A Thesis entitled

# ADAMANTANE AND RELATED RING SYSTEMS

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by

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Magdalen College

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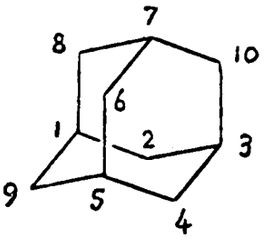
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# INTRODUCTION

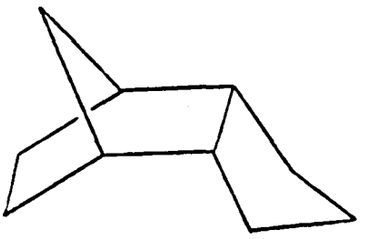
Attempts at the synthesis of diamond and investigations of its structure were a favourite research occupation at the turn of the century. Consequently, it was only natural that attention was devoted later to the construction of hydrocarbon systems having diamond-like structures. The first and basic member of such a series is the tricyclic hydrocarbon, adamantane (I).



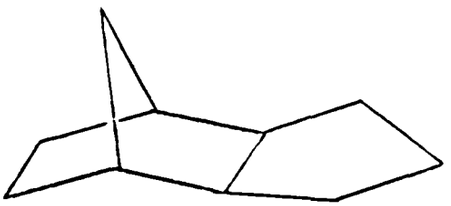

I

This compound was first isolated by Landa[1] from crude petroleum, and at first its synthesis was achieved by ring closure of some bicyclo [3,3,1] nonane derivative, a step which could only be carried out in poor yield.

In 1956, however, Schleyer[2] found adamantane as a by-product from the isomerisation of endo-tetrahydrodicyclopentadiene (II) to its exo isomer (III) with aluminium chloride.



II



III

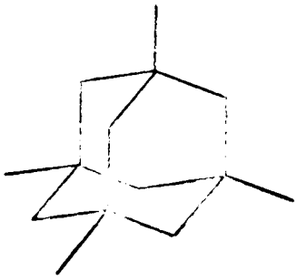
Research into the chemistry of adamantane has mushroomed since then, particularly in the pharmaceutical field, where it has been discovered that introduction of an adamantyl group into a molecule already known to be 'active' often tends to enhance significantly its potency.

It has been found[3,4] that adamantane and its bridgehead methyl derivatives can be made from almost any tricyclic saturated hydrocarbon, which contains five- or six-membered rings and from ten to fourteen carbon atoms. A simple, effective catalyst[5] has been developed to perform such rearrangements, in which the hydrocarbon is treated with anhydrous aluminium bromide and t-butyl bromide for 1-4 days at 55-60°. In fact, it is even possible to treat a crude hydrocarbon mixture with the catalyst and obtain a pure product directly from the work up, if all the compounds present in the crude mixture contain an equal number of carbon atoms.

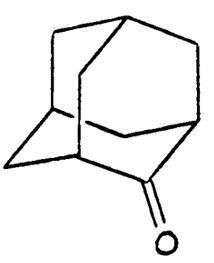
1-Substituted derivatives of adamantane can be readily

prepared by hydride ion abstraction[3], as the intermediate carbonium ion can only pick up a nucleophile and does not rearrange or eliminate.

Bromination, oxidation, and Koch-Haaf carboxylation are commonly used to introduce functional groups. It is generally much more difficult to obtain 2-substituted derivatives because the methylene groups are far less reactive in carbonium ion processes, but they can be prepared by taking advantage of the low selectivity of free radicals and the high ratio (12:4 in adamantane) of secondary to tertiary hydrogen atoms, and by blocking bridgehead positions with suitably inert groups. Recently, ozonolysis[6] and catalytic aerial oxidation[7] have been used, which provide examples of the former approach. 1,3,5,7-Tetramethyl-adamantane (IV) is an example of the latter, although derivatives of this hydrocarbon have been reported[8] only once. Geluk and Schlatmann[9,10] have shown that under specific conditions, 1-hydroxyadamantane and adamantane can be converted into 2-adamantanone (V) by concentrated sulphuric in good yield, but this is not generally applicable.



IV

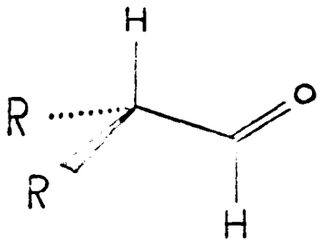



V

The rigid adamantane system, composed of three fused chair cyclohexane rings, is particularly suitable for studies requiring a molecule of known geometry without significant strain. Previously other cyclohexanoid systems such as diterpenes[11] and steroids[12], have been used as models for correlating structure with molecular parameters, but in such molecules, small deviations in bond angles from 109° 28' can result in large errors in distances and angles estimated, e.g. from Dreiding models. Nuclear magnetic resonance spectroscopy has been extensively used in the investigation of stereochemical problems from studies of both chemical shifts and coupling constants. For example, the effects of various substituents upon the chemical shifts of C-18 and C-19 angular methyl groups for many steroids of known structure have been tabulated by Zurcher[13], and are found to be additive in the absence of complicating interatomic interactions. Such empirical data has been used to obtain conformational information for steroids of unknown structure.

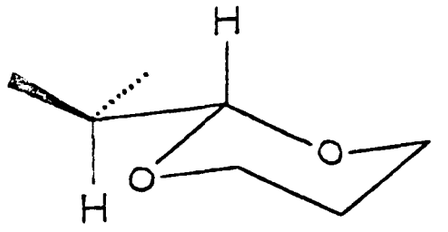
Variable temperature studies have been made on HH vicinal coupling constants, which vary with the dihedral angle between the coupled protons. These give information about the relative stability of conformers resulting from rotation about a single bond which is not part of a ring,

i.e. in acyclic compounds and in cyclic compounds with substituents of relatively low symmetry. Examples of such compounds are isobutyraldehyde (VIa)[14a] and 2-isopropyl-1,3-dioxane (VII)[14b]. Previously aliphatic molecules have



VIa R=$CH_3$

VIb R=$^tC_4H_9$



VII

been employed as models to derive individual coupling constants for conformers, which cannot be determined directly from a low temperature NMR spectrum. Such molecules, e.g. di-tert-butylacetaldehyde (VIb)[14a], can easily distort by bending, which prevents the molecular geometry from being confidently predicted, and makes them seriously suspect as models. Rigid adamantanes can provide better models.

Dipole moment measurements have been widely used in the past for the determination of chemical structure, and more recently for the solution of conformational problems. However, conjugated and aromatic systems have been used almost exclusively even when the inductive effects of different functional groups have been studied. In particular, very little direct evidence has been reported[15,16] concerning

the inductive effect of a methyl group when it is attached to a saturated carbon atom ($sp^3$ hybridization). The evidence available suggests that the bond dipole is small in magnitude ($\sim$ 0.1 D[17]), but probably opposed to the normally electron-donating character associated with a methyl group attached to an unsaturated carbon atom (sp or $sp^2$ hybridization). The sign has not yet been determined unambiguously by measuring the change in dipole moment of a polar molecule with a moment of known magnitude and direction caused by replacing $C(sp^3)$-H by $C(sp^3)$-$CH_3$. The sensitivity of this measurement in solution depends on molecules being used which have substantial dipole moments because the orientation polarization depends on the square of the dipole moment.

# SECTION ONE

## The synthesis of adamantane derivatives

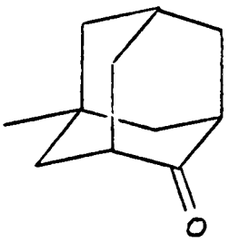
The oxidation of adamantane and its bridgehead methyl derivatives

A major part of the synthetic work has been concerned with the development of methods for the oxidation of methyl adamantanes to their monoketone derivatives. Recently, Geluk and Schlatmann[9] have studied the oxidation of adamantane with concentrated sulphuric acid, which provides a reasonable method of preparation of 2-adamantanone in yields of 30-50%. They have distinguished 4 distinct stages during the reaction, which are as follows:

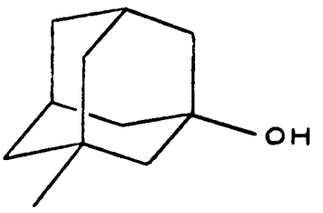
1. Oxidation of adamantane to 1-hydroxyadamantane by sulphuric acid.
2. Isomerisation of 1-hydroxyadamantane to 2-hydroxy adamantane by a 1,2-hydride shift.
3. Disproportionation of 2-hydroxyadamantane to adamantane and 2-adamantanone.
4. Oxidation of 1-hydroxyadamantane to 2-adamantanone by means of sulphuric acid probably via 2-hydroxyadamantane.

They report that alkyl homologues of adamantanone can also be formed by analogous reactions in sulphuric acid. For instance, 5-methyladamantan-2-one (VIII) was obtained from 3-methyladamantan-1-ol (IX) in 20% yield.

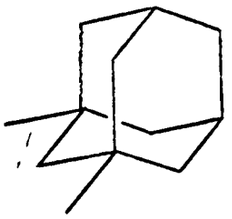
Therefore ox[illegible],3-dimethyl- (X) and 1,3,5-



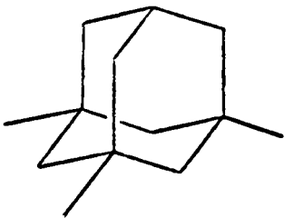

VIII



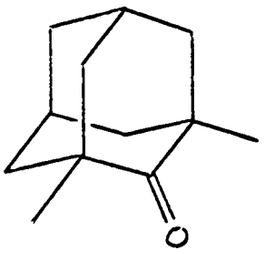

IX



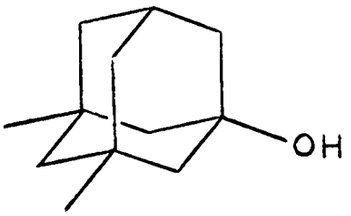
X



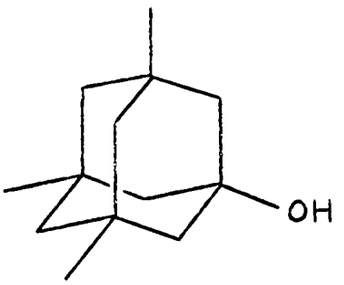
XI



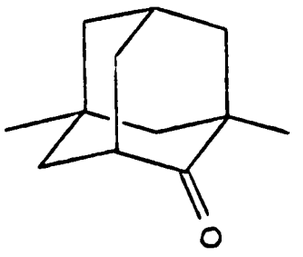

XIV



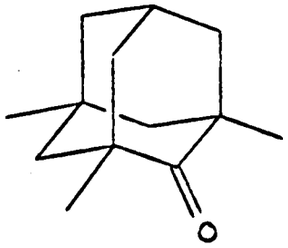

XII



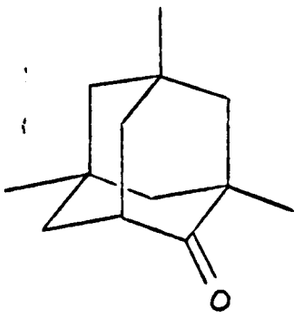

XIII



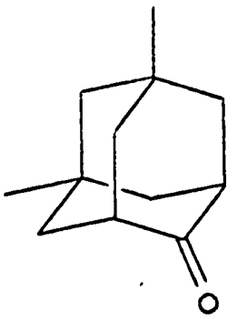

XV




XVII




XVIII




XVI

trimethyladamantane (XI) and their respective bridgehead monoalcohols, (XII) and (XIII), were carried out in 96% sulphuric acid at 60°, in an attempt to prepare all the possible isomeric monoketones of 1,3-dimethyl-, (XIV), (XV) and (XVI), and 1,3,5-trimethyladamantane, (XVII) and (XVIII). The products obtained from both hydrocarbons were in low yield (30-40%), and from infrared spectral evidence did not contain carbonyl compounds in sufficient quantities for any further isolation procedures to be undertaken. However, the oxidation of both monohydroxy compounds did provide evidence of the formation of ketones. As both reactions proceeded, two layers separated, the upper one being hydrocarbon probably formed by a disproportionation reaction. The products obtained from 1-hydroxy-3,5-dimethyladamantane (XII) were chromatographed over alumina and separated into hydrocarbon fractions, fractions containing an ether, fractions containing carbonyl compounds, and polyoxygenated material. The ether showed strong absorption in the infrared between 1080 and1100 $cm.^{-1}$, and the parent peak of the mass spectrum occurred at $^{m}/_{e}$ = 340, which is two mass units below that required for a tetramethyldiadamantyl ether. This product was not investigated further.

The isolation of pure monoketones from the fractions

containing carbonyl compounds was not achieved by further chromatography nor by preferential semicarbazone formation. All spectral and chromatographic evidence pointed to a mixture of many different carbonyl compounds being present, and only 5,7-dimethyladamantan-2-one (XVI) was identified in the mixture by characteristic infrared absorption.

The products obtained from 1-hydroxy-3,5,7-trimethyl-adamantane (XIII) were separated similarly into hydrocarbon fractions, fractions containing an ether ( $\nu_{max.}$ 1080 - 1090 $cm.^{-1}$), fractions containing carbonyl compounds, from which 1,5,7-trimethyladamantan-2-one (XVIII) was isolated in 3% overall yield, and polyoxygenated material. It is evident from these results that sulphuric acid is not convenient as an oxidant for 1,3-dimethyl- and 1,3,5-trimethyl-adamantane nor their respective monohydroxy bridgehead derivatives.

In 1967, Landa and Vodicka[6] reported that 2-adamantanone had been obtained from the ozonolysis of adamantane using di-tert-butyl peroxide as an initiator. It was not clear, however, from the paper in what yield 2-adamantanone had been prepared. If 1,3-dimethyl- or 1,3,5-trimethyladamantane were used as the substrate, the ratio of methylene to methine groups in the molecule would be 6:1 and 12:1 respectively. [illegible] favour radical attack at a secondary

position even more than for adamantane itself, where the ratio is only 3:1.

The ozonolyses of 1,3-dimethyl- and 1,3,5-trimethyl-adamantane were subsequently carried out using di-tert-butyl peroxide, and carbon tetrachloride as the solvent. The products from the former hydrocarbon (X) were separated by chromatography into the following components: 1,3-dimethyl-adamantane (X), 1,3-dimethyladamantan-2-one (XIV) in ca. 3% overall yield, and 1-hydroxy-3,5-dimethyladamantane (XII). Rather surprisingly, no 5,7-dimethyladamantan-2-one (XVI) could be detected by infrared. This isomer would result from attack at the least hindered methylene group in the hydrocarbon, and might be expected to be favoured, particularly over 1,3-dimethyladamantan-2-one (XIV). That this is not the case, suggests that the least hindered ketone (XVI) or an intermediate in its formation is open to further attack.

The products from the latter hydrocarbon (XI) were separated similarly into 1,3,5-trimethyladamantane (XI), 1,3,5-trimethyladamantan-2-one (XVII) in ca. 2% overall yield, 1,5,7-trimethyladamantan-2-one (XVIII) in ca. 1.5% overall yield, and 1-hydroxy-3,5,7-trimethyladamantane (XIII). In this case, both isomers are favoured equally on a statistical basis and the more hindered ketone (XVII) predominates, which is in agreement with the results above

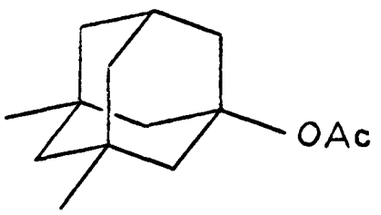
for 1,3-dimethyladamantane.

The difficulty with these ozonolyses and the sulphuric acid oxidation, ignoring the fact that in certain cases some isomers cannot be detected amongst the products, is that those isomers which are formed are almost always contaminated with impurities, which cannot be removed successfully by chromatography or by distillation.

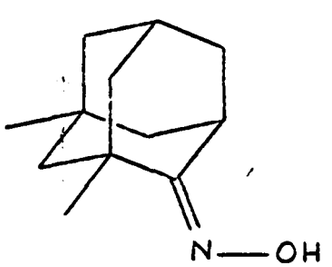
Smith and Williams[18] have described the oxidation of adamantane by air under pressure in an autoclave in the presence of di-tert-butyl peroxide and cobaltous acetate using glacial acetic acid and benzene as solvent at temperatures around 140°. This method has been applied to 1,3-dimethyladamantane[8] and resulted in the isolation of all three isomeric monoketones. The yields of pure 1,3-dimethyl (XIV) and 1,5-dimethyladamantan-2-one (XV) were very low (ca. 0.2%) because 1-acetoxy-3,5-dimethyladamantane (XIX) was eluted from the alumina column overlapping with both these ketones. Its removal by methanolic alkaline hydrolysis was successful, but still the method was clumsy and although impurities were absent, yields were low (ca.5% total for 3 isomers).

