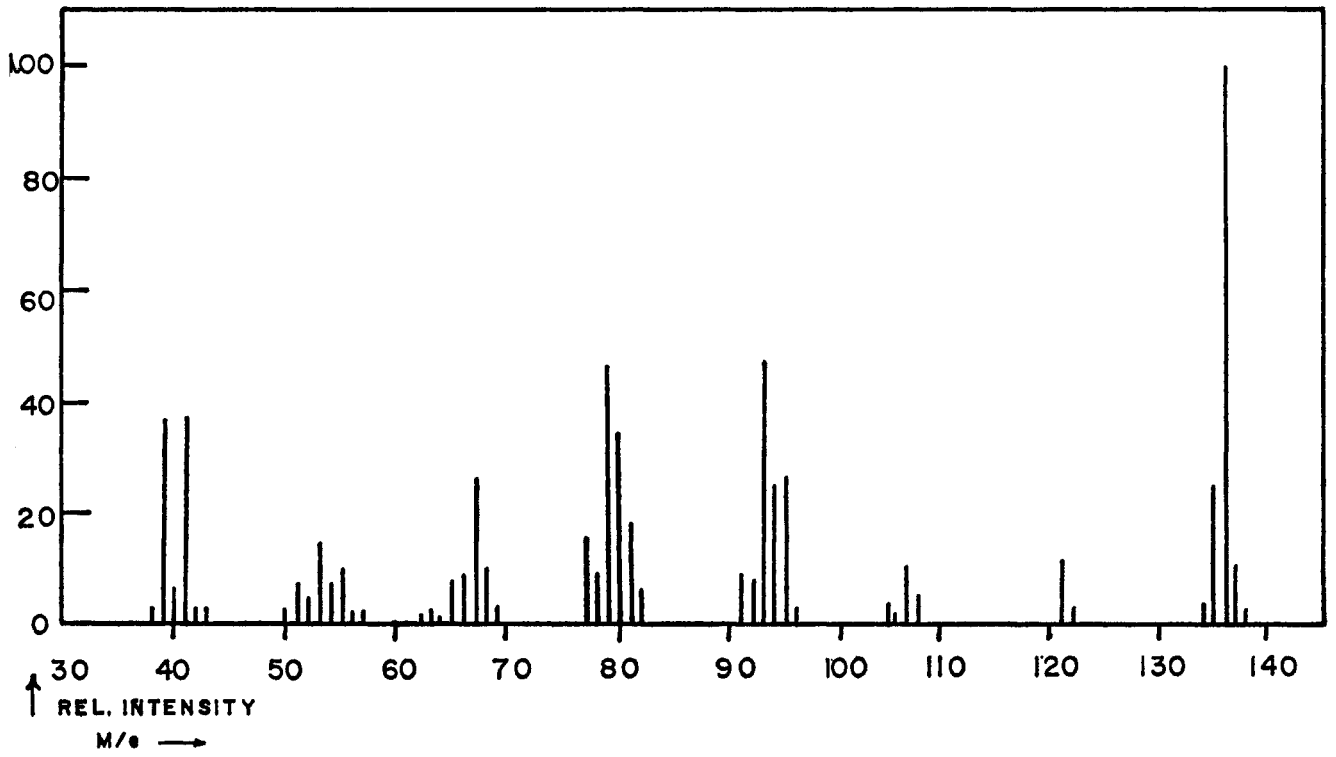


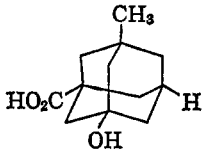
Fig. 1.—The mass spectrum of adamantane.

(in the 1-substituted case) from the protons by a sufficient number of bonds so that electronegativity effects on the coupling constants probably are negligible.

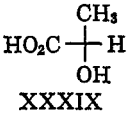
The mass spectrum of adamantane is also quite unusual (11). Unlike the behavior of most saturated hydrocarbons of moderate molecular weight, the parent peak (m/e = 136) of adamantane is the most intense in the whole spectrum, reflecting the inherent architectural rigidity of the interlocking ring systems. Effective fragmentation of the molecular ion requires that at least three C–C bonds be broken, and this is an energetically unfavorable process. A one-carbon fragment can be lost by rupture of only two bonds, but this process is seldom observed to any great extent with cyclic hydrocarbons, nor is it here: the M − 15 peak is weak. Ordinarily, the loss of two carbons (*e.g.*, as ethylene) is expected to be favorable. This is not the case with adamantane, which does not possess a $-CH_2-CH_2-$ grouping. Both M − 28 and M − 29 peaks are of low intensity because three C–C bonds and not just two must break before two carbons can be separated from the rest of the structure. Inspection of the adamantane mass spectrum (Fig. 1) shows that processes leading to the loss of three and four carbon atoms are most favorable in producing charged fragments.

Mass spectral analysis of derivatives of adamantane should be both interesting and useful for structural determination, but no studies have been reported.

The four bridgehead positions of adamantane resemble in an expanded form the four valences of carbon, extending tetrahedrally from a central point. Were the four bridgeheads to be substituted each with a different group, a compound capable of optical activity would result. An example of this type, such as XXXVIII, a formal analog of lactic acid (XXXIX), would be useful for testing theories of optical activity, which suggest that pairwise interactions, greatly reduced by distance in XXXVIII, are a basis for optical rotatory power (38).

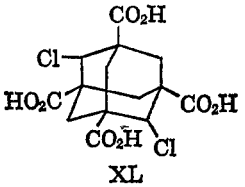


XXXVIII

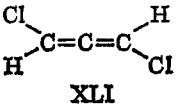


XXXIX

The only optically active adamantane derivative reported (118), XL, represents a different type of asymmetry—similar to that present in disubstituted allenes, *e.g.*, XLI. Rotations reported for the enantiomers of XL were $[\alpha]^{20}D$ +7.67 and −2.75°. The carboxyl groups in XL are superfluous; 2,6-dichloroadamantane itself would be asymmetric.



XL

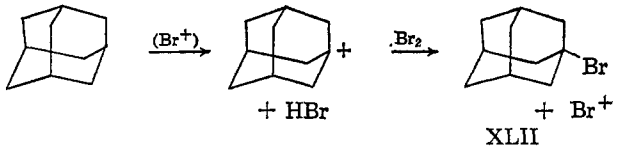


XLI

IV. CHEMICAL PROPERTIES

A. GENERAL CONSIDERATIONS

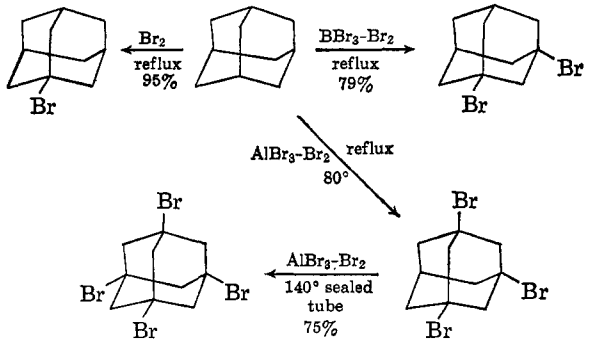
Treatment of adamantane with bromine at reflux produces a single, crystalline monobromide in excellent yield (62). The bridgehead-substituted structure XLII was assigned on essentially intuitive grounds, and later conclusively proved (128). It was also shown (128, 131) that the bromination is an ionic process (Eq. 19); it is catalyzed by Lewis acids and not by peroxides, azobis(isobutyronitrile), or light. It is also remarkably



(Eq. 19)

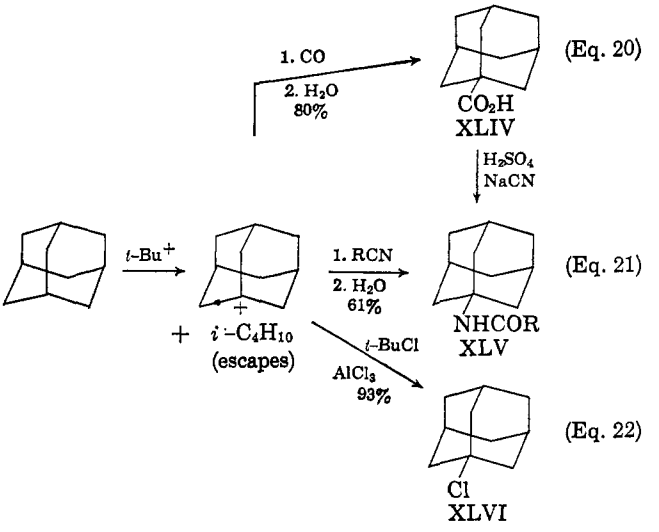
selective, in contrast to free-radical reactions. By proper choice of catalyst and severity of conditions, one to four bromines may be introduced sequentially into the adamantane molecule, all at bridgehead positions (Scheme II) each bromine being more difficult to introduce than the last (132). A trace impurity of $AlBr_3$ in the BBr_3 is needed to obtain 1,3-dibromoadamantane (2b).

SCHEME II



Thus, in adamantane, a carbonium ion process can occur with facility at a bridgehead—in direct contradiction to popular mechanistic generalizations (27). Other carbonium ion reactions proceed with equal ease; three of these, based on hydride exchange, represent particularly useful methods of introducing functional groups onto adamantane (Eq. 20–22).

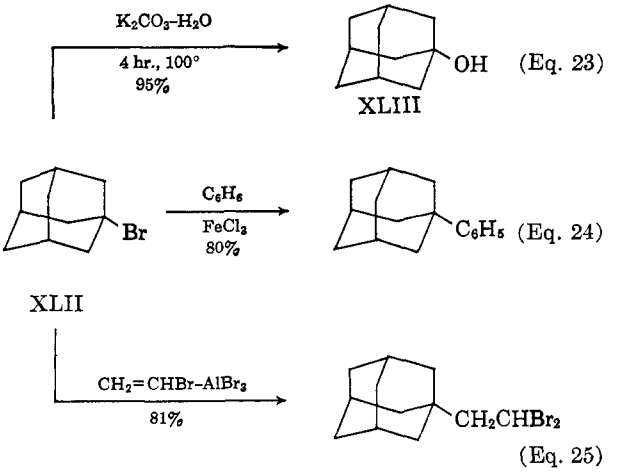
The first process (Eq. 20), the Koch–Haaf carboxylation (43), utilizes the *in situ* generation of CO from HCOOH in H_2SO_4, and the *t*-butyl cation generated from *t*-butyl alcohol. More conventional sources of the 1-adamantyl carbonium ion, such as 1-adamantanol (XLIII) (128) or 1-adamantyl bromide (XLII) (128), can also be used. The Ritter reaction (Eq. 21) requires similar conditions (concentrated H_2SO_4) and carbonium ion sources (*t*-butyl alcohol (29a) or 1-adamantanol (128)). The third reaction (Eq. 22) (24) is an example of hydrogen–halogen exchange (2). *t*-Butyl chloride



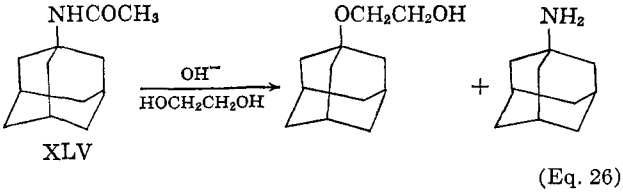
and $AlCl_3$ are used to generate the *t*-butyl cation. Direct interconversion of XLIV and XLV has been observed (29b).

From the bromide (XLII) the carboxylic acid (XLIV) and the amide (XLV) (R = CH_3), a large number of derivatives have been prepared by conventional methods (Tables VIII–XIII).

Some of these conversions also involve bridgehead carbonium ions, and proceed in high yield under moderate conditions (Eq. 23–25). In fact, ionic substitutions at the bridgehead are so facile that sometimes prepara-



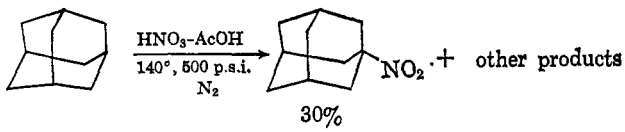
tive complications develop. For example, the attempted hydrolysis of XLV (Eq. 26) gave instead unwanted substitution (136).



(Eq. 26)

The direct nitration of adamantane has also been investigated, but the reaction requires high tempera-

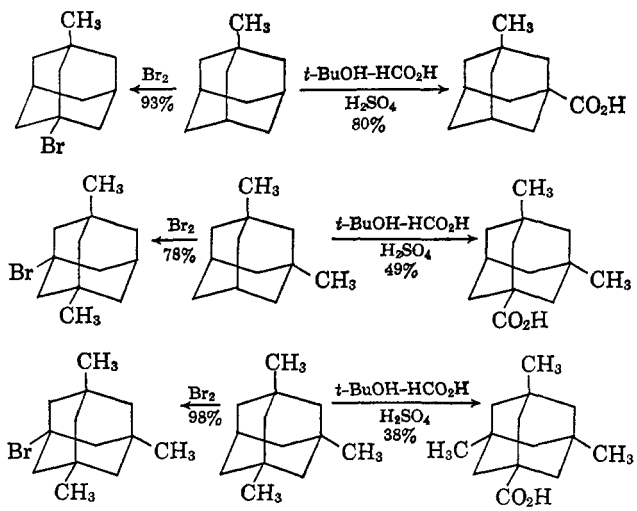
tures and pressures, and the product mixture is difficult to purify (Eq. 27) (114).



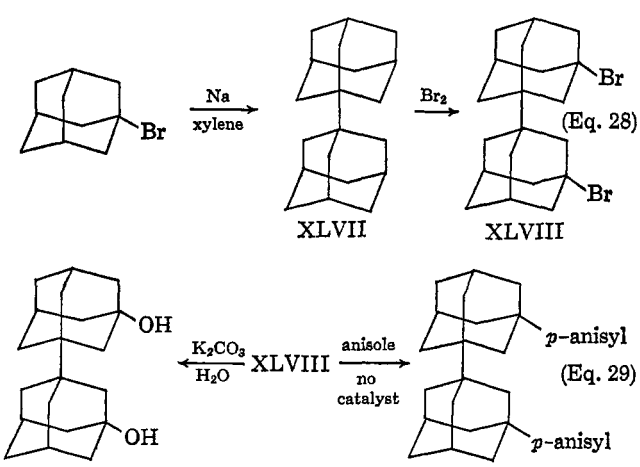
(Eq. 27)

Adamantane derivatives also undergo ionic substitution at the remaining available bridgeheads. The preparation of derivatives of the various methyl adamantanes (24, 41, 136) is illustrative (Scheme III).

SCHEME III



It should be recognized that in a 1-substituted adamantane the three remaining bridgehead positions are equivalent with respect to the group already present; introduction of a second bridgehead substituent can lead to only one product. Likewise, in a 1,3-disubstituted derivative, the two remaining bridgeheads are equivalent, and only one product can result from introduction of a third bridgehead substituent. The "fearful symmetry" of adamantane eases the task of the synthetic organic chemist.



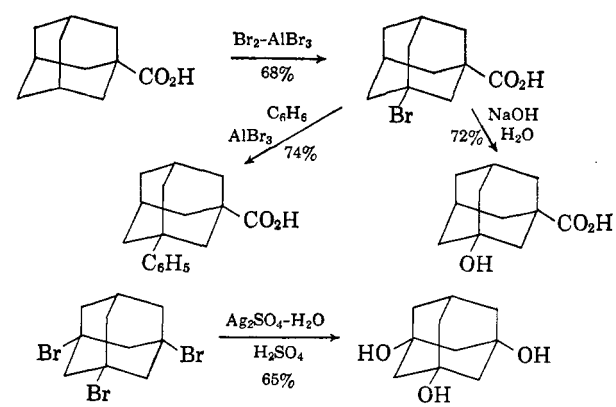
(Eqs. 28, 29)

Biadamantane (XLVII) may be obtained in good yield from 1-bromoadamantane and sodium in refluxing xylene (89). Bromination proceeds readily to give 3,3′-dibromo-1,1′-biadamantane (XLVIII) (Eq. 28). This compound undergoes all the reactions of 1-bromoadamantane, such as smooth hydrolysis to the diol and Friedel–Crafts alkylation (Eq. 29).

With an electron-withdrawing group attached to the adamantane nucleus, further substitution occurs with somewhat greater difficulty, as expected of a carbonium ion process, but the synthetic utility is in no way reduced (Scheme IV) (121, 132).

The value of the "backward approach" to synthesis is convincingly demonstrated here. Although the synthesis of adamantane itself proceeds in only 20% yield, the starting material is readily available, and subsequent reactions are those shown over many years to be reliable and fruitful. The large number of adamantane bridgehead derivatives which have been prepared have been enumerated in Tables VIII–XIII.

SCHEME IV

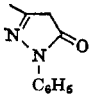
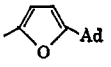
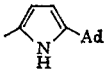


2-Substituted derivatives of adamantane are not nearly so easily obtained. The 2-position is considerably less reactive in carbonium ion processes than the bridgehead (see later discussion), and direct substitution at the 2-position, as demonstrated by the bromination results, occurs with far less facility.

Reaction at the 2-position might be achieved by taking advantage of the low selectivity of free radical reactions and the 12:4 ratio of 2° to 3° hydrogens in adamantane. Hydroxylation of adamantane with peracetic acid and ultraviolet light, or heat, gives a mixture of 1-adamantanol (XLIII) and 2-adamantanol (XLIX) (102) as shown in Eq. 30. Oxidation of the crude reaction mixture with CrO_3 in acetone converts the secondary alcohol XLIX to adamantanone (L) and facilitates separation by alumina chromatography. Adamantanone has been converted to other 2-substituted adamantanes (Scheme V).