A much simpler modification of this approach has been developed by Schneider[7], who was seeking methods for preparing dihydroxyalkyladamantanes on an industrial scale. Air or

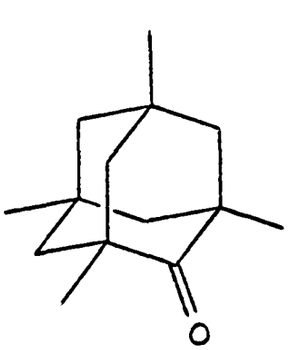
oxygen is bubbled into the liquid hydrocarbon containing cobalt naphthenate (50 p.p.m.) at temperatures from 160° to 200°. The advantages of this method are that neither a solvent nor an autoclave are required. It was not clear from the paper again, in what yields the alkyladamantanones were obtained, perhaps because their isolation was not attempted; in fact, reduction and rearrangement were then performed to give bridgehead hydroxy derivatives. Batches of 1,3-dimethyl- and 1,3,5-trimethyladamantane (50 g.) were therefore subjected to aerial oxidation at 175-185° in the presence of cobalt naphthenate. Air was bubbled into the hydrocarbon by applying gentle suction from a water pump to the condenser fitted to the reaction flask. A trap cooled by dry ice prevented volatile material from being lost. After 12 hours, the reaction was stopped as the carbonyl band intensity in the infrared spectrum failed to increase much by this stage. It was thought prudent to err on the side of imcomplete reaction rather than create difficulties with oxygenated impurities from side-reactions. A rough chromatographic separation of the products from 1,3-dimethyladamantane gave an 11% yield of dimethyladamantanones, free from impurities. Further chromatography over alumina of this monoketone fraction led to pure 1,3-dimethyladamantan-2-one (1%), 1,5-dimethyladamantan-2-one (3%), and




XIX




XX



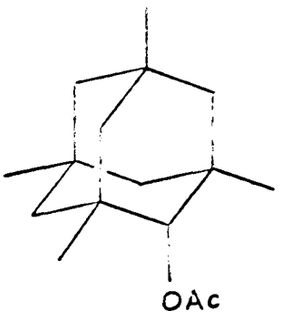

XXI

5,7-dimethyladamantan-2-one (1%). To assist in the complete separation of the first two isomers above, which were eluted in close succession from the column, intermediate fractions were added to a mixture of hydroxylamine hydrochloride and sodium hydroxide in ethyl alcohol. Almost immediately, the oxime of 1,5-dimethyladamantan-2-one (XX) was precipitated. The presence of methyl groups attached to both carbon atoms adjacent to the carbonyl group provides sufficient steric hindrance to prevent formation of an oxime under these conditions, and 1,3-dimethyladamantan-2-one (XIV) was easily separated with this technique. It was already known[8] that only partial formation (32%) of an oxime takes place when 1,3,5,7-tetramethyladamantan-2-one (XXI) is heated under reflux in ethyl alcohol with hydroxylamine for 10 hours.

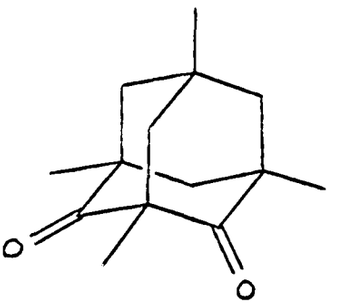
Similarly, a rough separation of the products from 1,3,5-trimethyladamantane gave a 10% yield of trimethyladamantanones, also free from impurities. Further chromatography over alumina led to pure 1,3,5-trimethyladamantan-2-one (XVII) in 3% yield, and 1,5,7-trimethyladamantan-2-one (XVIII) in 4% yield. Oxime formation was used again to separate the two ketones in intermediate fractions. This aerial oxidation[7] is a considerable

improvement upon all others that have so far been carried out. In addition, the unchanged hydrocarbon (60-70%) recovered from the reaction products can be reused immediately for further oxidation.

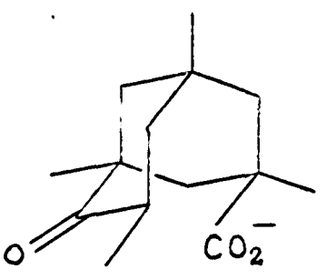
Chromic acid is one further oxidising agent that has been used on alkyladamantanes. Both 1,3-dimethyl-[8] and 1,3,5-trimethyladamantane have been treated with chromium trioxide and sulphuric acid in glacial acetic acid (the oxidation of cycloparaffins using these reagents has been described by Mares, Rocek and Sicher[19]), primarily to obtain the monoalcohol as a precurser for other derivatives. In both cases, the bridgehead monohydroxy derivative was the major product, but all the isomeric monoketones were also formed in small quantities and isolated. The yields were again very low and formation of acetates was common to both. As 1,3,5,7-tetramethyladamantane (IV) has no methine groups, its oxidation by this reagent can only occur at secondary positions, and although at least 3 major products are formed, the reaction has been extensively studied.[8] When 1,3,5,7-tetramethyladamantane (1 mol.) is dissolved in glacial acetic acid at 50-60°, and chromium trioxide (2 mols.) and sulphuric acid (3 mols.) are added, the major products formed are 1,3,5,7-tetramethyladamantan-2-one (XXI), 2-acetoxy-1,3,5,7-tetramethyladamantane (XII) and 1,3,5,7-tetramethyladamantan-



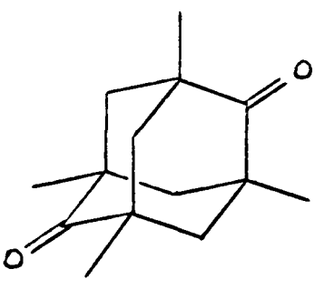

XXII



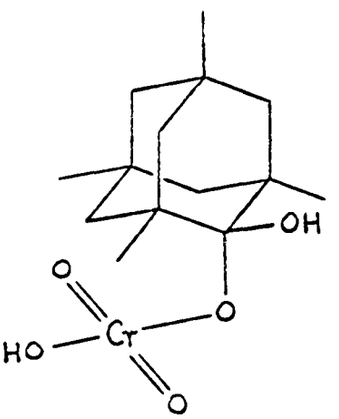

XXIII




XXIV

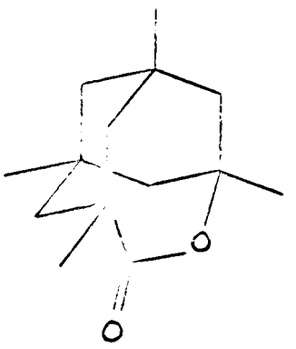



XXV

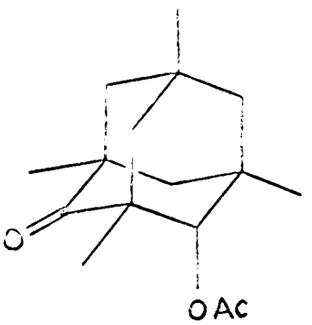



XXVI

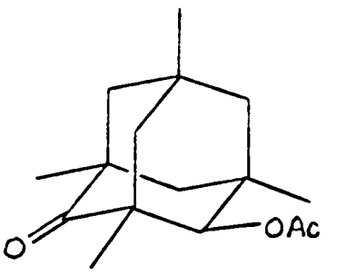
2,4-dione (XXIII) identified from infrared, NMR and mass spectral analysis. The product mixture is first hydrolysed by methanolic potassium hydroxide and the neutral material is separated and oxidised by Jones reagent.[20] Alumina chromatography then leads to pure 1,3,5,7-tetramethyladamantan-2-one (55%) by removing traces of unreacted hydrocarbon (IV). After the alkaline filtrate from the above has been acidified and left to stand at $0^{\circ}$ for a few days, 1,3,5,7-tetramethyl-adamantan-2,4-dione (13%) can be collected. The conditions of alkaline hydrolysis presumably cause ring opening in the dione (XXIII) to form the keto carboxylate anion (XXIV), which subsequently reverts to the dione on acidification. Surprisingly, 1,3,5,7-tetramethyladamantan-2,6-dione (XXV) has never been isolated from alumina chromatography of the neutral portion. One might expect that with formation of the monoketone, further oxidation via hydride ion abstraction would occur at a point in the molecule as far from the electron withdrawing influence of the carbonyl group as possible, which would lead to formation of the 2,6-dione (XXV). Instead, the 2,4-dione (XXIII) is overwhelmingly favoured which suggests that there must be some facile method of attack at one of the four neighbouring equivalent methylene positions, possibly via a hydroxy chromate ester, e.g. (XXVI), acting intramolecularly.



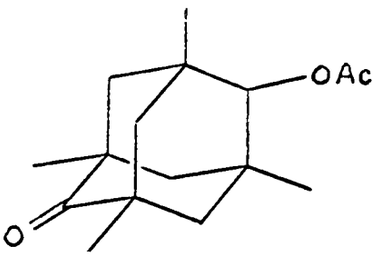
XXVII




XXVIII




XXIX




XXX

In an attempt to isolate and characterize the elusive 1,3,5,7-tetramethyladamantan-2,6-dione, 1,3,5,7-tetramethyladamantan-2-one was treated with an excess of chromic acid, followed by methanolic alkaline hydrolysis. The neutral portion was separated by alumina chromatography into 1,3,5,7-tetramethyladamantan-2-one (13%) and 4-oxa-1,3,6,8-tetramethylhomoadamantan-5-one (XXVII) in 3% yield. The latter compound was identified by its mass spectrum (molecular ion at $^{m}/e$ = 222), NMR spectrum (2:1:1 pattern of $CH_3$ singlets), and was confirmed by elemental analysis. The alkaline filtrate was acidified giving only 1,3,5,7-tetramethyladamantan-2,4-dione (XXIII) in 28% yield. No other compounds were detected. It is indeed strange that under the conditions of alkaline hydrolysis, the lactone (XXVII) apparently fails to open, but the β-diketone (XXIII) does so readily and also recloses on acidification. After the 2,4-dione (XXIII) had been collected, no further examination of the acidic filtrate was carried out.

Next 2-acetoxy-1,3,5,7-tetramethyladamantane (XXII) was treated with an excess of chromic acid, and the products were chromatographed without alkaline hydrolysis. 1,3,5,7-Tetramethyladamantan-2-one (47%) and 2-acetoxy-1,3,5,7-tetramethyladamantane (23%) were isolated and identified together with more polar material, which showed three acetoxyl methyl groups in the NMR spectrum at 7.91, 7.95 and 7.99 τ ,

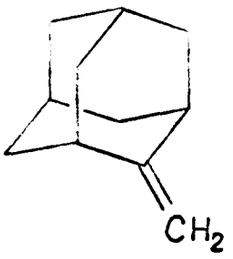
and two strong bands in the carbonyl region of the infrared at 1720 and 1742 $cm.^{-1}$ There are three possible isomeric ketoacetates, (XXVIII), (XXIX), and (XXX), of 1,3,5,7-tetramethyladamantane, two of which, (XXVIII) and (XXIX), are related to the 2,4-dione, and one (XXX), to the 2,6-dione. In the hope that one of the acetates, indicated by the NMR spectrum, was indeed 6-acetoxy-1,3,5,7-tetramethyladamantan-2-one (XXX), the more polar material above was subjected to alkaline hydrolysis, oxidation with Jones reagent, and further alkaline hydrolysis. The NMR spectrum of the neutral portion from the last stage consisted of two signals of intensity 3:2 at 9.01 and 8.14 $\tau$, respectively, which provided an excellent characterization for 1,3,5,7-tetramethyladamantan-2,6-dione (8% overall yield). To confirm the presence of the two ketoacetates, (XXVIII) and (XXIX) derived from 1,3,5,7-tetramethyladamantan-2,4-dione in the polar material described earlier, they were synthesised from the 2,4-dione, which was first reduced by lithium aluminium hydride to a mixture of isomeric 1,3-diols, which was carefully reoxidised with Jones reagent (sufficient oxidant was added to arrive at the ketoalcohol). The keto-alcohol mixture was acetylated with acetic anhydride and sulphuric acid, and the products were chromatographed over alumina and separated into two major components, the first

with an acetoxyl methyl at 7.99 and a secondary acetate proton at 5.14 $\tau$ , and the other with an acetoxyl methyl at 7.95 and a secondary acetate proton at 5.45 $\tau$ . The same molecular formula was confirmed for both compounds by mass spectral and elemental analysis. To distinguish between the two ketoacetate isomers, (XXVIII) and (XXIX), the NMR signal given by the hydrogen atom at $C_4$ is of interest. When this proton is equatorial to the cyclohexanone ring, it would be deshielded by the carbonyl group (relative to an axial proton at $C_4$) and could couple only significantly with the equatorial proton at $C_9$ via long range coupling, and in the absence of virtual coupling would give a doublet. In fact, the first component (XXVIII) eluted from column shows a doublet at 5.14 $\tau$ with coupling of 2.5 cps. When the $C_4$ proton is axial to the cyclohexanone ring, it could couple with two other protons at $C_6$ and $C_{10}$. The second component (XXIX) shows an apparent singlet ($W_h$ = 3 cps.) at 5.45 $\tau$ , attributable to a close unresolved multiplet arising from narrowing of a 1:2:1 triplet by virtual coupling because both protons at $C_6$ and $C_{10}$ have very similar chemical shifts.

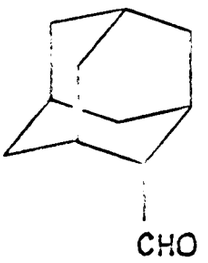
The preparation of derivatives from adamantane

A great number of bridgehead derivatives of adamantane have been synthesised, but until recently, very little work has been done to prepare 2-substituted derivatives.[21,22] Since it was found that 2-adamantanone could be made directly from adamantane in 30-50% yield by sulphuric acid oxidation[9,10], the synthesis of such derivatives has become practicable.

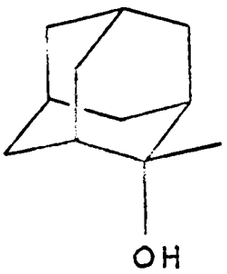
Following the method described by Schleyer[21], a synthesis of 2-methyleneadamantane (XXXI) was undertaken as a step towards adamantane-2-aldehyde (XXXII), not as yet reported[23] in the literature. 2-Adamantanone (V) was treated with methyl magnesium iodide to obtain 2-methyladamantan-2-ol (XXXIII), which was then dehydrated with 85% phosphoric acid. The major product isolated was not the olefin (XXXI) as expected, but 2-methyladamant-2-yl-2',2'-adamantylidene methane (XXXIV) in 70% yield as the solid residue from a steam distillation of the crude product, which separated the much more volatile 2-methyleneadamantane (XXXI) in 15% yield. Under the acidic conditions, it appears that the olefin (XXXI) can attack the carbonium ion generated from the alcohol (XXXIII), and the subsequent intermediate then loses a proton to give the less volatile olefin (XXXIV).



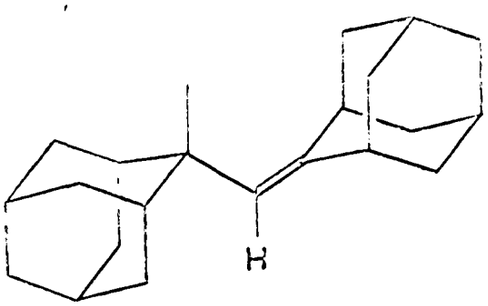

XXXI



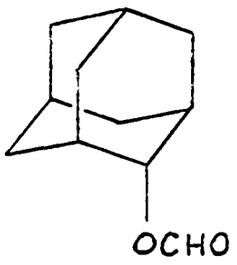

XXXII



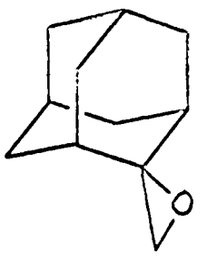

XXXIII



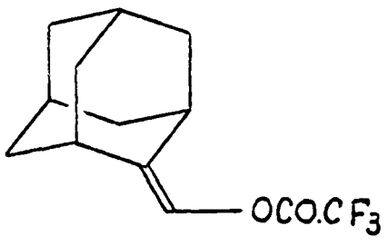

XXXIV




XXXV




XXXVI

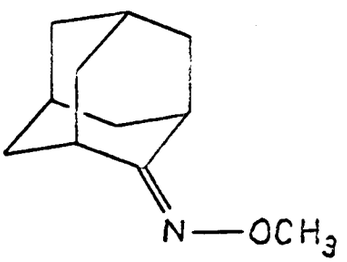



XXXVII

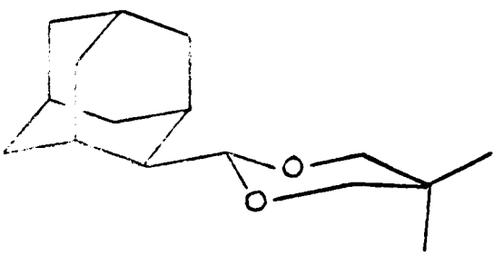
The two olefins were distinguished by NMR ( (XXXI) 2 vinyl protons, 5.54; (XXXIV) 1 vinyl proton, 4.88, and 1 methyl singlet, 8.81 $\tau$ ) and mass spectral evidence.

The dehydration was then carried out under milder conditions using phosphorus oxychloride in pyridine, which gave 2-methyleneadamantane in 88% yield.

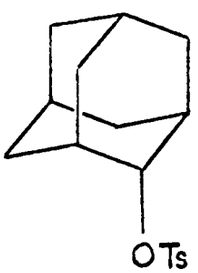
Epoxidation of the olefin (XXXI) with buffered pertrifluoracetic acid [24] followed, and the product mixture showed a strong carbonyl band at 1720 $cm.^{-1}$ in the infrared spectrum, and a singlet proton at 2.0 $\tau$ in the NMR spectrum. The compound responsible for these absorptions was apparently 2-adamantyl formate (XXXV), which had been produced because mistakenly a 100% excess of peracid had been used, which was reactive enough to rearrange and further oxidise the epoxide (XXXVI). The mass spectrum of the product mixture showed a peak at $^{m}/e$ = 180 corresponding to the formate ester (XXXV), and another peak at $^{m}/e$ = 260, which could correspond to the trifluoroacetate ester of the enolic form of the aldehyde, i.e. (XXXVII). After alkaline hydrolysis of the product mixture, 2-adamantanol (XL) was identified from characteristic bands in the infrared spectrum. In a second epoxidation, the milder peracetic acid was used and 2-methyleneadamantane oxide (XXXVI) was isolated in 84% yield. The epoxide was isomerised by boron trifluoride etherate in benzene to



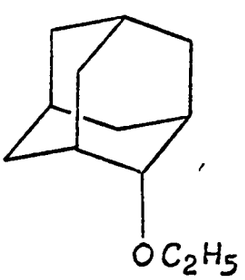

XXXVIII



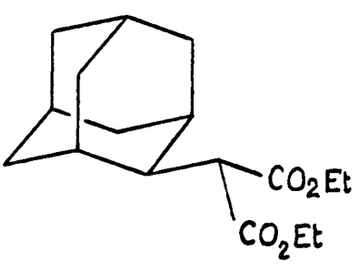
XXXIX



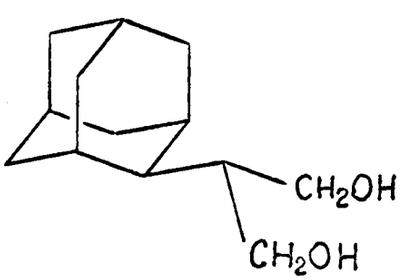

XLI



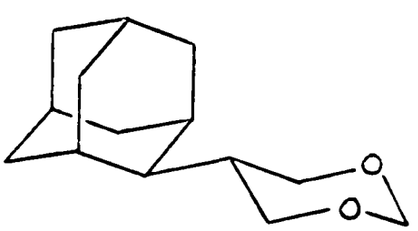

XLII




XLIII




XLIV

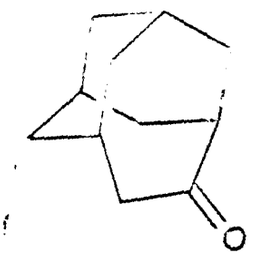


XLV

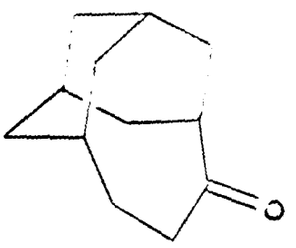
adamantane-2-aldehyde (XXXII). Two derivatives were made: the O-methyl oxime (XXXVIII) with methoxylamine hydrochloride, and a 1,3-dioxane (XXXIX)with 2,2-dimethyl-propan-1,3-diol.

Another series of reactions was carried out to prepare a further 1,3-dioxane, but with the 2-adamantyl group attached to the 5-position instead of the 2 position. 2-Adamantanone was reduced with lithium aluminium hydride to 2-adamantanol, (XL) which was converted into 2-adamantyl toluene-p-sulphonate (XLI) with toluene-p-sulphonyl chloride in pyridine. The tosylate (XLI) was heated under reflux in ethanol with malonic ester and sodium ethoxide for 3 days. The product mixture was chromatographed over alumina to remove 2-ethoxyadamantane (XLII), and the malonic ester fractions were evacuated on a boiling water bath at 0.3 mm leaving a liquid residue of diethyl 2-adamantylmalonate (XLIII) in 29% yield. The crude diester (XLIII) was reduced by lithium aluminium hydride in 1,4-dioxan to 2-(2-adamantyl) propane-1,3-diol (XLIV) in 72% yield. 5-(2-Adamantyl)-1,3-dioxane (XLV) was prepared from the diol (XLIV) with paraformaldehyde, toluene-p-sulphonic acid and anhydrous copper sulphate in methylene chloride. (For details of the NMR spectra of 1,3-dioxanes, (XXXIX) and (XLV), see p. 51 ).

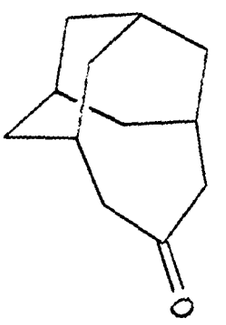
The action of diazomethane on 2-adamantanone was studied using two sets of conditions. Firstly, an ethereal solution of diazomethane (2 mols) was added to a solution of 2-adamantanone (1 mol.) in ether in the presence of anhydrous aluminium chloride[25]. A mass spectrum of the crude product showed a base peak at $^{m}/e = 164$, and peaks at $^{m}/e = 178$ (8%), $^{m}/e = 192$ (20%), and $^{m}/e = 206$ (13%), which would correspond to a monohomo derivative (XLVI) and three successively higher homologues. The product mixture was chromatographed over alumina, but the only compound isolated and identified was 4-homoadamantanone (XLVI) in 48% yield. Other carbonyl compounds were detected, but they did not separate on the column. Schleyer[26] has recently reported that addition of ethereal diazomethane to 2-adamantanone in methanol gives 4-homoadamantanone (XLVI) in 80-85% yield. This reaction was carried out using 2.5 mols. of diazomethane to 1 mol. of 2-adamantanone, and 4-homoadamantanone (XLVI) was isolated in 75% yield. When a five fold excess of diazomethane was used, the product mixture was analysed by GLC (Silicon oil at 140°). Four peaks were observed: (i) after 31 mins., 86% (4-homoadamantanone); (ii) 33 mins., 4%; (iii) 36 mins.,8%; (iv) 40 mins., 2%, Of particular interest was the fact that (ii) was partially split into 2



XLVI



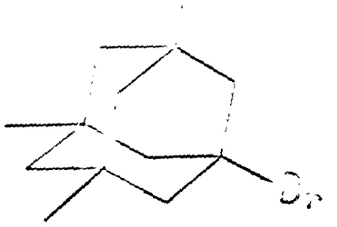
XLVII



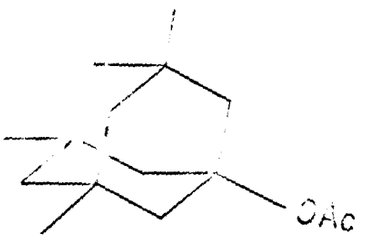
XLVIII

peaks of equal area, which might result from both bis-homologues (XLVII) and (XLVIII) being present, and (iii) was partially split into two peaks, one 3 times the area of the other.. In fact, of the two trishomologues possible, one is favoured 3 times over the other (on a statistical basis), assuming that both bishomologues are present in some concentration, and react with diazomethane to the same extent. However, the catalysed homologation[25] of 2-adamantanone is a better approach to the isolation of reasonable yields of bishomo and higher homologues of 2-adamantanone. As a proof of structure, 4-homoadamantanone was reduced under Wolff-Kishner conditions to homoadamantane (tricyclo $[4,3,1,1^{6,8}]$ undecane).

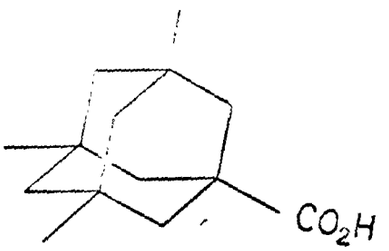
1,3-Dibromoadamantane[27] was converted into adamantane-1,3-dicarboxylic acid[28] with formic acid, sulphuric acid and dry silver sulphate in 92% yield. The dicarboxylic acid was treated with thionyl chloride and dimethylformamide, followed by liquid ammonia and further thionyl chloride to give 1,3-dicyanoadamantane[29] in 56% yield, which was used for dipole moment measurements (see p. 55 ).



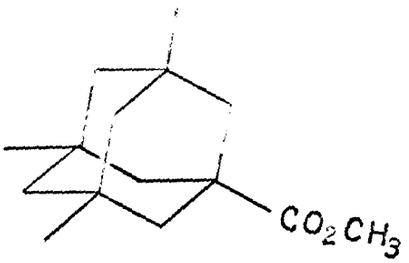
IL



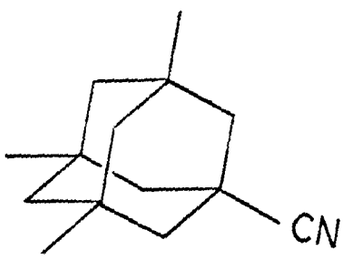

L




LI




LII




LIII

The preparation of derivatives of 1,3,5-trimethyladamantane[30]

1-Bromo-3,5,7-trimethyladamantane (IL) was prepared directly from the hydrocarbon (XI) on treatment with bromine. The chromic acid oxidation of the hydrocarbon produced 1-hydroxy-3,5,7-trimethyladamantane (XIII) in 59% yield, from which 1-acetoxy-3,5,7-trimethyladamantane (L) was prepared with acetic anhydride and sulphuric acid, and 3,5,7-trimethyladamantane-1-carboxylic acid (LI) was made by Koch-Haaf carbonylation. The carboxylic acid (LI) was treated with diazomethane to give the methyl ester (LII), and with thionyl chloride and dimethylformamide to give the acid chloride, which was converted into the carboxamide by ammonia (d.0.88) which on further treatment with thionyl chloride gave 1-cyano-3,5,7-trimethyladamantane (LIII). The results of dipole moment measurements on the bromide (IL) and nitrile (LIII) are given on p. 55 . The NMR spectra of all these monosubstituted 1,3,5-trimethyl-adamantanes are of interest as further examples[31], which show the effects of changing substituents upon the chemical shifts of other protons in the molecule. As the compounds are 1,3,5,7-tetrasubstituted, an unusually simple spectrum (no vicinal coupling) is obtained, in which all the protons attached to different carbon atoms in the molecule can be distinguished. The six methylene protons on carbon atoms

adjacent to $C_1$ are all equivalent and give rise to a single line ($W_h$ = 2 cps.), whereas the remaining methylene protons are of two kinds, which give rise to a broader signal ($W_h$ = 4 cps.), an unresolved AB quartet.

TABLE 1 Chemical shifts (in units) taken from 100 Mc/s. NMR spectra of 1-substituted-3,5,7-trimethyladamantanes (see Figure 1), as 10% (w/v) solutions in carbon tetrachloride.

| | R | $CH_3$(3,5,7) | $CH_2$(2,8,9) | $CH_2$(4,6,10) | Others |
|---|---|---|---|---|---|
| (XI) | H | 9.204 | 8.72 | 8.92 | 7.98 |
| (IV) | $CH_3$ | 9.195 | 8.99 | | |
| (LII) | $CO_2CH_3$ | 9.150 | 8.59 | 8.92 | 6.43 |
| (LIII) | CN | 9.138 | 8.42 | 8.88 | |
| (LI) | $CO_2H$ | 9.130 | 8.54 | 8.90 | |
| (XIII) | OH | 9.130 | 8.75 | 8.96 | |
| (IL) | Br | 9.129 | 8.12 | 8.86 | |
| (L) | OAc | 9.124 | 8.35 | 8.92 | 8.15 |

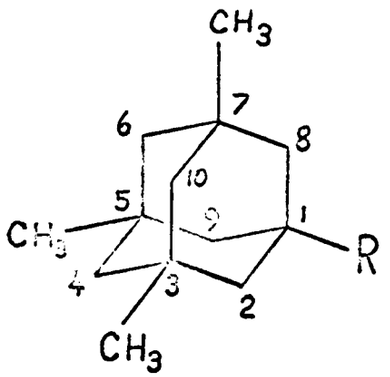


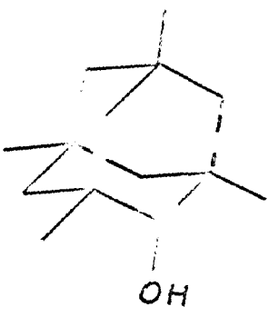

Figure 1

The reaction of derivatives of 1,3,5,7-tetramethyladamantane

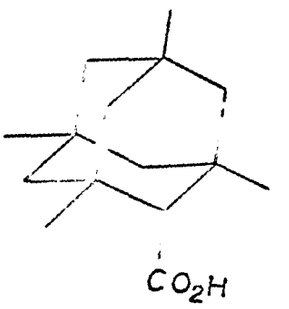
The availability of 1,3,5,7-tetramethyladamantan-2-one and to a lesser extent, 1,3,5,7-tetramethyladamantan-2,4-dione has allowed several derivatives to be prepared, many of which are structurally interesting compounds.

1,3,5,7-Tetramethyladamantan-2-one (XXI) was reduced to the alcohol (LIV), from which three compounds were prepared: the monocarboxylic acid (LV) by Koch-Haaf carbonylation[3], the monoacetate (XXII) from acetyl chloride in pyridine, and the monobromide (LVI) by brominolysis. Peterson and Wahl[32] reported recently the brominolysis of monofunctional bridgehead adamantane derivatives in which groups such as OH, Cl and F were replaced by Br (80-90% yield) after treatment with anhydrous bromine either after 4 hours at reflux or 24 hours at room temperature. Thus the monoalcohol (LIV) provided an opportunity of seeing whether this reaction could be extended to secondary alcohols. In fact, 1,3,5,7-tetramethyladamantan-2-ol dissolved immediately in bromine at room temperature, and the products after 3 days were separated into 2-bromo-1,3,5,7-tetramethyladamantane (LVI) in 58% yield, and 1,3,5,7-tetramethyladamantan-2-one (37%).

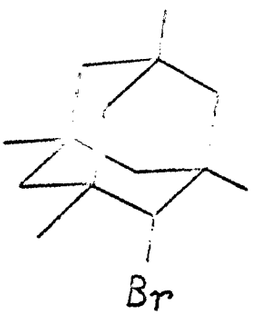
However, it is quite possible for bromine to oxidise the alcohol (LIV) to the monoketone (XXI) thereby liberating two



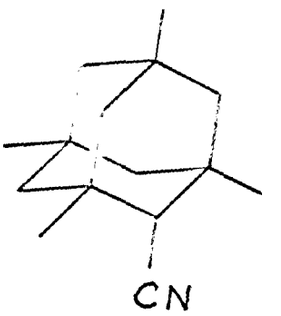

LIV



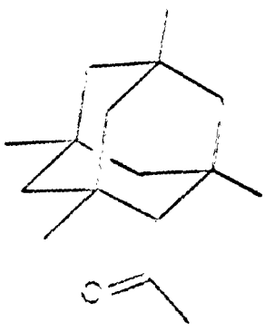

LV



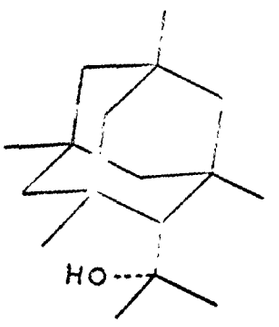

LVI




LVIII




LIX



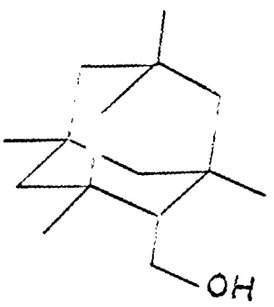

LX

molecules of hydrogen bromide, which could convert the alcohol (LIV) into the bromide in the usual manner. This reaction sequence would lead to a minimum yield of ketone of 33%, and a maximum yield of bromide of 67%, limits which are close to those yields found experimentally.

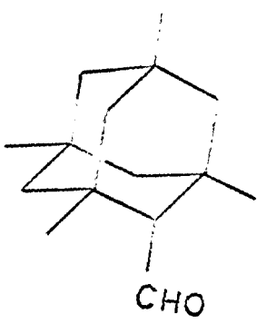
1,3,5,7-Tetramethyladamantane-2-carboxylic acid (LV) was used to prepare derivatives in which a group CO.R was attached to $C_2$, and evidence for the conformation of the carbonyl group in these compounds was obtained from NMR spectra (see p. 47 ). The acid chloride (LVII), made by treating the carboxylic acid (LV) with thionyl chloride and dimethylformamide, was unusually stable and was only converted into the carboxamide by treatment with sodamide in liquid ammonia (very little reaction occurred with 0.88 ammonia!). The carboxamide was dehydrated with thionyl chloride and dimethylformamide to give 2-cyano-1,3,5,7-tetramethyladamantane (LVIII). The methyl ketone (LIX) was prepared in 8% yield after alumina chromatography from the acid chloride with methyl magnesium iodide making use of the steric hindrance to nucleophilic attack of the carbonyl group in this system. A compound thought to be 1,3,5,7-tetramethyladamant-2-yl dimethyl carbinol (LX) was also eluted from the alumina with ether in 12% yield. The low stability of this compound prevented full character-



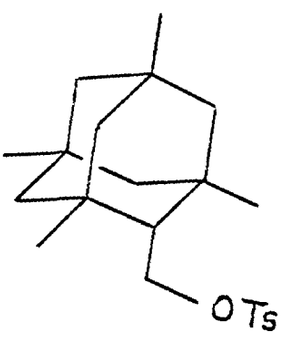

LXI



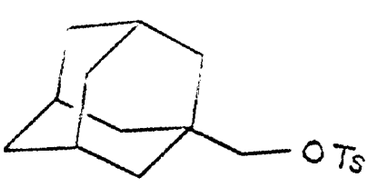

LXII



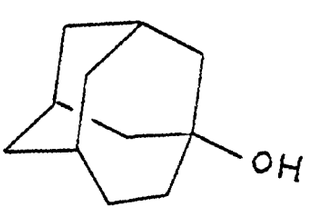

LXIII




LXIV



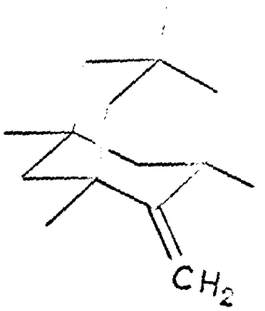

LXVI



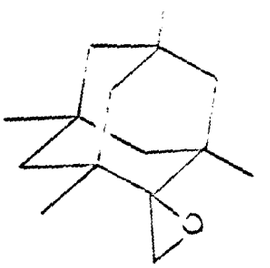

LXV

isation. The carboxylic acid (LV) was treated with an ethereal solution of diazomethane to give the methyl ester (LXI), which was reduced by lithium aluminium hydride in 1,4-dioxan to 2-hydroxymethyl-1,3,5,7-tetramethyladamantane (LXII). An attempt was made to oxidise this alcohol (LXII) with chromium trioxide in pyridine to 1,3,5,7-tetramethyl-adamantane-2-aldehyde (LXIII), but the product isolated was almost entirely the carboxylic acid (LV). 1,3,5,7-Tetramethyladamant-2-ylmethyl toluene-p-sulphonate (LXIV) was prepared from the alcohol (LXII) with toluene-p-sulphonyl chloride in pyridine, and solvolysed in 65% (v/v) aqueous diglyme with sodium carbonate under conditions described by Nordlander et al.[33] who isolated 3-homoadamantanol (LXV) in 96% yield from the solvolysis of 1-adamantylmethyl toluene-p-sulphonate (LXVI). However, instead of a tetra-methylhomoadamantanol being produced, elimination occurred and the only product detected and isolated was 2-methylene-1,3,5,7-tetramethyladamantane (LXVII) in 63% yield.