TABLE VIII

1-SUBSTITUTED ADAMANTANES

Substituent[a]	Reference	Substituent[a]	Reference
F	101	$CONH_2$	125
Cl	128	$NHCO_2CH_3$	125, 133
Br	62, 132	COC_6H_5	126
I	62, 103	$CO(NH)_2COAd$	126
OH	62, 128	$CONHNH_2$	126
NH_2	29, 125	CONHNHTs	126
NO_2	114, 125	$C(OH)(C_6H_5)_2$	126
CO_2H	43, 128	$CCl(C_6H_5)_2$	126
$CO_2C_2H_5$	128	$C(OCH_3)(C_6H_5)_2$	126
CH_2OH	128	COCH(OH)Ad	126
CHO	126	COCOAd	126
$COCH_3$	57	CH(OH)CH(OH)Ad	126
C_2H_5	55, 57	$COCH_2Ad$	126
C_6H_5	55, 128	$COCH(CO_2C_2H_5)_2$	127
1-Ad	55, 89	$COCH_2CO_2C_2H_5$	127
n-C_3H_7	55		
C_6H_{11}	5		127
NHCHO	29		
$OCO(CH_2)_2CO_2H$	34		
$OCH_2C_6H_5$	64		
$CH(OH)C_6H_5$	65		
$O(CH_2)_2OCH_2C_6H_5$	90		
$O(CH_2)_2OH$	90, 101	$CH(OH)CH_3$	127
$O(CH_2)_2OTs$	90	$COCH_2Br$	127
$O(CH_2)_2CN$	90		
$O(CH_2)_2CO_2H$	90		127
CH_2OTs	128		
CH_3	104, 128		
COCl	128		127
CH_2CO_2H	128		
$NHCOCH_3$	128		
NHTs	125		
$COCH{=}C(C_6H_5)_2$	120	$CO(CH_2)_2COAd$	127
$C{\equiv}CC(CH_3)_2OH$	120	$COCH_2CH(CO_2C_2H_5)COAd$	127
$C{\equiv}CC{\equiv}CAd$	120	CH_2CH_2Br	120
$(CH_2)_4Ad$	120	CH_2CHBr_2	120
NCO	133	$CH{=}CHBr$	120
NHCONHAd	133	$C{\equiv}CH$	120
$NHCONHSO_2$-p-$C_6H_4CH_3$	24	$COCH{=}CH_2$	120
		$C{\equiv}CCO_2H$	120
$NHCONHSO_2$-p-$C_6H_4C_2H_5$	24	$C{\equiv}CCH(OH)C_6H_5$	120
		$NHCONH_2$	133
$NHCONHSO_2$-p-C_6H_4Cl	24	$NHCON_2^+$	133
		NCS	133
$NHCONHSO_2$-p-C_6H_4-i-C_3H_7	24	NHCSNHAd	133
		NCNAd	133
$NHCONHSO_2$-3-NH_2-4-$CH_3C_6H_3$	24	CH_2Cl	121
		CH_2Br	121
$CH_2NHCONHSO_2$-p-$C_6H_4C_2H_5$	24	$NHCONHSO_2$-p-$C_6H_4SCH_3$	24
		$NHCONHSO_2$-p-$C_6H_4COCH_3$	24
$CH_2NHCONHSO_2$-p-$C_6H_4COCH_3$	24		

[a] Ad = 1-adamantyl.

TABLE IX

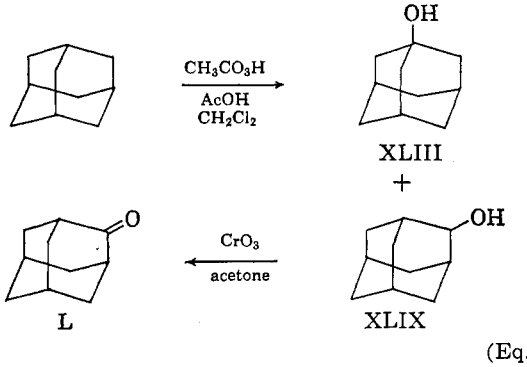
1,3-DISUBSTITUTED ADAMANTANES

1-Substituent	3-Substituent	Reference
CH_3	Br	24, 101
CH_3	$NHCOCH_3$	24
CH_3	NH_2	24
CO_2CH_3	CO_2CH_3	58
$C(CH_3)_2OH$	$C(CH_3)_2OH$	58
$C(CH_3)_2Cl$	$C(CH_3)_2Cl$	58
$C(CH_3){=}CH_2$	$C(CH_3){=}CH_2$	58
i-C_3H_7	i-C_3H_7	58
CH_2OH	CH_2OH	58
CH_2Cl	CH_2Cl	58
CH_2Br	CH_2Br	58
CH_2I	CH_2I	58
CH_3	CH_3	58, 104
CO_2H	CO_2H	87, 132
$CONH_2$	$CONH_2$	88
NH_2	NH_2	88, 132
Br	Br	88, 132
CO_2H	C_6H_5	121
CO_2H	OH	121
CO_2H	OCH_3	121
CO_2H	I	121
CO_2H	Br	121
CO_2H	Cl	121
CO_2H	F	121
$CONH_2$	Br	130
$NHCO_2CH_3$	Br	130
CH_3	OH	101
CH_3	$NHCONHSO_2$-p-$C_6H_4CH_3$	24
NO_2	NO_2	114
OH	OH	132
$NHCOCH_3$	$NHCOCH_3$	132
CH_3	CO_2H	41
CH_3	CH_2OH	41
CH_3	CH_2OTs	41

TABLE X

3,3′-DISUBSTITUTED 1,1′-BIADAMANTANES

3-Substituent	3′-Substituent	Reference
Br	Br	89
CN	CN	89
CO_2H	CO_2H	89
COCl	COCl	89
CO_2CH_3	CO_2CH_3	89
CH_2OH	CH_2OH	89
p-$C_6H_4OCH_3$	p-$C_6H_4OCH_3$	89
p-C_6H_4OH	p-C_6H_4OH	89
C_6H_5	C_6H_5	89
$CH_2NH_2 \cdot HCl$	$CH_2NH_2 \cdot HCl$	89
CH_2NH_2	CH_2NH_2	89
OH	OH	89



(Eq. 30)

Adamantanone has also been obtained directly from the oxidation of adamantane with CrO_3 in acetic acid–acetic anhydride solution in the cold (79, 105); yields of 71% 1-adamantanol (XLIII) and 9% adamantanone

SCHEME V

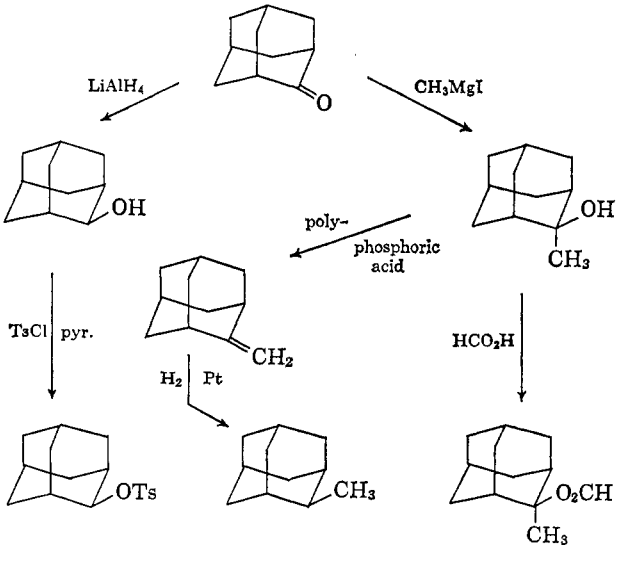


TABLE XI
1,3,5-TRISUBSTITUTED ADAMANTANES

1-Substituent	3-Substituent	5-Substituent	Reference
CH_3	CH_3	Br	24, 101
CH_3	CH_3	OH	101
CH_3	CH_3	$NHCOCH_3$	24
CH_3	CH_3	NH_2	24
Br	Br	Br	132
OH	OH	OH	132
CH_3	CH_3	$NHCONHSO_2$-*p*-$C_6H_4CH_3$	24
CH_3	CH_3	CO_2H	41
CH_3	CH_3	CH_2OH	41
CH_3	CH_3	CH_2OTs	41
CH_3	CH_3	CH_3	41

TABLE XII
1,3,5,7-TETRASUBSTITUTED ADAMANTANES

1-Substituent	3-Substituent	5-Substituent	7-Substituent	Reference
CO_2H	CO_2H	CO_2H	CO_2H	7
CH_3	CH_3	CH_3	CH_3	41, 59
CH_2OH	CH_2OH	CH_2OH	CH_2OH	59
CH_2Cl	CH_2Cl	CH_2Cl	CH_2Cl	59
Br	Br	Br	Br	119, 132
CH_3	CH_3	CH_3	CO_2H	41
CH_3	CH_3	CH_3	CH_2OH	41
CH_3	CH_3	CH_3	CH_2OTs	41
CH_3	CH_3	CH_3	Br	41

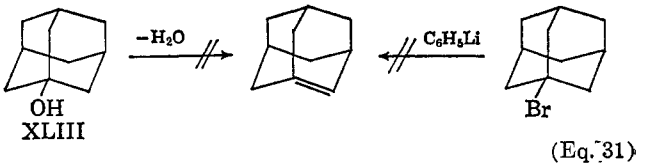
TABLE XIII
MISCELLANEOUS BRIDGEHEAD-SUBSTITUTED ADAMANTANES

Compound	Reference
1,3,5,7-Tetracarbomethoxyadamantane-2,6-dione	7
1,3,5,7-Tetracarboxyadamantane-2,6-dione	7
1,3,5,7-Tetracarboxyadamantane-2,6-diol	7
1,3-Dicarbomethoxyadamantane-2,6-dione	58, 87, 88
1,3,5,7-Tetracarboxy-2,6-dichloroadamantane	118, 119
1,3-Dihydroxy-2-nitro-8-methyl-8-dichloromethyladamantane	123

(L) were obtained, but the reaction has proven to be erratic upon repetition. Air oxidation of adamantane in benzene–acetic acid solution in the presence of cobalt acetate (140–145° and 800 p.s.i.) was said to give 10–12% of adamantanone in addition to 1-adamantanol and small amounts of unidentified hydroxylated material (114). However, the melting points of both the adamantanone and its 2,4-dinitrophenylhydrazone obtained from this reaction differ appreciably from the accepted values (102, 122), and it is not certain that authentic or pure materials were obtained.

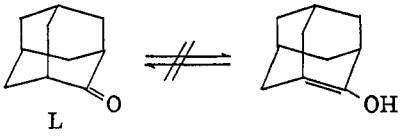
Conceptually, the direct oxidation of adamantane, by some process, to give at least in part the desired adamantanone, is an attractive method. Both 1-adamantanol and adamantanone should be stable to further oxidative degradation, which, for an alcohol, commonly involves dehydration to an olefin, and for a ketone often involves enolization. Both dehydration of XLIII and enolization of L are prohibited by the geometrical requirements of bonding ("Bredt's rule") (Eq. 31 and 32). In fact, a deliberate attempt to prepare, or at least to detect, "adamantene" from 1-bromoadamantane failed (76) (Eq. 31).

A potentially useful free-radical substitution of adamantane has been reported by Smith and Williams (114). Photochlorination of adamantane (Eq. 33) gave



XLIII

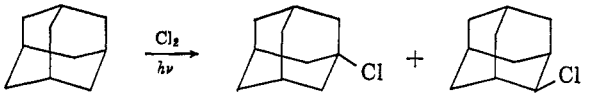
(Eq. 31)



L

(Eq. 32)

1-chloroadamantane and a second monochloride, presumed to be 2-chloroadamantane (LI). The product



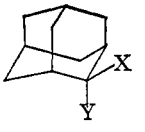
XLVI LI

(Eq. 33)

ratio XLVI:LI varied with solvent: in CS_2, the ratio was 2.1:1.0; in C_6H_6, 1.17:1.0; and in CCl_4, 0.63:1.0. In CCl_4, the largest amount of 2-chloroadamantane was obtained, but "a fair amount" of polychlorination also occurred. Yields in this reaction were not reported, and the process was not exploited for the preparation of other 2-substituted adamantanes.

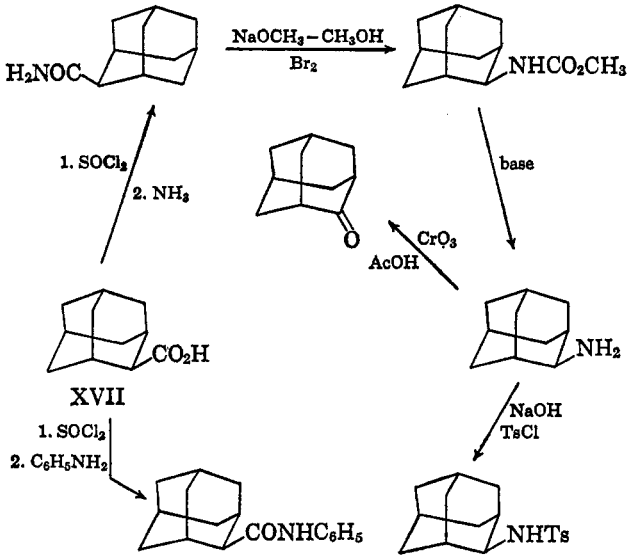
A more promising approach to 2-adamantyl compounds is the ring closure reaction previously discussed (122), which gives adamantane-2-carboxylic acid. Scheme VI illustrates the preparation of some 2-substituted adamantanes from this precursor. Table XIV lists the rather limited number of 2-substituted adamantanes which have been reported.

TABLE XIV
2-SUBSTITUTED ADAMANTANES



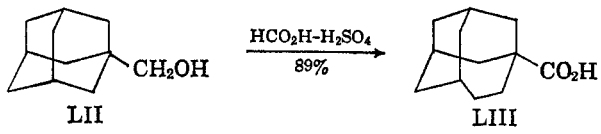
Substituent X	Substituent Y	Reference
OH	H	102
OH	CH_3	102
O_2CH	CH_3	102
CH_3	H	102
OTs	H	102
X = Y = =O		102, 122
X = Y = $=CH_2$		102
Cl	H	114
CO_2H	H	122
COCl	H	122
$CONH_2$	H	122
$NHCO_2CH_3$	H	122
NH_2	H	24, 122
NHTs	H	122
$CONHC_6H_5$	H	122
$NHCONHSO_2$-*p*-$C_6H_4CH_3$	H	24
Miscellaneous		
2-Carbomethoxyadamantane-4,8-dione		122
2-Amino-1,3-dihydroxy-6,6-dimethyladamantane		122
2-Nitro-1,3-dihydroxyadamantane		130

SCHEME VI



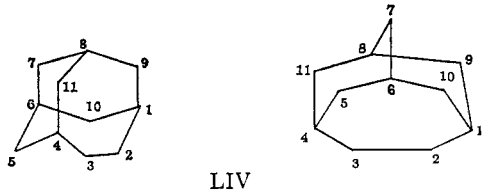
B. HOMOADAMANTANE (TRICYCLO[4.3.1.1^{3,8}]UNDECANE)

The Koch–Haaf carboxylation of 1-hydroxymethyladamantane (LII) gives surprising results (126). The product, assigned structure LIII, homoadamantane-1-



LII LIII

carboxylic acid, represents a net increase of ring strain, contrary to the usual thermodynamically controlled course of Koch–Haaf reactions (42). Conformational calculations on homoadamantane (LIV) suggest it to be strained to the extent of about 10 kcal./mole; adamantane, of course, should be strain free.

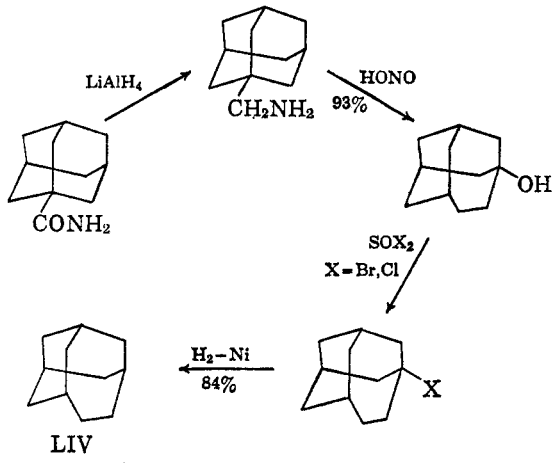


LIV

Preparation of the parent hydrocarbon, whose melting point (258–259°) is almost as high as that of adamantane, was achieved by a different route (121) utilizing the Demjanov reaction as the key ring expansion step (Scheme VII). Solvolysis of 1-hydroxymethyladamantyl tosylate (LV) in acetic acid–sodium acetate also leads to the homoadamantane skeleton (81), but if the salt is omitted, unrearranged acetate results (79, 81) as shown in Eq. 34.

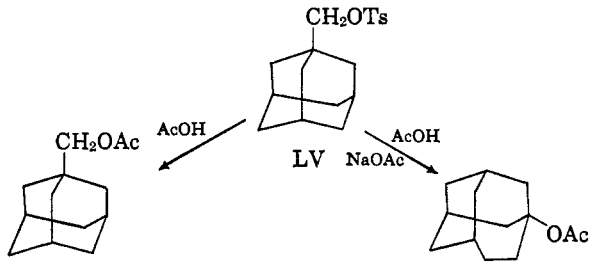
A remarkable regeneration of the adamantane nucleus from 1-homoadamantanol (LVI) has been shown (121) to occur upon treatment of LVI with hydrogen halides in acetic acid at 150° (Eq. 35).