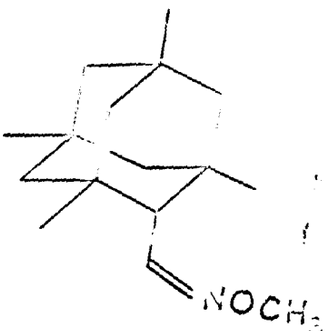
A second route was devised to obtain 1,3,5,7-tetra-methyladamantane-2-aldehyde (LXIII) starting from 2-methylene-1,3,5,7-tetramethyladamantane[8] which is readily available from 1,3,5,7-tetramethyladamantan-2-one via methyl magnesium iodide followed by dehydration in 85% phosphoric acid. Epoxidation of the olefin (LXVII) with pertrifluoracetic



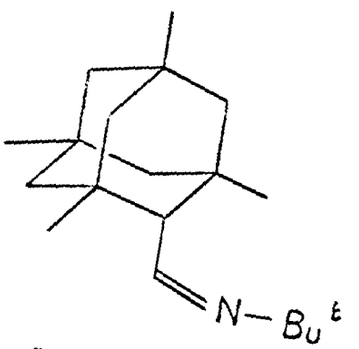

LXVII



LXVIII




LXIX




LXX

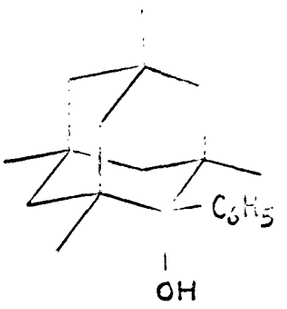
acid[24] in methylene chloride buffered with anhydrous sodium carbonate gave the crude epoxide (LXVIII), a viscous liquid, which was not purified, but treated with boron trifluoride etherate in benzene. The product was chromatographed over alumina and 1,3,5,7-tetramethyladamantane-2-aldehyde (LXIII) was isolated in 51% yield (based on olefin). The aldehyde was kept below 0° and before use (see p. 50 ) was passed over alumina to remove traces of carboxylic acid formed by aerial oxidation. The O-methyl oxime (LXIX) was prepared as a derivative (see p. 51 ). An attempt to prepare the t-butyl imine (LXX) failed even after heating the aldehyde under reflux in t-butylamine over potassium hydroxide for 5 days. Unchanged aldehyde and the t-butyl-ammonium carboxylate salt only were recovered.

When 1,3,5,7-tetramethyladamantan-2-one (XXI) was treated with phenyl magnesium bromide or phenyl lithium, a viscous liquid product was obtained which from NMR (2:1:1 pattern of $CH_3$ singlets at 9.47, 9.13 and 9.04 $\tau$ : aromatic CH around 2.27 and 2.80 $\tau$) and infrared (OH str., 3570 $cm.^{-1}$; aromatic bands, 1600 and 700 $cm.^{-1}$) spectral evidence appeared to be 2-phenyl-2-hydroxy-1,3,5,7-tetramethyladamantane (LXXI). However, attempts to crystallise the material failed. To obtain a solid derivative, the crude material was subjected to Koch-Haaf carbonylation.[7] The product isolated appeared to be the formate ester (LXXII) from infrared evidence

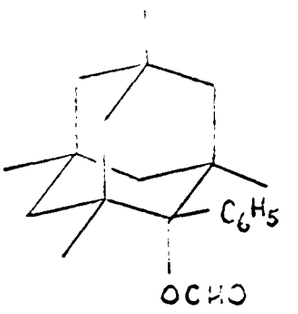
(CO str., 1720 cm.$^{-1}$, no hydrogen bonding ), but the NMR spectrum did not entirely support this structure (no carboxyl OH, possible formyl CH amongst aromatic signals between 2.4 and 2.9 $\tau$ , but 1:1:1:1 pattern of $CH_3$ singlets at 8.80, 9.00, 9.03 and 9.24 $\tau$ ). It is very unlikely that steric hindrance in the molecule (LXXII) would separate the signals of methyl groups at $C_1$ and $C_3$ in the NMR spectrum

Much interest has been shown in the homoadamantane system,[26,33,34] but as yet, no tetramethylhomoadamantanoid derivative has been reported.

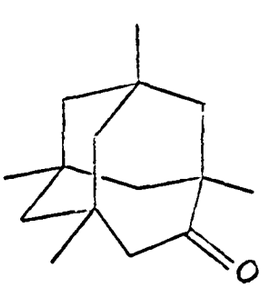
The method of Mueller[25] for the catalysed homologation of cycloaliphatic ketones by diazomethane with anhydrous aluminium chloride was used in an attempt to prepare a monohomo derivative and higher homologues of 1,3,5,7-tetramethyladamantan-2-one. Diazomethane (2.5 mols.) was used with the monoketone (XXI) (1 mol.) and the fractions from alumina chromatography of the product were analysed by GLC. (Silicon oil column at 175°). One fraction contained 95% of 1,3,6,8-tetramethylhomoadamantan-4-one (LXXIII) (M.W.220 from mass spectrum, M.W.222 after base-catalysed deuterium exchange). The carbonyl stretching band in the infrared spectrum was 20 cm.$^{-1}$ lower than the parent monoketone at 1696 cm.$^{-1}$ (cf. 4-homoadamantanone 1698 cm.$^{-1}$). A fraction [illegible] the monoketone (XXI) but before the



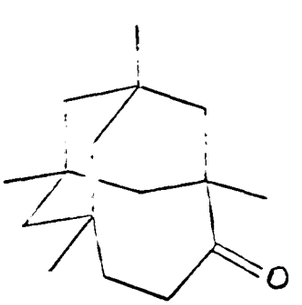

LXXI




LXXII




LXXIII

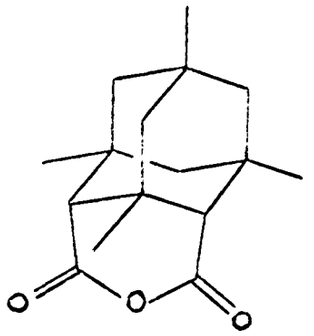



LXXIV

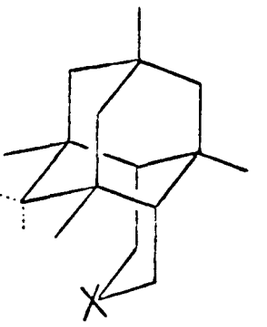
bulk of its monohomoderivative (LXXIII) was identified as containing 36% of a bishomo derivative, 1,3,7,9-tetramethyltricyclo[5,3,1,$1^{7,9}$] dodecan-4-one (LXXIV), (M.W. 234 from mass spectrum, M.W. 234,235 and 236 after base-catalysed deuterium exchange). A far slower rate of deuterium exchange occurs with the bishomo derivative (LXXIV), indicated by the low intensity of peaks at $^{m}/_{e}$ = 235 and 236 in the mass spectrum. This is to be expected from an inspection of molecular models, which shows that formation of an enolate anion is extremely unfavourable for the bishomo derivative (LXXIV), but relatively easy for the monohomo derivative (LXXIII).

No homologues of 1,3,5,7-tetramethyladamantan-2-one were found when an ethereal solution of diazomethane was added to the monoketone (XXI) in methanol using conditions described by Schleyer et al[26] for the preparation of 4-homoadamantanone (XLVI) from 2-adamantanone.

Some compounds derived from 1,3,5,7-tetramethyladamantan-2,4-dione have been prepared. The 2,4-dione (XXIII) was reduced with lithium aluminium hydride to a mixture of isomeric 1,3-diols, which was not investigated further but was treated with formic acid and sulphuric acid hoping to produce the corresponding isomeric mixture of 1,3-dicarboxylic acids, from which the cyclic anhydride (LXXV)

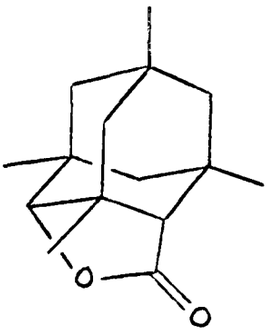


LXXV

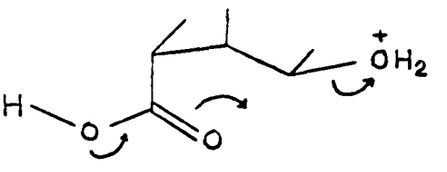


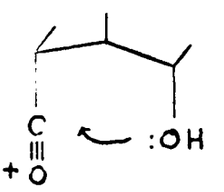
LXXVI

Figure 2.



LXXVII

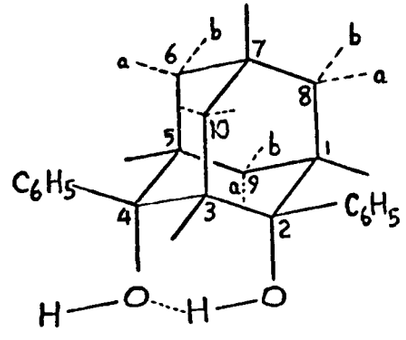


could be made. A whole series of derivatives analogous to the bicyclo [ 3,3,1] nonane system might then be prepared in which the bicyclic system would be constrained to a two chair conformation including a hetero atom (O, S, N) as shown in (LXXVI). However, the major product of the carbonylation was the lactone (LXXVII), which was isolated in 65% yield, and characterised from infrared (CO str., 1790 $cm.^{-1}$), NMR (1:1:1:1 pattern of $CH_3$ singlets and CH signals at 6.38 and 8.32 $\tau$ ) and mass spectral evidence (M.W.234). Two possible mechanisms can be invoked to explain the formation of the lactone (see Figure 2 ). A solid residue, which was heated under reflux in acetic anhydride with anhydrous sodium acetate for 16 hours, was recovered from the alkaline washings of the ethereal extract after acidification. The product was 1,3,5,7-tetramethyl-adamantane-2,4-dicarboxylic anhydride (LXXV), but preparative uses were not considered practicable because of a 2% yield.

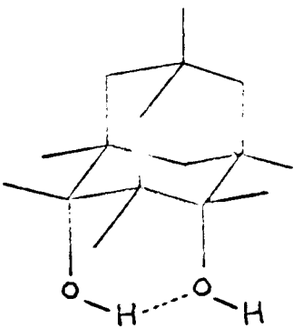
1,3,5,7-Tetramethyladamantan-2,4-dione was treated with methyl magnesium iodide, and the products were chromatographed over alumina. Only one compound, syn-cis-2,4-dihydroxy-1,2,3,4,5,7-hexamethyladamantane (LXXVIII), was fully characterised, although NMR spectral evidence (2 low-field $CH_3$ singlets) pointed to another isomer, ($\pm$)-trans-2,4-dihydroxy-1,2,3,4,5,7-hexamethyladamantane (LXXIX), being

FIGURE 3

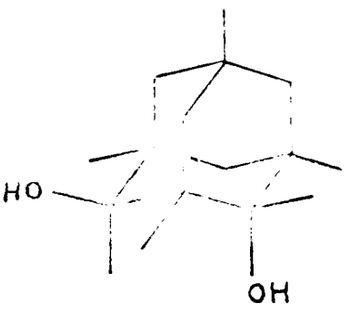

a
b
6
7
b
a
8
5
10
b
1
$C_6H_5$
a
9
4
3
2
$C_6H_5$
H—O···H—O


OH
$C_{6,8}-H_a$
$C_{9a}-H$
$C_{10}-H$
$C_{6,8}-H_b$
$C_{9b}-H$
Me-7
Me-1,5
Me-3
5·0
7·0
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8·5
9·0
9·5 τ

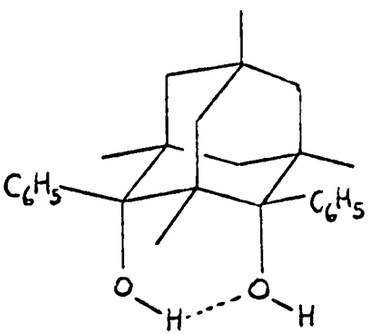
present in fractions eluted first from the column. The intramolecular hydrogen bond spectral shift for the former diol (LXXVIII) was found to be 144 cm.$^{-1}$ Hoping to prepare an intramolecularly hydrogen bonded diol with an even greater spectral shift, 1,3,5,7-tetramethyladamantan-2,4-dione was treated with phenyl lithium. Two crystalline compounds, syn-cis-2,4-dihydroxy-2,4-diphenyl-1,3,5,7-tetramethyladamantane (LXXX) and 4-axial-hydroxy-4-phenyl-1,3,5,7-tetramethyladamantan-2-one (LXXXI), were separated from different fractions after alumina chromatography of the crude product. The NMR spectrum of the diol (LXXX) is reproduced in Figure 3. The value of the intramolecular hydrogen bond spectral shift of the diol (LXXX) increased to 172 cm.$^{-1}$ Previously, the highest spectral shift reported[35] for a 1,3-diol was 131 cm.$^{-1}$, which is shown by (LXXXII). Indeed, the largest value for a 1,2-diol is reported to be 170 cm.$^{-1}$, arising from 1,1,2,2-tetra-tert-butylethylene glycol. The extremely high value of the spectral shift for the diphenyl diol (LXXX) arises because both phenyl groups are in a sterically crowded situation, and help to push both hydroxyl groups closer together. The other compound (LXXXI) isolated was reduced with lithium aluminium hydride in order to prove its structure. The product obtained was syn-cis-2,4-dihydroxy-2-phenyl-1,3,5,7-tetramethyladamantane (LXXXIII), which was identified by its



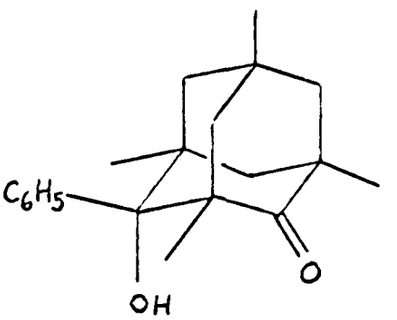

LXXVIII



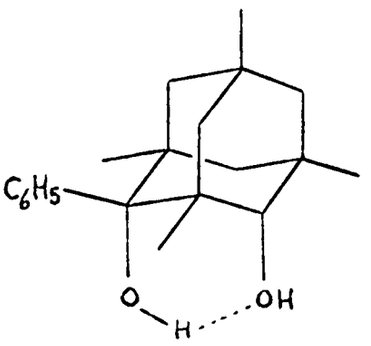

LXXIX



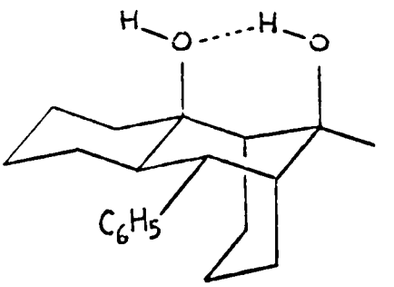

LXXX




LXXXI




LXXXIII




LXXXII

intramolecular hydrogen bond ( $\Delta\nu$ = 160 cm.$^{-1}$). This diol (LXXXIII) could only arise from a ketoalcohol in which the hydroxyl group was axial to the cyclohexanone ring. The NMR spectrum of the monophenyl diol (LXXXIII) is most unusual, and is reproduced in Figure 4. One hydrogen bonded OH signal occurs for one proton at 5.28 $\tau$ , while an AB quartet (J = 6 cps.) arises from coupling of the mainly non-hydrogen bonded OH with the proton attached to $C_4$ ($H_A$ at 6.29, and $H_B$ at 6.83 $\tau$ ).

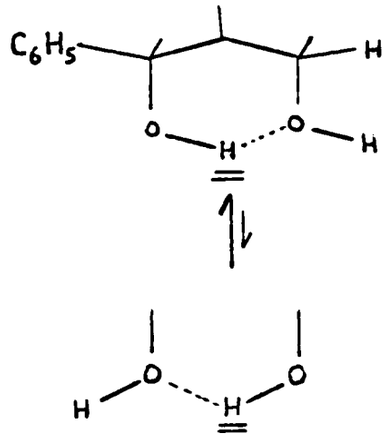
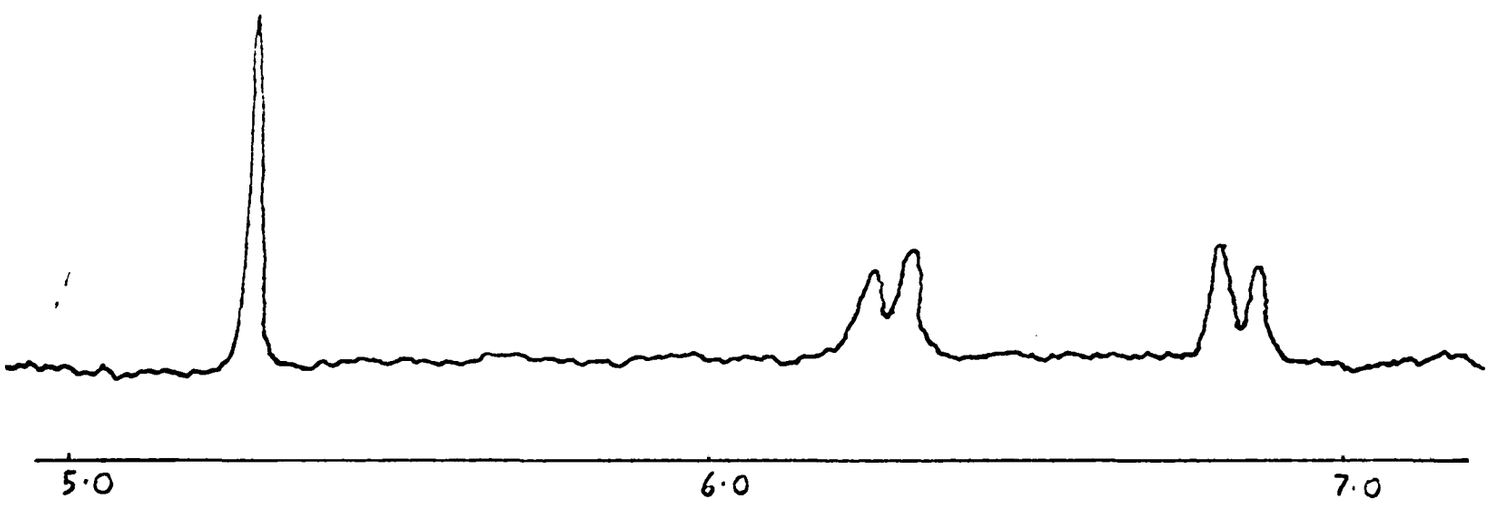
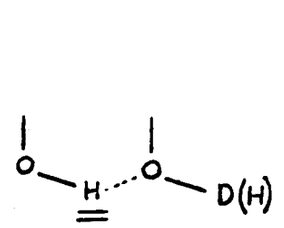
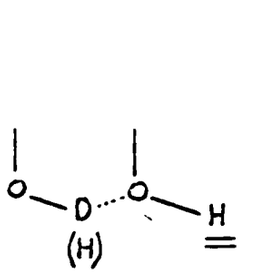


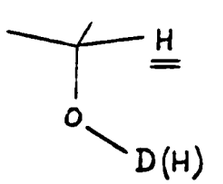
Figure 4.