SCHEME VII

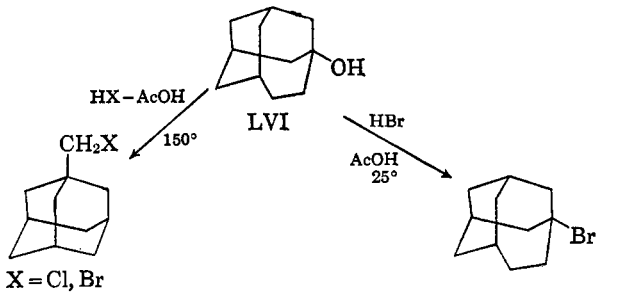


LIV

Milder conditions or different reagents accomplish substitution while maintaining skeletal integrity (Eq. 35, Scheme VII).



(Eq. 34)



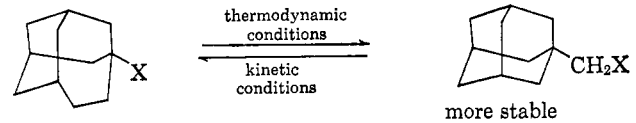
(Eq. 35)

These reactions illustrate well the interplay of thermodynamic and kinetic factors in product determination. The tertiary 1-homoadamantyl carbonium ion (LVII) is much more stable than the primary 1-adamantyl carbinyl cation (LVIII), and the former will be

LVII LVIII

produced under almost all conditions which generate positive ions as reaction intermediates. Direct substitution by SN2 processes on 1-adamantyl carbinyl derivatives, such as LV, should be inhibited by the neopentyl-type structure. Most replacement reactions will therefore proceed through LVII as the chief

ionic species; if product formation occurs irreversibly, the homoadamantane skeleton will result. However, homoadamantane is about 10 kcal. less stable than adamantane, and this difference in ring strain is sufficient to overcome the inherent greater stability of tertiary compounds over primary (Table XV) (19, 113). Under thermodynamic conditions in which ionic intermediates are generated repeatedly, the more stable 1-adamantyl carbinyl products will eventually result (Eq. 36).

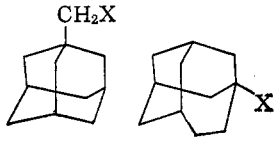


formed more rapidly

more stable

(Eq. 36)

TABLE XV
TERTIARY *vs.* PRIMARY STABILITY



Ring strain, kcal. (136)		0	*ca.* +10
Relative substituent stability, kcal. (19, 113)	X = Br	0	−3.4
	X = Cl	0	−5.7
	X = OH	0	−7.0

C. QUANTITATIVE STUDIES OF ADAMANTANE REACTIVITY

A growing body of quantitative data on the reactivity of adamantane and homoadamantane derivatives is available and is instructive concerning both the unusual reactivity of the bridgehead position in adamantane and the problem of bridgehead reactivity in general. These data are summarized in Table XVI, with model compounds included for comparison.

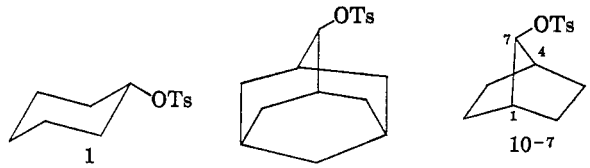
TABLE XVI
SOLVOLYTIC REACTIVITIES, 25°

Compound	Solvent	k_1, sec.$^{-1}$	ΔH^*, kcal.	ΔS^*, e.u.	Ref.
1-Bromoadamantane	80% EtOH	1.16×10^{-7}[a]	...	...	125
1-Bromoadamantane	80% EtOH	4.38×10^{-7}[c]	22.6	−12.0	103
1-Chloroadamantane	80% EtOH	7.59×10^{-9}[c]	25.5	−10.2	103
1-Iodoadamantane	80% EtOH	8.45×10^{-7}[c]	23.2	−8.6	103
1-Bromohomoadamantane	80% EtOH	1.64×10^{-4}	...	...	121
1-Chlorohomoadamantane	80% EtOH	3.45×10^{-6}	...	...	121
t-Butyl chloride	80% EtOH	9.24×10^{-6}	22.3	−6.6	28
t-Butyl bromide	80% EtOH	3.58×10^{-4}	21.5	−2.3	20
t-Butyl iodide	80% EtOH	9.26×10^{-4}	21.6	−0.1	109
1-Bromobicyclo[2.2.2]octane	80% EtOH	8.68×10^{-11}[c]	26.4	−16.0	21
1-Bromonorbornane	80% EtOH	7×10^{-13}[b]	...	...	21
1-Adamantyl tosylate	AcOH	5.68×10^{-4}	...	...	103
2-Adamantyl tosylate	AcOH	3.25×10^{-5}[c]	30.0	+3.2	102
Cyclohexyl tosylate	AcOH	4.88×10^{-8}[c]	27.0	−1.1	146
7-Norbornyl tosylate	AcOH	6.36×10^{-13}[c]	37.5	+2.3	147

[a] Run carried to 3% completion. [b] Estimated from rate in 40% EtOH at 216°; *cf.* ref. 103. [c] Calculated from rates at other temperatures.

It is immediately seen why ionic substitution reactions in adamantane proceed exclusively at the bridgehead. The factor of 10^5 separating 1- from 2-adamantyl tosylate reflects the greater stability of the 1-carbonium ion.

The rate of solvolysis of 2-adamantyl tosylate is in itself interesting, for it allows an unequivocal explanation of the extremely slow rate of 7-norbornyl tosylate. The relative reactivities of some 2° tosylates are shown below.



Various explanations have been offered for the diminished reactivity of 7-norbornyl compounds: (a) steric hindrance to solvation, by the *exo*-hydrogens, (b) steric inhibition of C–H hyperconjugation since the hydrogens adjacent to the positive charge are at bridgehead positions (Bredt's rule), (c) the favorable skew relationship of the substituents at C_1, C_7, and C_4 would be converted to eclipsed interactions as the transition state is approached, and (d) the C_1–C_7–C_4 angle is highly strained in the ground state; rehybridization of C_7 to sp^2, with a preferred 120° angle, should dramatically increase the strain.

In a 2-substituted adamantane, factors (b) and (c) should be equally applicable since the relation to the bridgehead hydrogens is the same. Hindrance to solvation (a) by the nearby hydrogens, if there is any difference, should be slightly greater in the adamantane system. The only significant difference between the two compounds is the internal angle at the substituted position: 98.3° (108) for norbornane, and 109.5° for adamantane. Clearly, the major portion of the 10^6 rate difference between norbornyl and adamantyl must be the result of angle strain. The small difference ($10^{1.2}$) between cyclohexyl and adamantyl is likewise explicable in this manner, since the cyclohexane ring can more easily contain a 120° angle without strain (14). These conclusions are substantiated by reports of a correlation between carbonyl stretching frequency (as a measure of angle strain) and the logarithm of the solvolysis rate for a wide variety of 2° tosylates (22, 97).

Angle strain considerations may be invoked also to explain the enhanced reactivity of the bridgehead position of adamantane. A bridgehead carbonium ion must adopt a configuration intermediate between planar and tetrahedral; either extreme is prohibitively strained (103, 107).

The angles in adamantane are all unstrained; as a consequence, the small angle distortions required for

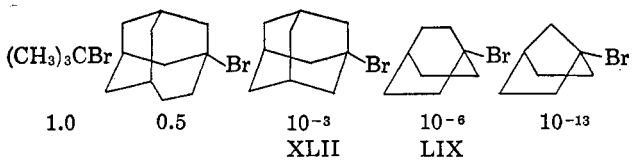


Fig. 2.—Relative solvolytic reactivities of halides.

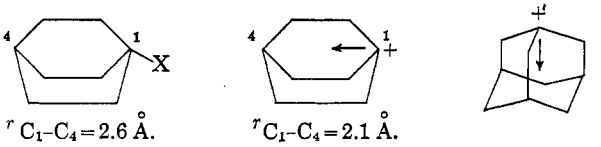


Fig. 3.—Bridgehead "bumping" in polycyclic systems.

achieving a "comfortable" flattened, but nonplanar, configuration are not energetically expensive. A figure of 3.5 kcal. has been calculated for the strain difference between *t*-butyl and 1-adamantyl carbonium ions (103). This is in good agreement with the rate difference of 10^3.

All of the angles in norbornane are highly strained in the ground state. As the bridgehead position flattens, the resultant energy gain is quickly overwhelmed by a tremendous increase in strain due to the deformation of the other angles in the molecule, and 1-norbornyl derivatives are therefore extremely unreactive (Fig. 2). Indeed, complete flattening of the ion would require that several bond angles be much less than 90°.

The difference between adamantane and bicyclo[2.2.2]octane is not so readily explained, for models show that the latter system can assume exactly the same configuration about the bridgehead as can adamantane, and angle strain calculations do not indicate that there should be any appreciable difference between the solvolysis rates of XLII and LIX (103). Unlike adamantane, bicyclo[2.2.2]octane, constructed of boat cyclohexanes, possesses considerable torsional strain (98). Were this ground state torsional strain to increase somehow in going to the transition state, the rate difference of 10^3 between XLII and LIX would be understandable. But no reasonable mechanism appears to be available for such an increase.

It has been suggested that the relative reactivities of the series of compounds shown above may be explained by the variations in the flexibility of the molecules (121). According to this proposal, the flexibility of bicyclic and tricyclic systems increases with the number of atoms, and *t*-butyl is the most flexible because it is acyclic.

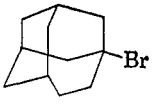
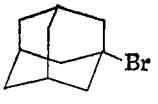
"Flexible," however, is a misleading word to apply to adamantane. Examination of models shows rather clearly that the adamantane skeleton is rigidly fixed; the molecule is not at all "flexible." The presence of extra carbon atoms is more than compensated for by the extra ring. If, in fact, the usual sense of the word is understood, bicyclo[2.2.2]octane is more "flexible" than adamantane, since it can twist around the C_1–C_4 bridgehead axis.

Adamantane may be considered more flexible than bicyclo[2.2.2]octane (or norbornane, for that matter) in that it is more easily able to accommodate a bridgehead carbonium ion. However, this would then not be an explanation, but only a restatement of experimental fact. The heightened reactivity of XLII over LIX is a result not of a greater number of atoms, *per se*, but of some structural difference between the two systems. It is probably better, therefore, to reserve the description "flexible" for molecules which are indeed flexible in the usual sense of the word.

A factor which has been overlooked, but may have considerable importance, is nonbonded repulsion. The distance between the C_1 and C_4 bridgehead atoms in bicyclo[2.2.2]octane, 2.6 Å. (Fig. 3), is considerably less than twice the van der Waals radius of carbon, *ca.* 1.6 Å. (33), so that some repulsive strain exists even in the ground state. Any lengthwise compression of the molecule, such as the flattening at a bridgehead experienced during ionization, should be resisted strongly because of the steepness of the van der Waals repulsive curve (141). This factor, not present in adamantane since the bridgehead positions are backed only by the "empty" interior of the molecule (Fig. 3), could be sufficiently large to account for the reactivity difference between 1-bicyclo[2.2.2]octyl and 1-adamantyl derivatives, provided that the van der Waals radius of a carbonium ion is not greatly different from that of un-ionized carbon.

In homoadamantane, models reveal, the additional carbon atom makes the structure more flexible than adamantane. The rates of solvolysis of 1-homoadamantyl derivatives are considerably greater than corresponding 1-adamantyl compounds and approach closely the rates of the *t*-butyl analogs (Tables XVI and XVII) (121).

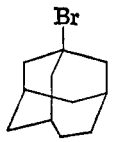
TABLE XVII
STRAIN EFFECTS UPON SOLVOLYSIS RATES

	$(CH_3)_3CBr$		
Relative rate	1.0	0.5	10^{-3}
Ground state strain	0	10 kcal.	0
Transition state strain	0	10 kcal.	4 kcal.
Strain increase upon ionization	0	0	4 kcal.

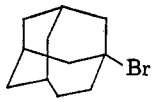
The principle of flexibility is not necessarily sustained by these results, however. Transition state theory tells us that the rate of a reaction is proportional to the energy difference between the ground state and the transition state for the given reaction. While

homoadamantane is more "flexible" than adamantane, it is also considerably more strained. The 1-homoadamantyl carbonium ion is also strained, but, fortuitously, to just about the same extent (13); therefore, no additional strain is introduced upon generation of the bridgehead ion. The rapid solvolysis rates of the homoadamantyl halides result from the ground state being very nearly as strained as the transition state (Table XVII).

The flexibility argument could be tested easily in the following manner. Homoadamantane possesses two different types of bridgehead positions. A structural analysis suggests that the 6-position of homoadamantane (LX) should resemble an adamantane bridgehead more closely than the 1-position (LXI) in that considerable strain increase must occur during carbonium ion formation from LX but not from LXI. If these con-



LX

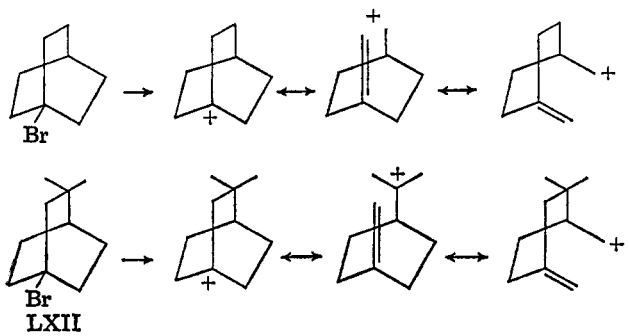


LXI

formational arguments are correct, the solvolysis rates of 6-homoadamantyl derivatives should be much slower than corresponding 1-homoadamantyl compounds. Both LX and LXI possess the same "flexibility"—the molecular skeleton is the same in both cases—and similar solvolysis rates would be predicted on this basis.

Although the foregoing discussion stresses the importance of conformational strain in determining the reactivity of bridgehead compounds, an electronic explanation can also be formulated. This is suggested by the observation that 3,3-dimethyl-1-bromobicyclo-[2.2.2]octane LXII solvolyzes about two times faster than the parent bromide (9.8×10^{-7} *vs.* 6.8×10^{-7} sec.$^{-1}$) in 70% dioxane at 100° (17). One obvious explanation is that the positive charge is being stabilized by C–C hyperconjugation, with the two methyl groups providing an extra measure of stabilization for any charge resonated to the 3-position (Scheme VIII).

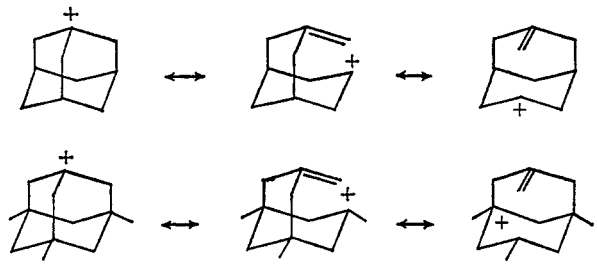
SCHEME VIII
HYPERCONJUGATION IN THE BICYCLO[2.2.2]OCTYL ION



LXII

The 1-adamantyl ion would then be more stable because all of the hyperconjugative forms are 2° rather than 1° (Scheme IX) as in the bicyclo[2.2.2]octyl ion.

SCHEME IX
HYPERCONJUGATION IN THE 1-ADAMANTYL ION



One would expect, if this explanation is sound, that substitution of methyls at the bridgehead positions of adamantane should further increase the stability of the ion, and consequently, a rate enhancement comparable to that in the bicyclooctyl system would be predicted. 1-Bromo-3-methyl- and 1-bromo-3,5-dimethyladamantane have been solvolyzed to test this contingency (101). In this event, the addition of methyl groups retards solvolysis slightly, as shown in Table XVIII.

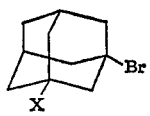
TABLE XVIII
SOLVOLYSIS OF METHYLBROMOADAMANTANES IN 80% ETHANOL, 70°

Compound	k_1, sec.$^{-1}$	Rel. rate	ΔH^*, kcal.	ΔS^*, e.u.
1-Bromoadamantane	8.76×10^{-5}	1.0	23.1	−10.1
1-Bromo-3-methyladamantane	6.05×10^{-5}	0.69	23.6	−9.7
1-Bromo-3,5-dimethyladamantane	4.12×10^{-5}	0.47	24.7	−9.3

While the slight decrease in rate upon methyl substitution was unanticipated, it does seem established that hyperconjugation is not responsible for the reactivity of adamantane.

The effect of electron-withdrawing substituents upon solvolysis rates of bridgehead adamantyl compounds has been studied (124). Qualitative expectations are fulfilled (Table XIX)—the rates are sharply decreased —but quantitative correlation with σ^* constants fails.

TABLE XIX
SOLVOLYSIS OF 3-SUBSTITUTED 1-BROMOADAMANTANES[a]



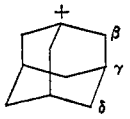
X	k_1, sec.$^{-1}$	Rel. rate
H	7.89×10^{-4}	1.0
CO_2H	1.30×10^{-5}	0.016
Br	2.40×10^{-6}	0.003

[a] In 70% aqueous dioxane at 100°.

1-Adamantyl carbonium ion itself, in the form of the SbF_6^- salt, has been obtained as a stable entity in SbF_5 solution (84). The n.m.r. spectrum (Table

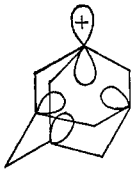
XX) is remarkable in that the γ-bridgehead hydrogens, and not the β, are the most deshielded, contrary to simple expectations based on distance from the charge. The C–C hyperconjugation argument, which might account for this, appears unattractive for reasons discussed above. An interesting alternative explanation is found in the possibility that the empty p-orbital

TABLE XX
THE N.M.R. SPECTRUM OF THE 1-ADAMANTYL CATION



Protons	Area, peak	δ, p.p.m. from TMS
β	6	4.50
γ	3	5.42
δ	6	2.67

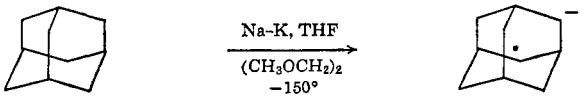
lobe of the 1-adamantyl carbonium ion, extending into the center of the molecule, can overlap with the "backsides" of the sp^3 orbitals of the three remaining bridgehead C–H bonds (LXIII). As a consequence, the bridgehead hydrogen resonances would be shifted to lower fields. Were this the case, the small decrease observed in solvolysis rates upon introduction of



LXIII

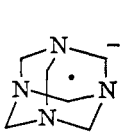
methyls at adamantane bridgeheads (Table XVII) could be explained by a decrease in backside orbital availability when a C–C bond is substituted for a C–H.