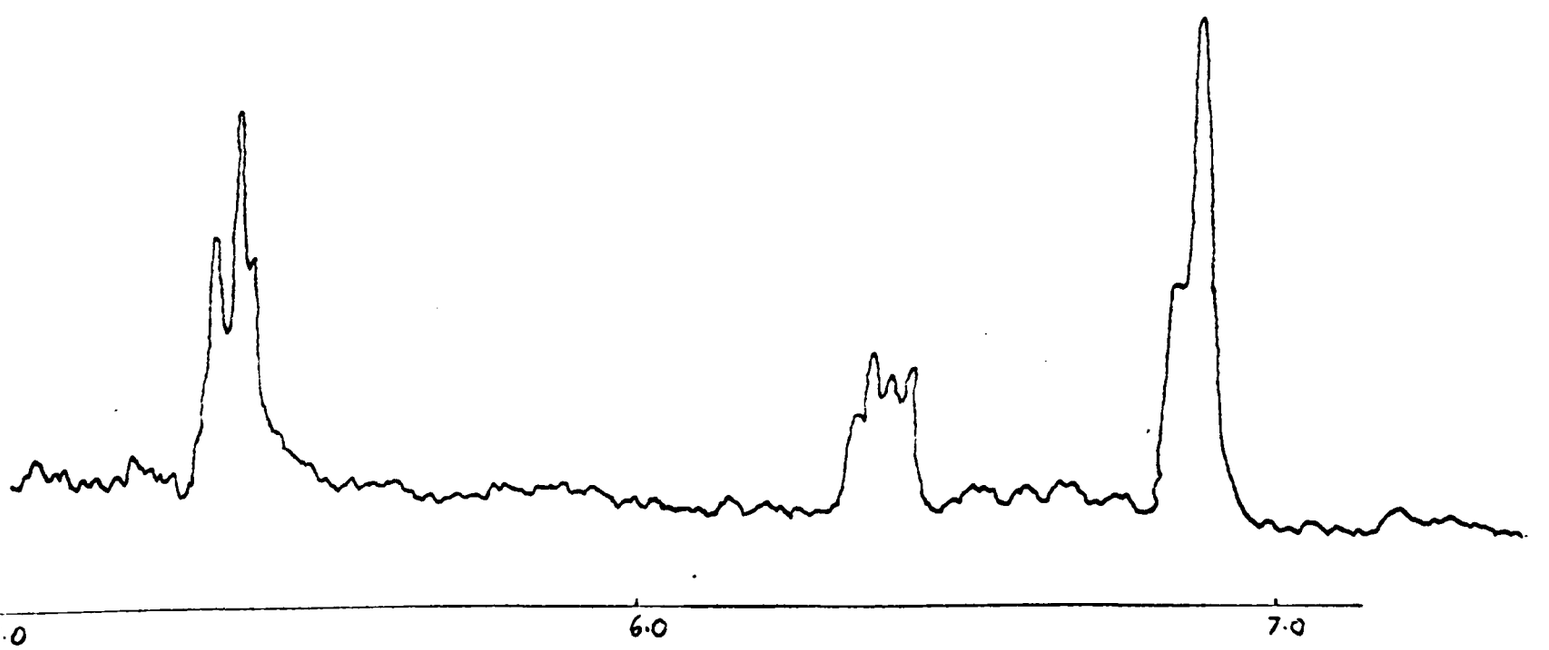



after partial deuterium exchange









# SECTION TWO

## Some aspects of the nuclear magnetic resonance spectra of adamantane derivatives.

An investigation of substituent effects on the chemical shift for a number of polymethyladamantanes and their respective monoketone derivatives

In dilute solutions in inert solvents, the most important factors which cause changes in the chemical shift parameter are predominantly intramolecular and are the inductive effect, the electric field effect and magnetic anisotropy.

If the chemical shifts of protons are compared for two adamantanoid molecules which differ only in their alkyl substituents, then the inductive effect should be negligible in any calculations. ApSimon et al.[36] have claimed that if the electric and magnetic dipoles are placed on the oxygen atom of the carbonyl group, then the electric field effect can also be ignored, and only magnetic anisotropy need be invoked in any calculations, but this simplification may not be generally valid.

A magnetically anisotropic centre in a molecule is provided by a group or bond having different values for the transverse ($\chi_T$) and longitudinal ($\chi_L$) components of its magnetic susceptibility. Whether the hydrogen nucleus is shielded or deshielded depends on the relative values of the susceptibility components of the nearby system and molecular geometry. The shielding effect of a distant

bond possessing axial symmetry upon a resonating nucleus may be calculated from the McConnell equation[37]:

$$\sigma = \frac{\Delta\chi}{3R^3} (1 - 3\cos^2\theta)$$

where $\Delta\chi = (\chi_L - \chi_T)$, R is the distance between the proton and the centre of the induced magnetic dipole of the bond, and $\theta$ is the angle between the direction of R and the symmetry axis. McConnell's equation only measures the contribution produced by the magnetic anisotropy of axially symmetric groups to the total chemical shift, and its use is restricted to those cases in which R is very much greater than the length of the induced magnetic dipole of the bond. It has been assumed[38] that this requirement is met when R is greater than 3Å.

A double bond, e.g. C=O, does not possess either cylindrical or conical symmetry and hence three susceptibilities (i.e. two anisotropies) are necessary to describe the anisotropy in the magnetic susceptibility. ApSimon et al.[12] have modified the McConnell equation for non-axially symmetrical groups, and the result is given below:

$$\sigma = \frac{1}{3R^3}\left[\Delta\chi_1(1-3\cos^2\theta) + \Delta\chi_2(1-3\sin^2\theta\cos^2\phi)\right]$$

where $\Delta\chi_1 = \chi_y - \chi_x$, and $\Delta\chi_2 = \chi_z - \chi_x$. The X-axis coincides with the bond axis and the Y-axis is the direction orthogonal to the nodal plane of the $\pi$-orbitals; $\theta$ is the angle subtended by the R direction to the Y-axis, and $\phi$ is the angle between the X-axis and the projection of the R direction in the XZ plane.

The modified McConnell equation has been used[8] to calculate shifts due to magnetic anisotropy produced by changing the methylene group at $C_2$ to a carbonyl group on other protons in adamantanoid systems using anisotropies derived by ApSimon *et al.*[12,36] Because of synthetic problems and the unexpected nature of the results, the work was not concluded. It appeared also that carbon tetrachloride might not be behaving as an inert solvent, in what is essentially a hydrocarbon system.

The synthetic difficulties have now been overcome, and the chemical shifts of almost all the protons in a series of 1,3-dimethyl-, 1,3,5-trimethyl-, and 1,3,5,7-tetramethyladamantane derivatives have been distinguished, and are set out in Tables 2,3 and 4. Assignments of the signals to specific protons was mostly straightforward, and in other cases, solvent shifts in benzene or mixed solvents

TABLE 2. Chemical shifts (in $\tau$ units) taken from 100 Mc/s. NMR spectra (10% w/v solutions) of 1,3,5,7-tetramethyladamantane (IV), 1,3,5,7-tetramethyladamantan-2-one (XXI), and 1,3,5,7-tetramethyladamantan-2,6-dione (XXV).

| Solvent | $CH_3$(1,3) | $CH_3$(5,7) | $CH_2$(6) | $CH_2$(4.8,9,10) | J'(cps)* |
|---|---|---|---|---|---|
| (IV) | | | | | |
| TMS | | 9.17 | | 8.96 | |
| $CCl_4$ | | 9.20 | | 8.99 | |
| $C_6H_6$ | | 9.17 | | 9.06 | |
| (XXI) | | | | | |
| TMS | 9.11 | 9.09 | 8.58 | 8.51 ; 8.64 | 12 |
| $CCl_4$ | 9.13 | 9.08 | 8.57 | 8.49 ; 8.62 | 12 |
| $C_6H_6$ | 9.01 | 9.30 | 8.96 | 8.76 ; 8.95 | 12 |
| (XXV) | | | | | |
| $CCl_4$ | | 9.01 | | 8.13 | |
| $C_6H_6$ | | 9.11 | | 8.64 | |

* J' is the apparent geminal coupling constant from first order analysis.

TABLE 3. Chemical shifts (in $\tau$ units) taken from 100 Mc/s. NMR spectra (10% w/v solutions) of 1,3,5-trimethyladamantane (XI), 1,3,5-trimethyladamantan-2-one (XVII), and 1,5,7-trimethyladamantan-2-one (XVIII).

| Solvent | $CH_3$(1,3) | $CH_3$(5,7) | CH(1,3) | CH(5,7) | $CH_2$(2,4,9) | $CH_2$(6;8,10) |
|---|---|---|---|---|---|---|
| (XI) | | | | | | |
| TMS | | 9.19 | | 7.97 | 8.89 | 8.69 |
| $CCl_4$ | | 9.21 | | 7.98 | 8.91 | 8.72 |
| $C_6H_6$ | | 9.18 | | 8.01 | 8.96 | 8.75 |
| (XVII) | | | | | | |
| TMS | 9.10 | 9.12 | | 7.87 | 8.52 | 8.40; 8.34 |
| $CCl_4$ | 9.12 | 9.11 | | 7.84 | 8.50 | 8.41; 8.32 |
| $C_6H_6$ | 8.99 | 9.32 | | 8.20 | 8.73 | 8.79; 8.56 |
| (XVIII) | | | | | | |
| TMS | 9.12 | 9.09 | 7.58 | | 8.39 | 8.54 |
| $CCl_4$ | 9.15 | 9.08 | 7.59 | | 8.37 | 8.52 |
| $C_6H_6$ | 9.02 | 9.32 | 7.56 | | * | * |

* Complex splitting pattern not resolved.

TABLE 4. Chemical shifts (in τ units) taken from 100 Mc/s. NMR spectra (10% w/v solutions) of 1,3-dimethyladamantane (X), 1,3-dimethyladamantan-2-one (XIV), 1,5-dimethyl-adamantan-2-one (XV), and 5,7-dimethyladamantan-2-one (XVI)

| Solvent | $CH_3$(1,3) | $CH_3$(5,7) | CH (1,3) | CH(5,7) | $CH_2$(2) | $CH_2$(6) | $CH_2$(4,8,9,10) | J'( cps) |
|---|---|---|---|---|---|---|---|---|
| (X) | | | | | | | | |
| TMS | 9.21 | | | 8.01 | 8.83 | 8.43 | 8.60 | |
| $CCl_4$ | 9.23 | | | 8.03 | 8.85 | 8.45 | 8.64 | |
| $C_6H_6$ | 9.19 | | | 8.07 | 8.90* | 8.48 | 8.69 | |
| (XIV) | | | | | | | | |
| TMS | 9.09 | | | 7.94 | | 8.21 | 8.26 | |
| $CCl_4$ | 9.10 | | | 7.93 | | 8.18 | 8.23 | |
| $C_6H_6$ | 8.97 | | | 8.26 | | 8.26 | 8.49 | |
| (XV) | | | | | | | | |
| TMS | 9.11 | 9.13 | 7.56 | 7.89 | | 8.49 | 8.14;8.33 | |
| $CCl_4$ | 9.14 | 9.12 | 7.57 | 7.88 | | 8.48 | 8.13;8.31 | |
| $C_6H_6$ | 9.00 | 9.35 | 7.52 | 8.25 | | 8.70 | 8.42;8.56 | |
| (XVI) | | | | | | | | |
| TMS | | 9.09 | 7.64 | | | 8.51 | 8.27;8.41 | 13 |
| $CCl_4$ | | 9.07 | 7.63 | | | 8.49 | 8.24;8.38 | 13.5 |
| $C_6H_6$ | | 9.35 | 7.61 | | | 8.89 | 8.50;8.75 | 12.5 |

were used. Tetramethylsilane was used as an example of a non-polar solvent, whose hydrocarbon-like character most closely resembles that of methyladamantanes. No trouble was found in distinguishing methyl singlets up to 9.2 $\tau$ in tetramethylsilane, because the first low field signal to arise from the use of this solvent was a spinning side-band at $\sim 9.\overset{7}{\cancel{4}}\ \tau$ ~~from~~ and the tetramethylsilane $C^{13}$ satellite at $9.\overset{4}{\cancel{8}}\ \tau$ . A comparison of calculated shifts due to magnetic anisotropy against those measured in tetramethylsilane as solvent is shown in Tables 5 and 6.

Two points emerge from the results shown in Tables 5 and 6. Firstly, the calculated shift is much smaller than the measured shifts in two out of the three series, and secondly, there is considerable variation amongst the measured shifts depending on the extent and position of methyl substitution. The anisotropies derived by ApSimon et al.[12,36] may not be applicable to the adamantane system. In particular, the two anisotropies of the carbonyl group were derived from chemical shift data of the C-18 and C-19 methyl groups in mono-oxoandrostanes, of which the geometry was estimated using Dreiding models. Dreiding models tend to underestimate the flattening of cyclohexane and cyclohexanone rings and therefore to overestimate the

TABLE 5. The change in chemical shift of the methylene protons at $C_6$ produced by changing the methylene group at $C_2$ to a carbonyl group in methyladamantanes, in tetramethylsilane as solvent (figures in brackets refer to carbon tetrachloride as solvent) (See Figure 5 ).

| | Hydrocarbon | Ketone | Shift(τ units) |
|---|---|---|---|
| $R,R_1,R_2,R_3=CH_3$ | 8.96 (8.99) | 8.58 (8.57) | -0.38 (-0.42) |
| $R,R_2,R_3=CH_3,R_1=H$ | 8.89 (8.91) | 8.54 (8.52) | -0.35 (-0.39) |
| $R,R_1,R_2=CH_3,R_3=H$ | 8.69 (8.72) | 8.40 (8.41) | -0.29 (-0.31) |
| $R,R_1=H,R_2,R_3=CH_3$ | 8.83 (8.85) | 8.51 (8.49) | -0.32 (-0.36) |
| $R,R_2=H,R_1,R_3=CH_3$ | 8.60 (8.64) | 8.33 (8.31) | -0.27 (-0.33) |
| $R,R_1=CH_3,R_2,R_3=H$ | 8.43 (8.45) | 8.21 (8.18) | -0.22 (0.27) |
| $R,R_1,R_2,R_3=H$ | - (8.22) | - (7.98) | (-0.24) |

Calculated shift due to magnetic anisotropy -0.12

Figure 5.

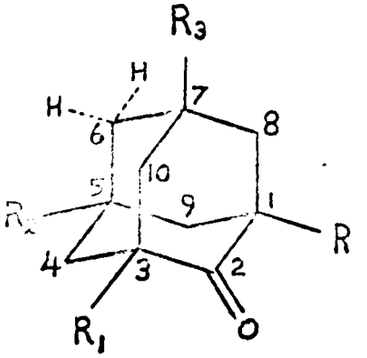


TABLE 6. The change in chemical shift of (A) a methyl group at $C_5$ and (B) a methine proton at $C_5$ produced by changing the methylene group at $C_2$ to a carbonyl group in methyladamantanes, in tetramethylsilane as solvent (see Figure 6 ).

| | Hydrocarbon | Ketone | Shift A | Shift B |
|---|---|---|---|---|
| $R,R_1,R_2 = CH_3$ | 9.17 | 9.09 | -0.08 | |
| | 7.97 | 7.87 | | -0.10 |
| $R,R_1=CH_3,R_2=H$ | 9.19 | 9.12 | -0.07 | |
| | 8.01 | 7.94 | | -0.07 |
| $R,R_2=CH_3,R_1=H$ | 9.19 | 9.09 | -0.10 | |
| | 8.01 | 7.89 | | -0.12 |
| $R,R_2=H,R_1=CH_3$ | 9.21 | 9.13 | -0.08 | |
| Calculated shift due to magnetic anisotropy | | | -0.04 | -0.10 |

Figure 6.