Support of a different kind for this backside orbital interaction argument stems from another source. Observation of the adamantane radical anion (9), prepared according to Eq. 37, suggests that the odd electron is located inside the molecular cavity of the adamantane molecule. The e.p.r. spectrum of the ion consists of five broad lines of approximately binomial intensity with a line separation, $a^H = 3.9$ gauss, ascribed to interaction of the electron with the four bridgehead

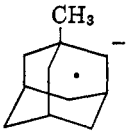


(Eq. 37)

hydrogens. Hexamethylenetetramine radical anion (LXIV) similarly shows the nine-line pattern to be expected if the electron is located inside the molecule and is interacting with the four bridgehead nitrogens (9). In this case, $a^N = 4.2$ gauss. 1-Methyladamantane radical anion (LXV), gives the four-line e.s.r. spectrum consonant with this interpretation, since only three bridgehead hydrogens are available for interaction. The line separation, $a^H = 1.8$ gauss, significantly smaller than that of adamantane radical anion, suggests that the methyl group is electron *withdrawing* (8).



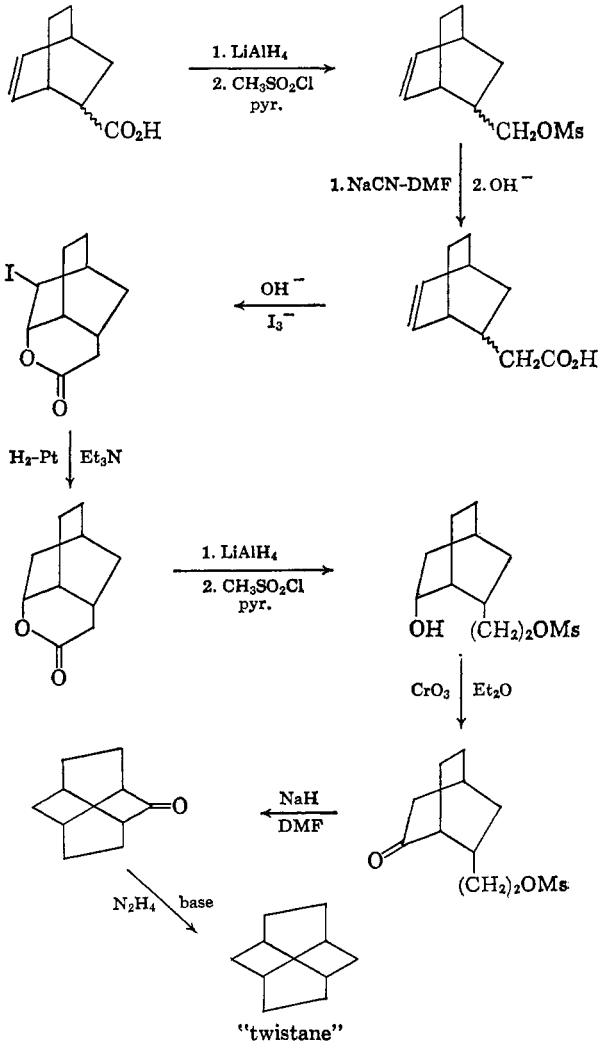
LXIV



LXV

Contrary to the well-documented electron-releasing ability of methyl when attached to an sp^2 or sp hybridized carbon, there appears to be increasing evidence that methyl can be electron withdrawing relative to a hydrogen which it is replacing, when attached to certain sp^3-hybridized carbons (*e.g.*, 44). The rate-depressing effect of bridgehead methyl substitution upon 1-adamantyl solvolyses (Table XVIII)

SCHEME X
THE SYNTHESIS OF TWISTANE



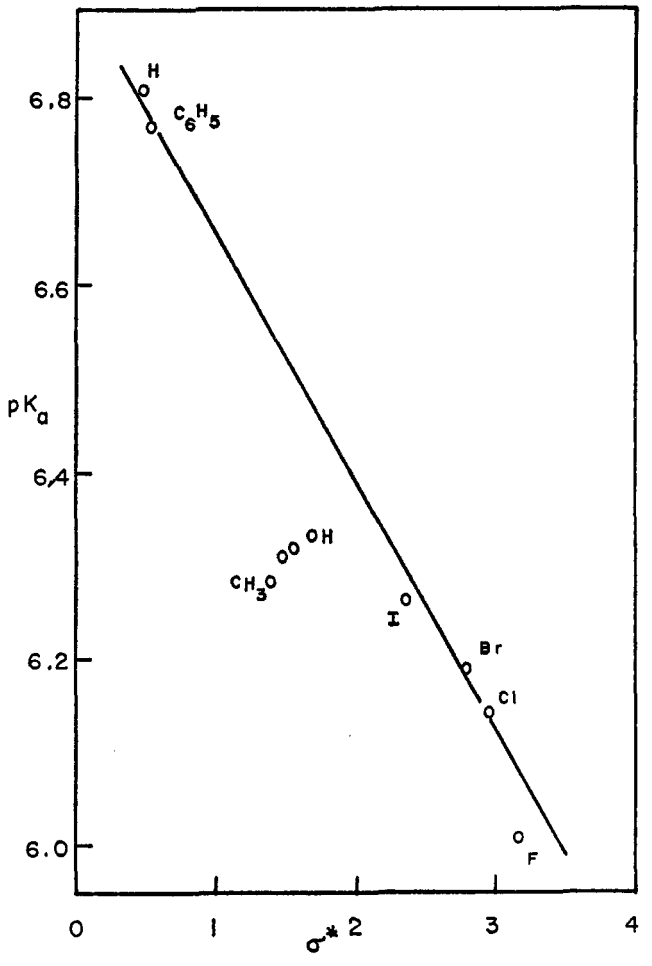


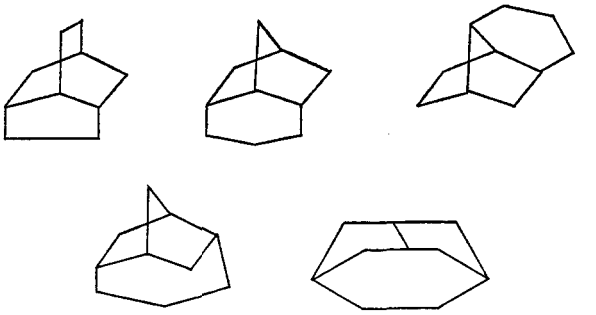
Fig. 4.—pK_a values of adamantanecarboxylic acids.

can be explained on this basis, as well as the e.s.r. spectra of the radical anions. $J_{^{13}CH}$, a measure of carbon hybridization (35), indicates that carbon in methyl ($J_{^{13}CH}$ = 125 c.p.s. in typical saturated hydrocarbons (77)) has more s character, and should be more electronegative, than carbon in adamantane ($J_{^{13}CH}$ = 120 ± 1 c.p.s.). The small dipole moments of propane (69) and isobutane (69) can also be explained on the assumption that methyl is electron withdrawing relative to the central carbons.

D. TWISTANE (TRICYCLO[4.4.0.0^{3,8}]DECANE)

Whitlock has recently carried out (143) an elegant synthesis of "twistane," an isomer of adamantane in which the six-membered rings are all in the twist-boat form (Scheme X). This substance melts at 163–165°, more than 100° lower than adamantane. In contrast to that of adamantane, its n.m.r. spectrum shows three sorts of hydrogens, at τ 8.37, 8.45, and 8.65, corresponding to the bridgeheads and the two sorts of methylenes. Studies of the chemistry of twistane should provide an interesting contrast to adamantane. For example, it should be considerably less stable than adamantane and should rearrange readily to the latter compound when treated with Lewis acids.

Other adamantane isomers which should be capable of ready preparation are shown below. None of these has been reported, but several, such as LXVI are of



LXVI

particular interest as possible intermediates in the adamantane rearrangement.

E. MISCELLANEOUS

Stetter and Mayer (124) have provided a quantitative demonstration of the transmission of inductive effects through the adamantane molecule: the pK_a values of a series of 3-substituted adamantane-1-carboxylic acids. Table XXI compares these with the corresponding *trans*-4-substituted cyclohexanecarboxylic acids (110) and 4-substituted bicyclo[2.2.2]-octane-1-carboxylic acids (91).

The acidities of the adamantyl compounds are qualitatively in the expected order; however, a plot of pK_a *vs.* σ^* does not give a particularly good correlation (Fig. 4), unless points for OH, OCH_3, and F are excluded. No reason may be advanced for this behavior at present.

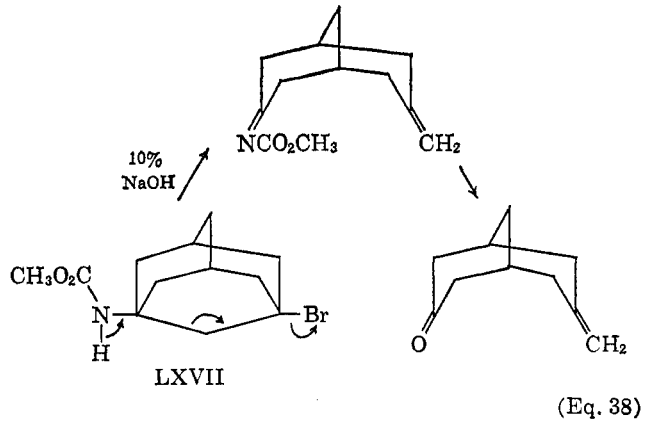
TABLE XXI
pK_a VALUES OF SUBSTITUTED CARBOXYLIC ACIDS[a]

X	3-Adamantyl	4-Cyclohexyl	4-Bicyclooctyl
H	6.81	6.40	6.75
C_6H_5	6.77	...	...
OH	6.32	6.07	6.33
OCH_3	6.30	6.02	...
I	6.26	...	...
Br	6.19	...	6.08
Cl	6.14	5.89	...
F	6.00	...	...

[a] In 50% aqueous ethanol at 25°; the pK_a of adamantane-2-carboxylic acid is 6.83 (122).

Although it might seem *a priori* an unfavorable process, the adamantane system can be reopened to the bicyclo[3.3.1]nonane skeleton (129, 130). Compound LXVII, when treated with base, fragments in the fashion shown in Eq. 38 to give a bicyclononane derivative.

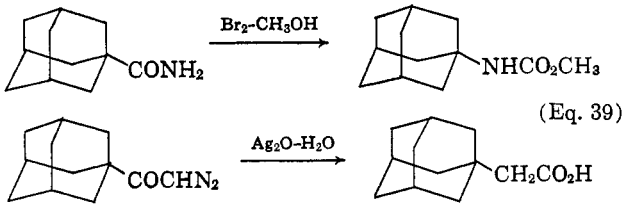
Rearrangements involving migration of an adamantyl group have been observed (Eq. 39 and 40). Bridge-



LXVII

(Eq. 38)

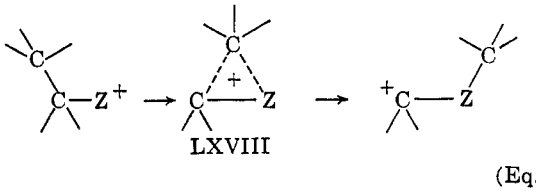
head carbon atoms usually migrate without difficulty even the highly strained bicyclo[2.2.1]heptane system (107). It has been argued that the facility of this rearrangement indicates essentially sp^3 hybridization in the transition state (LXVIII) for the migrating



(Eq. 39)

(Eq. 40)

carbon (Eq. 41). Were the hybridization to be more nearly sp^2 in LXVIII, the rearrangement of strained



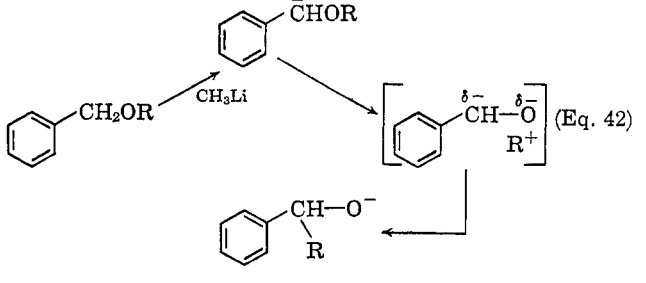
LXVIII

(Eq. 41)

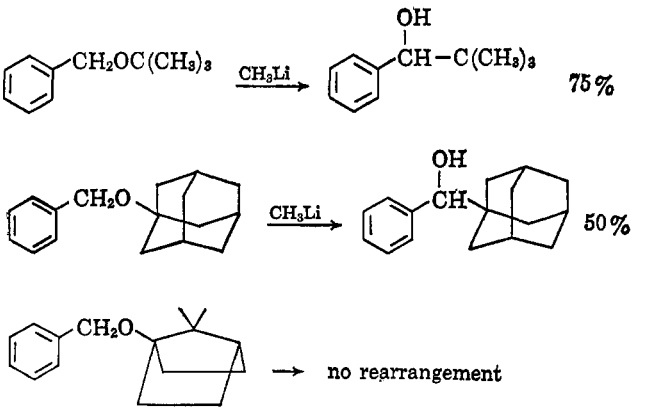
tertiary carbons should be inhibited relative to unstrained ones.

This principle has been applied (64) to the study of the mechanism of the Wittig rearrangement (Scheme XI). The results, it was suggested (64), support a mechanism in which considerable positive charge is generated on the migrating carbon during rearrangement (Eq. 42).

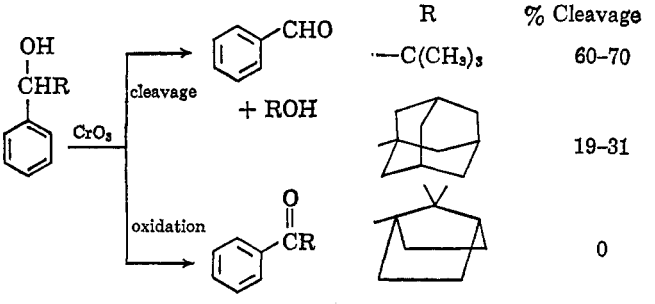
SCHEME XI



(Eq. 42)



A similar line of reasoning has been followed in an investigation of the chromic acid cleavage of certain secondary alcohols (65), as shown below.



The gradation in the amount of cleavage is said to confirm the accepted mechanism, in which the alcohol, ROH, is produced from a carbonium ion intermediate, R^+.

The polarographic reduction of 1-bromoadamantane has been examined (149). Table XXII compares the half-wave potential for this process with those for the reduction of several other aliphatic monobromides.

TABLE XXII
POLAROGRAPHIC REDUCTION OF ALKYL BROMIDES

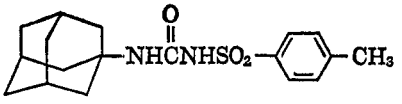
Compound	$E_{1/2}$, v.
n-Butyl bromide	−1.90
Isopropyl bromide	−1.91
Cyclohexyl bromide	−1.91
Cyclodecyl bromide	−1.92
2-Bromobicyclo[2.2.2]octane	−1.99
endo-8-Bromobicyclo[3.2.1]octane	−2.15
1-Bromoadamantane	−2.02

The values of $E_{1/2}$ are thought to reflect the difficulty of the approach of an electron to the rear of the bromine bearing carbon (46); however, a comparison of adamantyl bromide with the other compounds in the table perhaps is not strictly valid, since adamantyl bromide is 3°, while the others are 2° or 1°. Data on more suitable comparison molecules were not reported.

The physiological properties of an increasing number of adamantane compounds are being examined. One might expect that the pronounced lipophilic character

associated with a globular hydrocarbon residue could have profound effects upon the biological potency of molecules (24).

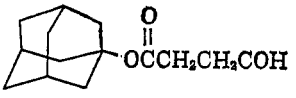
With this thought in mind, several N-arylsulfonyl-N'-adamantyl ureas were evaluated as hypoglycemic agents (24). A distinct enhancement of efficacy was found for some of these. For example, LXVIII has a potency of 15.5 relative to the commonly used tolbutamide, when tested on rats. Preliminary clinical studies on adult human diabetics indicate this compound to be a most



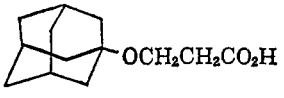
LXVIII

satisfactory, potent, oral hypoglycemic agent.

Two adamantane derivatives (LXIX and LXX) having choleretic activity have been patented (34, 90), and several polychlorinated adamantanes (140) promise to aid humanity in controlling *musca domestica*, the common house fly.



LXIX



LXX

V. CONCLUSIONS

Although the synthetic aspects of adamantane chemistry are relatively well established—the parent hydrocarbon and its simple derivatives can be prepared easily—most of the reactions already studied are those which many other hydrocarbons would undergo. The properties specific to adamantane have not been sufficiently exploited. The prospect that adamantane may have unique behavior associated specifically with its cage structure and "empty" interior is a prospect only now being realized. By and large, little advantage has been taken of the structural features peculiar to adamantane: rigid, strain-free, cyclohexane rings locked into chairs, incapable of double bond formation and skeletal rearrangements, and possessing a structure of some complexity for which geometries can confidently be calculated.

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