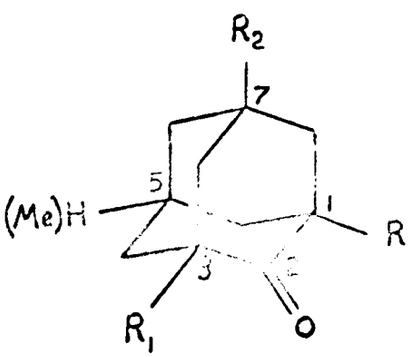
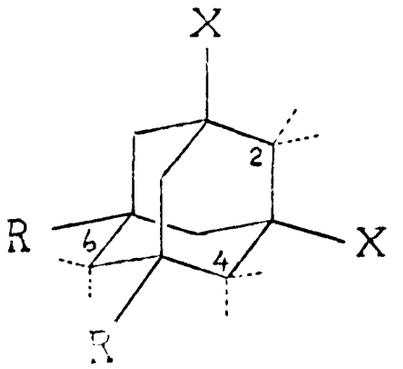


TABLE 7



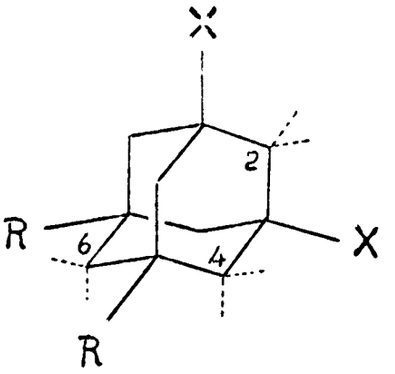

| | Hydrocarbon X=H | 1,3-Dibromide X=Br | Shift difference |
|---|---|---|---|
| $C_2$-H | | | |
| R=H | 8.22 | 7.18[a] | -1.04 |
| R=$CH_3$ | 8.45 | 7.35 | -1.10 |
| | | | -0.06 |
| $C_4$-H | | | |
| R=H | 8.22 | 7.71[a] | -0.51 |
| R=$CH_3$ | 8.64 | 8.04 | -0.60 |
| | | | -0.09 |
| $C_6$-H | | | |
| R=H | 8.22 | 8.39(?)[a] | +0.17 |
| R=$CH_3$ | 8.84 | 8.77 | -0.07 |
| | | | -0.24 |

[a] Values taken from reference 31.

changes in the 'geometric factor' with changes in structure for methyl groups in the more deshielding regions around the carbonyl group (as in 3-oxo-5 or -5 - androstane), which are of particular importance for the adamantane derivatives studied here. Over estimating changes in the 'geometric factor' leads to a compensating underestimate of the magnetic anisotropy, since the experimentally observed differences of chemical shift are assumed to be equal to the algebraic sum of products of magnetic anisotropies and the corresponding 'geometric factors'.

The much more important and hitherto unrecognised effect of the local environment of a C-H group on that group's susceptibility to influences of a relatively distant substituent casts doubt on the present basis for explaining substituent effects on chemical shifts. At present values of magnetic anisotropy and of k (the proportionality constant for field effects)[36] are obtained assuming that the only significant factors are the properties of the substituent and the perturbed C-H group and the geometrical relationship between them. In the methyladamantanones in Table 5 the geometry, change of substituent and the C-H group remain the same yet the observed differences of chemical shift vary from -0.22 to -0.38 p.p.m. (tetramethyl-

TABLE 8




| | Hydrocarbon X=H | Hydrocarbon X=$CH_3$ | Shift Difference |
|---|---|---|---|
| $C_2$-H | | | |
| R=H | 8.22 | 8.85 | +0.63 |
| R=$CH_3$ | 8.45 | 8.99 | +0.54 |
| | | | -0.09 |
| $C_4$-H | | | |
| R=H | 8.22 | 8.64 | +0.42 |
| R=$CH_3$ | 8.64 | 8.99 | +0.35 |
| | | | -0.07 |
| $C_6$-H | | | |
| R=H | 8.22 | 8.45 | +0.23 |
| R=$CH_3$ | 8.85 | 8.99 | +0.14 |
| | | | -0.09 |

silane) and from -0.24 to -0.42 p.p.m. (carbon tetrachloride). Significantly, the largest discrepancies are found when the methyl groups are distant from the carbonyl group but close to the $C_6$ methylene. Qualitatively similar effects are found for differences between hydrocarbons and bromides (Table 7), and for hydrocarbons with differing numbers of methyl groups (Table 8). In all instances additional methyl groups change the substituent effects in a deshielding sense. For the bromides the additional methyl groups have the greatest effect when adjacent to the C-H group being considered, and therefore do not appear to operate by modifying the substituent .

TABLE 9 Chemical shifts (in $\tau$ units) taken from 100 Mc/s. NMR spectra (5% w/v solutions) of 1,3,5,7-tetramethyladamantane-2-carboxylic acid and related compounds (see Figure 7 ).

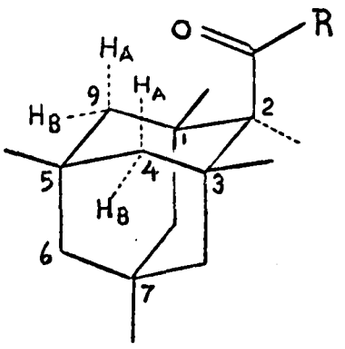
| Solvent | $CH_3(1,3)$ | $CH_3(5)$ | $CH_3(7)$ | $C_2$-H | $C_{4,9}$-$H_A$ | $C_{4,9}$-$H_B$ | $CH_2(8,10)$ | $CH_2(6)$ |
|---|---|---|---|---|---|---|---|---|
| R=OH | | | | | | | | |
| $CCl_4$ | 9.11 | 9.14 | 9.19 | 8.01 | 8.11 | 9.22 | 8.88 | 8.95 |
| $C_6H_6$ | 9.09 | 9.16 | 9.29 | 7.99 | 8.01 | 9.33 | 9.14 | |
| $R=O^-$ | | | | | | | | |
| (1:1)$CD_3OD$ | 9.17 | 9.17 | 9.23 | 8.15 | 7.99 | 9.34 | 8.96 | 9.00 |
| N NaOH | | | | | | | | |
| $R=OCH_3$ | | | | | | | | |
| $CCl_4$ | 9.24 | 9.14 | 9.21 | 8.06 | 8.12 | 9.27 | 8.92 | 8.96 |
| $R=CH_3$ | | | | | | | | |
| $CCl_4$ | 9.22 | 9.15 | 9.21 | 7.80 | 8.14 | 9.34 | 8.96 | |
| $C_6H_6$ | 9.28 | 9.10 | 9.24 | 8.05 | 7.91 | 9.36 | 9.12 | |
| R=H | | | | | | | | |
| $CCl_4$ | 9.15 | 9.10 | 9.18 | 8.29 | 8.35 | * | 8.90 | |

* Not visible, hidden by methyl absorption

The conformation of 1,3,5,7-tetramethyladamantane-2-carboxylic acid (LV) and related compounds

The preferred conformation of the carbonyl group in 1,3,5,7-tetramethyladamantane-2-carboxylic acid and related compounds can be determined from their NMR spectra (the chemical shifts are shown in Table 9). When the group R is large (i.e. not H), the axial protons attached to $C_4$ and $C_9$ are considerably deshielded, whilst the equatorial protons are shielded, which gives rise to a well separated AB quartet. A large group R cannot be turned into the ring and therefore conformations in which the group R is situated far away from the ring skeleton are favoured, thereby bringing the carbonyl group into close proximity with the axial protons ($C_{4,9}$-$H_A$). However, in

Figure 7.

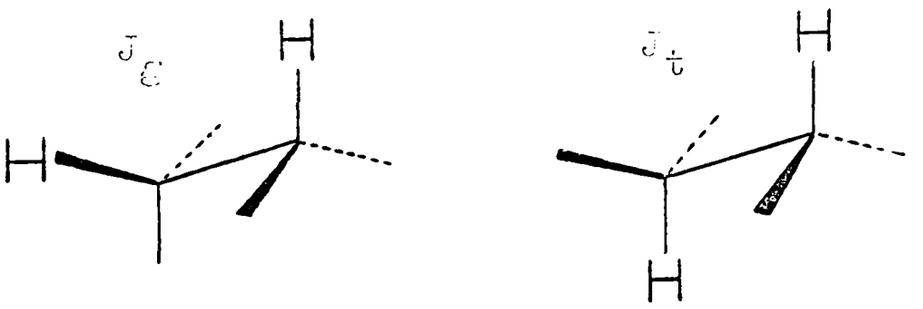



the spectrum of 1,3,5,7-tetramethyladamantane-2-aldehyde (LXIII), the AB quartet is not as well separated, and the proton at

$C_2$ is at higher field, which indicate that far greater contributions are made to the chemical shifts of these protons by conformations in which the carbonyl group points away from the ring skeleton. Furthermore, the vicinal coupling constant observed from the aldehydic proton splitting is at 5.1 cps. ($+34^{\circ}$), which is relatively close to the value expected for $J_{trans}$ in such a system (cf., di-t-butyl-acetaldehyde:[14a] $J_{vic}$ = 6.0 cps., ($+ 36^{\circ}$) in carbon tetrachloride).

Studies of the variation of vicinal coupling constants and chemical shifts with temperature for some derivatives of adamantane

For a system in which there are two vicinal protons, the trans and gauche conformations can be represented as shown below:




The observed coupling constant, $J_{lbsd.}$ can be expressed in the form

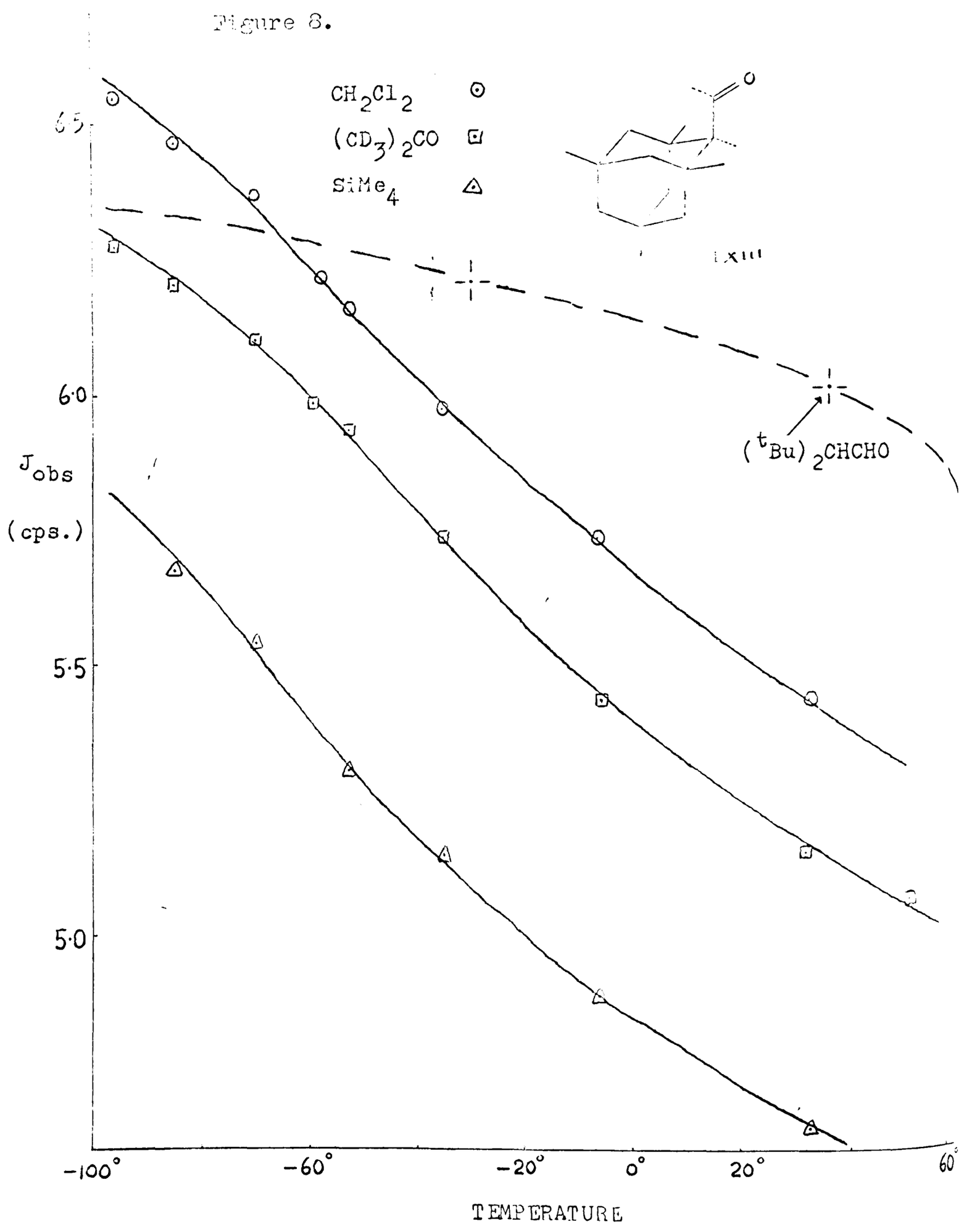
$$J_{obsd} = x\, J_t + (1-x)\, Jg$$

where x is the fractional population of the trans conformer, and the equilibrium, K is given by

$$K = \frac{x}{1-x} = \frac{J_{obsd} - J_g}{J_t - J_{obsd.}}$$

If $J_g$ and $J_t$ are known then a value for the equilibrium constant may be obtained from the experimental data. Model compounds, which are locked in one conformation have been

Figure 8.

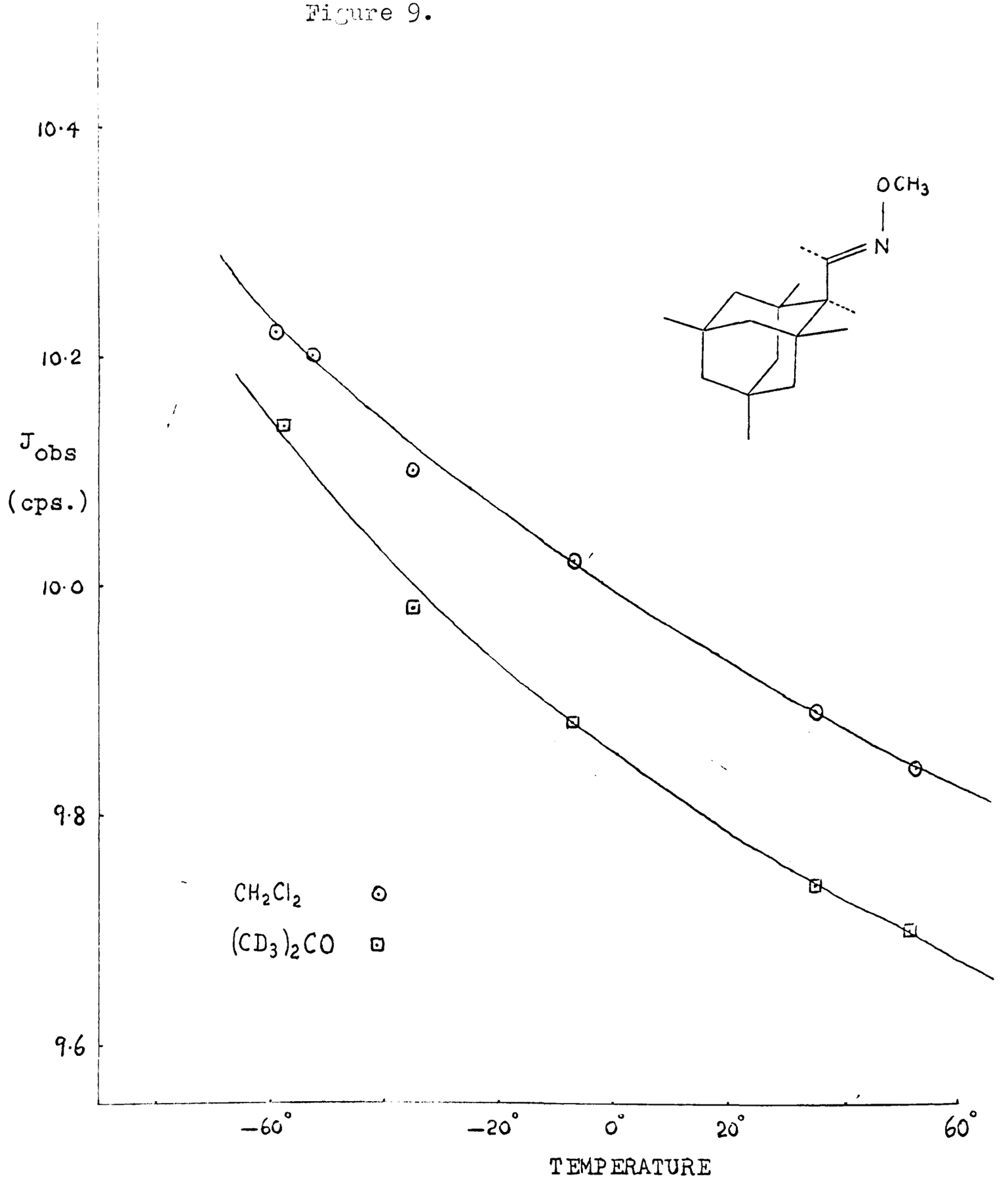

$CH_2Cl_2$
$(CD_3)_2CO$
$SiMe_4$
6·5
6·0
5·5
5·0
$J_{obs}$
(cps.)
$(^tBu)_2CHCHO$
-100°
-60°
-20°
0°
20°
60°
TEMPERATURE

used in the past to determine $J_g$ and $J_t$, but this method is not generally applicable. Curve fitting has also been attempted, but this technique is open to serious error.

Some aldehyde, O-methyl oxime and 1,3-dioxane derivatives of adamantane have been prepared, and the observed coupling constants studied over a temperature range of $+50^\circ$ to $-90^\circ$. At present, the work is not complete, but the data obtained so far is presented. A Hewlett Packard Programmable Calculator (Model 9100 A) was used for calculations.

Aldehydes. Abraham and Pople[39] have assumed that $J_g$ and $J_t$ have the same values in acetaldehyde and propionaldehyde and by solving sets of simultaneous equations found $J_g = 0.1$ and $J_t = 8.3$ cps. Karabatsos[14a] has studied many different diphatic aldehydes and found that using the values $J_t = 7.6$ and $J_g = 0.5$ cps. give the most consistent results. Di-t-butylacetaldehyde has been employed as a model for determining $J_{trans}$, but the angle between the two t-butyl groups must be much larger than that found between the methyl groups in isobutyraldehyde. The 2-substituted aldehydes of adamantane (XXIII) and 1,3,5,7-tetramethyladamantane (LXIII) correspond to di-isopropyl- and di-t-butylacetaldehyde, respectively, in which

Figure 9.


10·4
10·2
10·0
9·8
9·6
$J_{obs}$ (cps.)
OCH3
N
$CH_2Cl_2$
$(CD_3)_2CO$
−60°
−20°
0°
20°
60°
TEMPERATURE

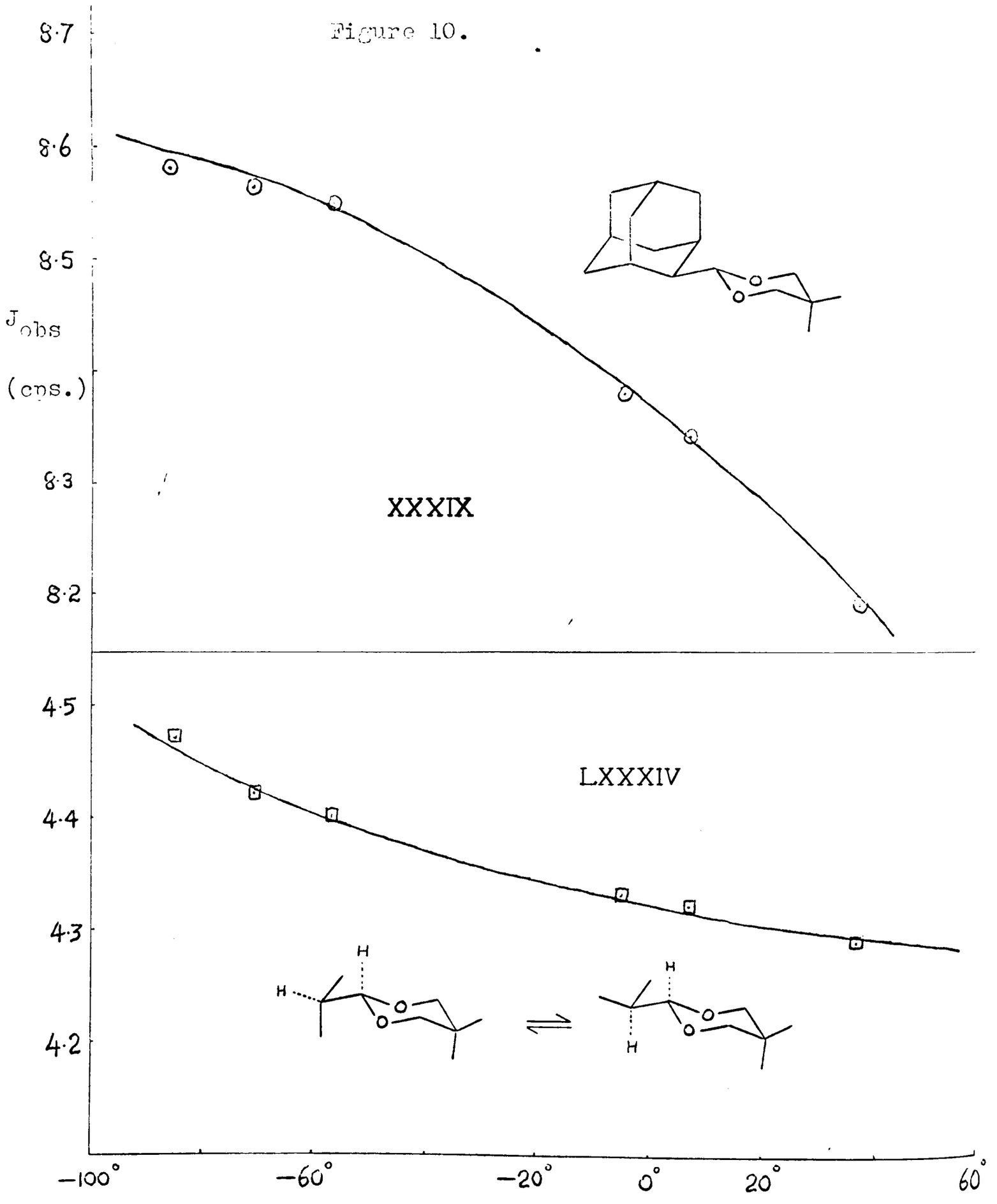
the alkyl substituents are constrained into a rigid skeleton of known geometry. The vicinal coupling constants of (XXIII in carbon tetrachloride at 35° is found to be ~ 0, whereas under the same conditions, $J_{vic}$ for (LXIII) is 5.1 cps., which shows that the presence of methyl groups in the 1- and 3-positions in (LXIII) results in the trans conformer being overwhelmingly favoured to the gauche conformer.

Figure 8 shows the coupling constants for (LXIII) plotted against temperature in three solvents, methylene chloride, hexadeuteroacetone and tetramethylsilane. It can be seen that the upper limit ($J_t$), which the observed coupling constant approaches as the temperature is decreased is probably ~ 7.0 cps. for (LXIII), whilst only ~6.4 cps. for di-t-butylacetaldehyde.

Figure 9 shows the same plot for the O-methyl oxime of the aldehyde (LXIX), in two solvents, methylene chloride and hexadeuteroacetone. In this case the curve is still rising at -60°, so that an estimate of $J_t$ is not possible. Karabatsos[40] has reported the value $J_t$ = 11.3 cps. for the O-methyl oxime of propionaldehyde.

<u>1,3-dioxanes</u> Figure 10 shows a coupling constant-temperature plot for the 2-adamantyl 1,3-dioxane (XXXIX) and for 2-isopropyl-5,5'-dimethyl-1,3-dioxane (LXXXIV), both in trichlorofluoromethane. It is clear that (XXXIX)

Figure 10.


8·7
8·6
8·5
8·3
8·2
$J_{obs}$
(cps.)
XXXIX
4·5
4·4
4·3
4·2
LXXXIV
H
H
H
H
−100°
−60°
−20°
0°
20°
60°
TEMPERATURE

exists almost exclusively in the trans conformation and the upper limit of the observed coupling constant approached at low temperatures is $J_t \sim 8.7$ cps.

The analogous 1,3-dioxane (LXXXIV), however, exists in both forms as almost free rotation of groups is possible around the bond in question. Riddell[14b] has determined $J_t$ for 2-isopropyl-1,3-dioxan in chloroform and his value is $6.8 \pm 1.6$ cps.

A study of the variation in chemical shifts with temperature of the axial and equatorial protons in the 5-adamantyl 1,3-dioxane (XLV) is also in progress so that a comparison with 5-isopropyl-1,3-dioxane can be made.

# SECTION THREE

## Dipole moment measurements of some adamantane derivatives.

The polarity of C-$CH_3$ relative to C-H

It is well established that a methyl group is electron-donating relative to hydrogen when attached to unsaturated carbon atoms, as, for example, in toluene or methylacetylene. However, little evidence has been obtained about the magnitude, and more especially the sign, of the methyl group moment relative to C-H when attached to saturated ($sp^3$) carbon.

Only the magnitude of this moment has been determined from the dipole moment measurements of propane[17a] and isobutane[17b] using the microwave Stark effect, and the values obtained were 0.083 and 0.132 $\pm$ 0.001 D, respectively. However an elegant series of experiments on the deuterium isotope effect[15] on molecular dipole moments, also using the microwave Stark effect, indicates that while the methyl group in methylacetylene is at the positive end of the molecule the methyl groups in propane are at the negative end.

Further indirect evidence has been obtained from kinetic studies. In particular, Fort and Schleyer[16] have studied the solvolysis of 1-adamantyl bromides in 80% ethyl alcohol at 70°. They found that the relative rate decreased by two-thirds for each successive substitution of a methyl group at a bridgehead position, which could be

explained by the small electron-withdrawing effect of a methyl group attached to saturated ($sp^3$) carbon. However, this kinetic result could also be explained by geometrical distortion in the carbonium ion intermediate.

In order to determine both the magnitude and direction of the $CH_3$-C($sp^3$) group moment relative to H-C($sp^3$), the dipole moments of the adamantane derivatives illustrated in Figure *11* were measured. The advantages of the adamantanoid system for such measurements are as follows:

(i) All the compounds possess an axis of symmetry which coincides with the direction of the molecular dipole.

(ii) The geometry of the system is known and therefore enables calculations of induced moments to be carried out with a high degree of confidence.

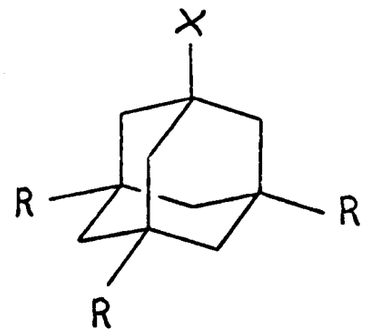
(iii) The system is rigid, which ensures no appreciable distortion occurring when hydrogen is replaced by methyl.

(iv) All the compounds are very nearly spherical and thus satisfy the requirements in the theory of dipole moments.

The dipole moment measurements were carried out in the Physical Chemistry Laboratory, Oxford by C.W. Atkin and K.M. Jinks, and the results are listed in Table 10 .

All the compounds, except (3c) were purified by sublimation, recrystallisation and a final sublimation.

Figure 11.

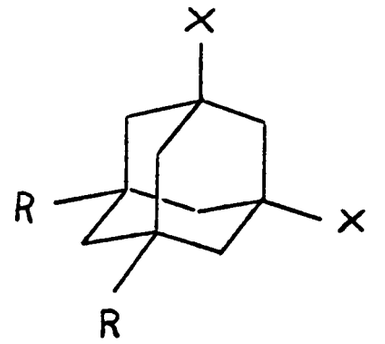



(1a) X=Br, R=H.

(1b) X=Br, R=Me.

(1c) X=CN, R=H.

(1d) X=CN, R=Me.

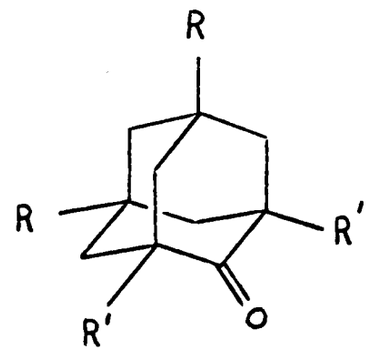



(2a) X=Br, R=H.

(2b) X=Br, R=Me.

(2c) X=CN, R=H.

(2d) X=CN, R=Me.




(3a) R=R'=H.

(3b) R=Me, R'=H.

(3c) R=H, R'=Me.

(3d) R=R'=Me.

TABLE 10

| Compound (see Figure 11) | Observed Moment (D) | "Corrected" Moment (D) |
|---|---|---|
| (1a) 1-Bromoadamantane[a] | 2.61 ± 0.01 | |
| (1b) 1-Bromo-3,5,7-trimethyladamantane[a] | 2.55 ± 0.01 | 2.53 |
| (1c) 1-Cyanoadamantane[b] | 3.99 ± 0.01 | |
| (1d) 1-Cyano-3,5,7-trimethyladamantane[a] | 3.94 ± 0.02 | 3.91 |
| (2a) 1,3-Dibromoadamantane[b] | 2.86 ± 0.02 | |
| (2b) 1,3-Dibromo-5,7-dimethyladamantane[a] | 2.82 ± 0.02 | 2.80 |
| (2c) 1,3-Dicyanoadamantane[c] | 4.51 ± 0.01 | |
| (2d) 1,3-Dicyano-5,7-dimethyl-adamantane[a] | 4.41 ± 0.03 | 3.39 |
| (3a) 2-Adamantanone[c] | 3.29 ± 0.01 | |
| (3b) 5,7-Dimethyl-adamantan-2-one[c] | 3.19 ± 0.01 | 3.17 |
| (3c) 1,3-Dimethyl-adamantan-2-one[c] | 2.97 ± 0.01 | |
| (3d) 1,3,5,7-Tetramethyl-adamantan-2-one[c] | 2.96 ± 0.02 | 2.94 |

a. Prepared by the author[8]

b. Prepared by N.W.J. Pumphrey[29]

c. Prepared by the author (see experimental section).

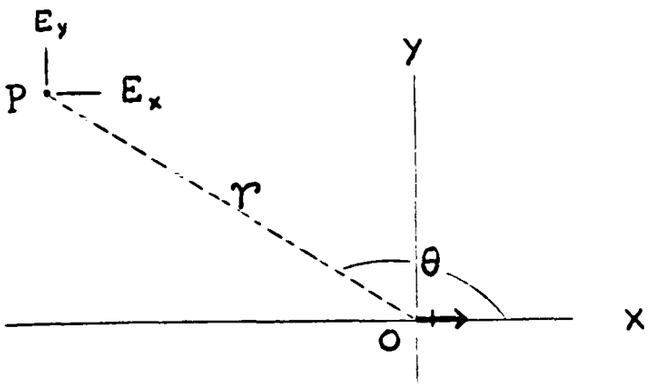
The ketone (3c) was distilled.

Before comparing the dipole moments of the compounds with methyl groups with those with hydrogen, it is necessary to make a correction to the moments of the former in order to allow for moments induced in the methyl groups by the polar group or groups. These induced moments were calculated by the method of Smallwood and Herzfeld [41], in which polarizable bonds are assumed to be points of isotropic polarizability $\alpha$ given by $\alpha = 3R_D / 4\pi N$, where $R_D$ is the bond refraction. If the inducing dipole moment $\mu$ is taken to be a point dipole acting at the origin in the X-direction, then the field at point P, a distance r away is given by

$$E_x = \frac{\mu}{\epsilon r^3} (3 \cos^2\theta - 1)$$

$$E_y = \frac{\mu}{\epsilon r^3} (3 \cos\theta \sin\theta)$$

where $\theta$ is the angle between OP and the X-direction and $\epsilon$ is the dielectric constant of the medium between O and P.



The total induced field in the y-direction (Ey) is zero for all the systems under consideration, and is therefore ignored. The estimate of induced moments is necessarily crude but their contribution is small.

The assumptions used in these calculations are summarized below:

i) The values of the bond lengths used were $r\left[C(sp^3)-C(sp^3)\right] = 1.535$ Å, $r\left[C(sp^3)-C(sp^2)\right] = 1.515$ Å, $r\left[C-H\right] = 1.090$ Å, $r\left[C=O\right] = 1.215$ Å, $r\left[C-Br\right] = 1.94$ Å, $r\left[C-CN\right] = 1.46$ Å, and $r\left[C\equiv N\right] = 1.16$ Å.

ii) All bond angles were taken as tetrahedral ($109^{\circ}$ 28'), except that the presence of a carbonyl group at $C_2$ altered the adamantane skeleton by shortening the two adjacent bonds from $C(sp^3)-C(sp^3)$ to $C(sp^2)-C(sp^3)$, which consequently included widening the $C_1-C_2-C_3$ angle by about two degrees so that the geometry of all other parts of the molecule was unaffected.

iii) The C-Br bond moment [42] was assumed to act at the point where the two covalent radii meet (i.e. 0.77 Å from the carbon atom $C_1$), and to have the value 1.8 D; the C-CN bond moment [42] was assumed to act at the midpoint of the CN bond (i.e. 2.04 Å from $C_1$) and to have the value 3.4 D; the C=O bond moment [42] was assumed to act at the

midpoint of the CO bond and to have the value 2.3 D.

iv) C-H and C-C bonds were considered as points of isotropic polarizability with $R_D$ = 1.68 and 1.30 cc. respectively. The three C-H bonds of the methyl group were considered as a single point of isotropic polarizability with $R_D$ = 5.03 cc. acting 1.72 Å from the ring carbon atom along the axis of the $C-CH_3$ bond.

v) Values of the dielectric constant $\epsilon$ were evaluated by assuming the difference between the measured dipole moment and the bond moment is caused by the moments induced in all the C-C and C-H bonds in the molecule by the polar group. The values of $\epsilon$ found were 2.46 for 1-bromoadamantane, 2.91 for 1-cyanoadamantane, and 2.63 for 2-adamantanone.

The procedure adopted in the calculation was to determine the moment induced in the C-H bond and then to replace this bond by a C-C bond and a methyl group and then calculate the new induced moments, the correction to the observed dipole moment being the difference of the two induced moments. A value of the $CH_3-C(sp^3)$ bond moment relative to the $H-C(sp^3)$ bond moment was determined by substracting the dipole moment of the unmethylated compound from the "corrected" dipole moment of the corresponding methyl derivative. For dimethyl compounds, this difference must be divided by a factor (2 cos 54° 44'), which reduces the resultant of the

TABLE 11.

| Compound | $\Delta\mu$ (D) | Methyl Moment (D) |
|---|---|---|
| (1a) 1-Bromoadamantane | -0.08 | -0.08 |
| (1b) 1-Bromo-3,5,7-trimethyladamantane | | |
| (1c) 1-Cyanoadamantane | -0.08 | -0.08 |
| (1d) 1-Cyano-3,5,7-trimethyladamantane | | |
| (2a) 1,3-Dibromoadamantane | -0.06 | -0.05 |
| (2b) 1,3-Dibromo-5,7-dimethyladamantane | | |
| (2c) 1,3-Dicyanoadamantane | -0.12 | -0.10 |
| (2d) 1,3-Dicyano-5,7-dimethyladamantane | | |
| (3a) 2-Adamantanone | -0.12 | -0.10 |
| (3b) 5,7-Dimethyladamantan-2-one | | |
| (3c) 1,3-Dimethyladamantan-2-one | -0.03 | -0.03 |
| (3d) 1,3,5,7-Tetramethyl-adamantan-2-one | | |

two methyl groups acting along the dipole axis to that of one methyl group. The results are shown in Table 11. In all six cases, the methyl group is found to be electron-withdrawing relative to hydrogen, and an average of the first five values is -0.082 ± 0.02 D, which is in excellent agreement with previous results.[15,17] However, the sixth value (-0.03 D), does not agree so well with the first five values. A possible explanation is that one ketone of the pair, namely 1,3-dimethyladamantan-2-one (3c), was not available in as great a quantity as the other compounds, and was purified by distillation, an inferior purification technique to recrystallisation and sublimation.

# SECTION FOUR

# Experimental

# EXPERIMENTAL

## Summary of procedures and instruments used

Melting points were recorded in an aluminium block (Gallenkamp MF-370) using uncorrected thermometers.
Infrared spectra were recorded on Unicam S.P.200 and Perkin Elmer 257 instruments in carbon tetrachloride solution using cells of path length 0.1 mm. or 1 cm.
Nuclear magnetic resonance (NMR) spectra were recorded by Mrs. R.E. Richards and her assistants on a Perkin Elmer 14 R (100 Mc./s. spectrometer, and by Dr. M.J.T. Robinson on a J.E.O.L. Model JNM-4H-100 spectrometer using tetramethylsilane as internal standard. Solutions were always prepared as 5% w./v. in carbon tetrachloride unless otherwise stated.
Mass spectra were determined by Dr. R.T. Aplin and his assistants on an A.E.I. M.S.9 high resolution spectrometer.
Microanalyses were undertaken by Drs. Weiler and Strauss and their staff.

Catalytic hydrogenations were carried out in an Autoclave Engineers 1 litre Magnedrive Autoclave A.K. 3220.

Gas liquid chromatography (GLC) was carried out on a Pye Series104 instrument.

Refractive indices of liquids were measured on an Abbé refractometer.

Activated alumina used for column chromatography was Type 'H' supplied by Laporte Industries Ltd.

Unbaked Keiselgel 'H' plates were used for thin layer chromatography, and these were developed either in iodine vapour or by heat after spraying with a solution of ammonium molybdate in sulphuric acid.

Diazomethane was prepared from the decomposition of N-methyl-N-nitrosourea in 50% potassium hydroxide solution under ether, and stored after distillation in ether over potassium hydroxide pellets.

Petroleum ether always refers to the fraction, b.p. 40-60°.

Dry ether was prepared by distillation from lithium aluminium hydride.

Extractions in ether, petroleum ether and methylene chloride were dried by being shaken with saturated brine and then being passed through magnesium sulphate monohydrate in a column, unless otherwise stated.

2-Adamantanone[21]

This reaction was performed several times and typical conditions are described. Adamantane (14.7 g., 1 mol.) was added to 97% sulphuric acid (200 ml., 33 mols.) and the mixture was stirred vigorously for 5 hours at 70°, then left to cool overnight. The reaction mixture was poured into iced water (1200 ml.) and extracted thoroughly with ether (600 ml.). A dark green sludge was removed by filtration, and the ethereal solution was dried and distilled leaving a yellow residue (4.9 g.), which was chromatographed over alumina (250 g.) giving 2-adamantanone. (4.5 g., 28%), m.p. 280-282° (sealed tube), after sublimation (lit.,[21] m.p. 281-283°). $\nu_{max.}$(CO) 1725 and 1734 cm.$^{-1}$. (Found: C, 79.73; H, 9.29. Calc. for $C_{10}H_{14}O$: C, 79.95; H. 9.39%).

2-Methyladamantan-2-ol

A solution of 2-adamantanone (4.0 g., 1 mol.) in dry ether (20 ml.) was added slowly to a Grignard reagent prepared from magnesium (5 g., 7 mols.) and methyl iodide (10 ml., 6 mols.) in dry ether (150 ml.). The mixture was heated under reflux for 2 hours, then cooled and poured into a saturated solution of ammonium chloride (200 ml.) and extracted with ether. The ethereal solution was dried and

distilled leaving 2-methyladamantan-2-ol (4.1 g., 93%), recrystallised as needles, m.p. 205.5-207° (sealed tube), from petroleum ether. (lit.,[21] m.p. 208-209°)
(Found: C, 79.40; H, 10.78. Calc. for $C_{11}H_{18}O$ : C, 79.46; H, 10.92%).

2-Methyleneadamantane

Phosphorus oxychloride (6 ml., 3 mols.) was added slowly to a solution of 2-methyladamantan-2-ol (3.3 g., 1 mol.) in pyridine (50 ml.), and the mixture was stirred for 18 hours at 40°, then cooled in ice as water (5 ml.) was added dropwise. The reaction mixture was diluted further with water (400 ml.) and extracted with petroleum ether (300 ml.). The petroleum extract was washed with N hydrochloric acid, dried and passed over alumina (20 g.) before distillation which left 2-methyleneadamantane (2.6 g., 88%) as a waxy solid, m.p. 131-133°, after sublimation. (lit.,[21] m.p. 135-136°)
NMR spectrum shows 2 vinyl protons at 5.54 τ.
(Found: C, 88.81; H, 11.05, Calc. for $C_{11}H_{16}$: C, 89.12; H, 10.88%).

When 2-methyladamantan-2-ol was treated with 85% phosphoric acid for ca. 4 hours at 70-80°, 2-methyleneadamantane (15%) was separated by steam distillation of the product mixture, however, the major product isolated was

2-methyladamant-2-yl-2-methyleneadamantane (70%), m.p. 87.5-89°, after recrystallisation from petroleum ether. Parent peak in the mass spectrum occurs at $^{m}/_{e}$ = 296, and loss of $CH_3$ follows to $^{m}/_{e}$ = 281. NMR spectrum shows 1 $CH_3$ singlet at 8.81 and 1 vinyl proton at 4.88 $\tau$. (Found: C, 89.14; H, 10.77. $C_{22}H_{32}$ requires C, 89.12; H, 10.88%).

2-Methyleneadamantane oxide

A solution of 40% peracetic acid in acetic acid (2 ml., 2 mols.), saturated with hydrated sodium acetate, was added to a solution of 2-methyleneadamantane (0.80 g., 1 mol.) in methylene chloride (25 ml.), and the mixture was stirred for 6 hours at 0°. The reaction mixture was filtered and distilled leaving a residue (0.90 g.), which was passed over alumina (10 g.,) in ether. Removal of the ether gave 2-methyleneadamantane oxide (0.75 g., 84%), m.p. 167-169°; NMR spectrum shows 1 $CH_2$ singlet at 7.54 $\tau$. (Found: C 80.12; H, 9.44. $C_{11}H_{16}O$ requires C, 80.44; H, 9.83%).

Adamantane-2-aldehyde

2-Methyleneadamantane oxide (0.50 g., 1 mol.) in benzene (5 ml.) was treated with boron trifluoride etherate (0.5 ml., 1.5 mols.) for 4 hours at room temperature. The mixture was poured into an ice-cold solution of potassium

bicarbonate, and extracted with ether (40 ml.) The ethereal solution was dried and distilled leaving adamantane-2-aldehyde (0.48 g., 96%), m.p. 159-163°, which was not purified further, but used immediately for the preparation of derivatives. $\nu$ max. (CO) 1728 cm.$^{-1}$. NMR spectrum shows 1 aldehydic proton at 0.33 $\tau$ ($J_{vic} \approx 0$).

Adamantane-2-(O-methyl)aldoxime

A mixture of adamantane-2-aldehyde (0.20 g., 1 mol.), methoxylamine hydrochloride (0.30 g., 3 mols.) pyridine (0.8 ml.) and ethyl alcohol (6 ml.) was heated under reflux for 2 hours, then added to water and extracted with petroleum ether. The petroleum solution was washed with dilute hydrochloric acid, dried, filtered through alumina (1 g.), and distilled leaving adamantane-2-(O-methyl) aldoxime (0.20 g., 85%), as a viscous liquid. NMR spectrum shows 1 methoxyl $CH_3$ at 6.25 $\tau$ and 1 aldoxime proton at 2.63 $\tau$. Parent peak in the mass spectrum occurs at $m/_e$ = 193.

2-(2-Adamantyl)-5,5-dimethyl-1,3-dioxane

A mixture of adamantane-2-aldehyde (0.46 g., 1 mol.) 2,2-dimethylpropan-1,3-diol (0.38 g., 1.3 mols.), toluene p-sulphonic acid (30 mg.) and anhydrous copper sulphate (0.8 g.) in methylene chloride (5 ml.) was heated under reflux

for 3 hours, then filtered through alumina and distilled leaving a glassy solid, 2-(2-adamantyl)-5,5-dimethyl-1,3-dioxane (0.51 g., 73%). NMR spectrum shows $CH_3$ singlets at 9.31 and 8.86 $\tau$. Parent peak in the mass spectrum occurs at $m/e = 250$.

2-Adamantanol

Lithium aluminium hydride (0.80 g., 1.1 mols.) was added to a solution of 2-adamantone (3.00 g., 1 mol.) in dry ether (100 ml.), and the mixture was heated under reflux for 50 minutes. Water was added dropwise until effervescence ceased, then the mixture was poured into dilute sulphuric acid and extracted with ether (100 ml.) The ethereal solution was dried and distilled leaving 2-adamantanol (2.75 g., 90%), m.p. 295-297° (sealed tube), after recrystallisation from methanol. (lit.,[21] m.p. 296-298°).

(Found: C, 78.99; H, 10.37. Calc. for $C_{10}H_{16}O$: C, 78.89; H, 10.59%).

2-Adamantyl toluene-p-sulphonate

A solution of 2-adamantanol (2.5 g., 1 mol.) and toluene p-sulphonyl chloride (5.0 g., 1.6 mols.) in pyridine (50 ml.) was left for 9 days at 0°. The reaction mixture was poured into iced water (250 ml.) and extracted with ether (150 ml.). The ethereal solution was dried and

distilled leaving an oily residue (4.7 g., ) from which 2-adamantyl toluene p-sulphonate (4.1 g., 81%) crystallised, m.p. 78-79°, after 3 days in petroleum ether at 0°. (lit.[21] m.p. 82-83°). Parent peak in the mass spectrum occurs at $^{m}/_{e}$ = 306. (Found: C, 66.58; H, 7.17. Calc. for $C_{17}H_{22}SO_3$: C, 66.66; H, 7.19%).

2-(2-Adamantyl)propan-1,3-diol

Diethyl malonate (12 ml., 6 mols) and 2-adamantyl toluene p-sulphonate (4.0 g., 1 mol.) were added to a solution of sodium (2.0 g., 7 mol.s) in dry ethanol (50 ml.), and the mixture was maintained at 80° for 3 days, then poured into dilute phosphoric acid and extracted with ether (200 ml.). The ethereal solution was dried and distilled leaving an orange liquid residue (9 g.) which was chromatographed over alumina (250 g.,) taking 150 ml. fractions, as follows:

| Eluting Solvents | Fractions | Wt.,g. | Comments |
|---|---|---|---|
| 100% petroleum ether | 1 - 2[a] | 1.0 | Mainly 2-ethoxyadamantane |
| 5% ether in petroleum ether | 3 - 4[b] | 5.2 | Mixture of diethyl malonate and diethyl 2-adamantyl-malonate |
| 10% ether in petroleum ether | 5 - 8 | 2.3 | Diethyl malonate |

| Eluting Solvents | Fractions | Wt., g. | Comments |
|---|---|---|---|
| 100% Ether | 9 -10 | 0.3 | 2-Adamantanol |

[a] NMR spectrum shows ethoxyl group by $CH_3$ triplet 8.83, $CH_2$ quartet 6.57 $\tau$ ($J_{vic}$ = 7 cps.).

[b] Fractions 3-4 were distilled (up to 100°/0.3 mm) leaving diethyl 2-adamantylmalonate (1.1 g., 29%), as a liquid residue which was used without further purification in the following preparation.

Diethyl 2-adamantylmalonate (1.10 g., 1 mol.) in 1,4-dioxan (15 ml.) was added dropwise to a solution of lithium aluminium hydride (1.0 g., 7.5 mols.) in 1,4-dioxan (60 ml.) heated under reflux. After 2 hours at reflux, water (200 ml.) was cautiously added to the reaction mixture and the precipitate was collected and dissolved in dilute sulphuric acid before extraction with ether together with the filtrate, which was concentrated to 30 ml. by distillation under reduced pressure. The ethereal solution was washed, dried with anhydrous potassium carbonate, and distilled leaving 2-(2-Adamantyl)propan-1,3-diol (0.56 g., 72%), m.p. 132-133° (from aqueous methanol). Parent peak in the mass spectrum corresponding to the ion (M-18) occurs at $^{m}/_{e}$ = 192.

(Found: C, 74.28; H, 10.43. $C_{13}H_{22}O_2$ requires C, 74.24;

H, 10.54%).

5-(2-Adamantyl)-1,3-dioxane

2-(2-Adamantyl)propan-1,3-diol (0.210 g., 1 mol.), paraformaldehyde (0.090 g., 3 mols.) toluene p-sulphonic acid (0.030 g., 0.2 mol.), and anhydrous copper sulphate (0.330 g., 2 mols.) were heated under reflux in methylene chloride (10 ml.) for 6 hours. After standing overnight, the reaction mixture was filtered through alumina (2 g.) in methylene chloride and distilled leaving 5-(2-adamantyl)-1,3-dioxane (0.218 g., 98%), a clear viscous liquid. NMR spectrum shows doublets at 5.17 and 5.54 $\tau$, which correspond to the equatorial and axial protons attached to $C_2$. Parent peak in the mass spectrum occurs at $^{m}/_{e} = 222$.

Adamantane-1,3-dicarboxylic acid

Formic acid (98-100%, 20 ml., 40 mols.) was added dropwise to a vigorously stirred mixture of 1,3-dibromo-adamantane (3.70 g., 1 mol.) in concentrated sulphuric acid (200 ml.) at 20° over a period of 1 hour. During this time freshly prepared dry silver sulphate (4.1 g., 1.1 mols.) was also added in small portions. After one further hour of stirring, the frothing subsided and a pale yellow precipitate of silver bromide was observed. The reaction

mixture was stirred overnight, filtered and poured into iced water (600 ml.) The white precipitate was collected, dissolved in dilute sodium hydroxide solution and filtered again to remove traces of basic silver salts still present. Concentrated hydrochloric acid was added to the filtrate, and adamantane-1,3-dicarboxylic acid (2.6 g., 92%) was collected and dried, m.p. 273-276°, and after recrystallisation from methanol had m.p. 276-277° (lit.[28] m.p. 276°). Lassaigne's test was negative for halogen.
(Found: C, 64.04; H, 7.14. Calc. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19%).

1,3-Dicyanoadamantane

Adamantane-1,3-dicarboxylic acid (1.6 g., 1 mol.) was added to thionyl chloride (20 ml., 20 mols.) and dimethylformamide (1 ml.). After standing for 30 minutes, the excess of thionyl chloride was distilled under vacuum and the residue was added to liquid ammonia (50 ml.). The excess of ammonia was allowed to evaporate and the residue recrystallised from aqueous methanol to give adamantane-1,3-dicarboxamide (1.1 g., 69%), m.p.256-258°. (lit.[29] m.p.257-258°).

Adamantane-1,3-dicarboxamide (0.66 g., 1 mol.), thionyl chloride (8 ml., 20 mols.) and dimethylformamide (0.5 ml.) gave 1,3-dicyanoadamantane (0.39 g., 70%)

after sublimation. Recrystallisation from methanol and sublimation (100-110°/ .2 mm) provided an analytical sample (0.31 g., 56%), m.p. 190-192° (lit.,[29] m.p. 198-200°). (Found: C, 77.60; H, 7.56; N, 14.83. Calc. for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04%).

The action of diazomethane on 2-adamantanone

A distilled ethereal solution of diazomethane (approx. 2M, 15 ml., 2 mols.) was added dropwise to a solution of 2-adamantanone (2.00 g., 1 mol.) and anhydrous aluminium chloride (0.2 g.) in dry ether (5 ml.). The ethereal solution was washed with dilute hydrochloric acid, dried and distilled leaving a solid residue (2.02 g.), which was chromatographed over alumina (200 g.). 4-Homoadamantanone (1.16 g., 48%) was eluted with 70% ether in petroleum ether, and recrystallised, m.p. 260-262° (sealed tube) from petroleum ether (lit.,[26] m.p. 269-270).

$\nu_{max.}$(CO) 1698 cm.$^{-1}$. Parent peak in the mass spectrum occurs at $^{m}/_{e}$ = 164, and initial loss of HCO fragment is confirmed by $^{m}/_{e}^{*}$ = 111.2.

(Found: C, 80.78; H, 9.43. $C_{11}H_{16}O$ requires C, 80.44; H, 9.83%). No other compounds were identified in fractions eluted with more, or less polar solvent mixtures.

4-Homoadamantanone was also prepared by a method reported recently.[26] An ethereal solution of diazomethane was added to 2-adamantanone (2.0 g., 1 mol.) in methanol. The reaction mixture was filtered through alumina and distilled leaving 4-homoadamantanone (1.64 g., 75%), which was recrystallised, m.p. 261-263° (sealed tube) from petroleum ether.

Tricyclo[4,3,1,1] undecane or homoadamantane

A mixture of 4-homoadamantanone (0.10 g., 1 mol.) hydrazine hydrate (1 ml., 30 mols.) and potassium hydroxide (3.0 g.) in diethylene glycol (30 ml.) was warmed to 100° (the difficulty caused by the sublimation of the starting material out of the flask into the condenser was overcome by shaking the contents up into the condenser to redissolve it). The excess of hydrazine and water were distilled off after 2 hours, then the mixture was heated under reflux at 220° for 9 hours. Homoadamantane (55 mg., 60%) was recovered from the condenser as a sublimate, m.p. 237-240° (lit.[43] m.p. 258-259°). Parent peak in the mass spectrum occurs at $^{m}/_{e}$ = 150.

1,3-Dimethyladamantane [5]

Perhydroacenaphthene (110 g., 1 mol.) was treated with anhydrous aluminium bromide (100 g., 0.3 mol.) and t-butyl bromide (2.5 ml.) for 24 hours at 55-60°. The upper hydrocarbon layer was decanted and, after adding to this the catalyst washings in petroleum ether, the mixture was distilled leaving 1,3-dimethyladamantane (90 g., 82%), $n_D^{21}$ = 1.4788 (lit.,[44] $n_D^{20}$ = 1.4783). The infrared spectrum (liquid film, 0.1 mm. cell) was unchanged after distillation of the product, b.p. 201-203°/760 mm.

Oxidation of 1,3-dimethyladamantane by air[7]

Air was bubbled slowly through 1,3-dimethyladamantane (50.0 g.) in the presence of cobalt naphthenate (50 mg.) as catalyst for 11 hours at 170-180° (external oil bath). The reaction mixture was diluted with petroleum ether (200 ml.), dried and chromatographed over alumina (500 g.), taking 200 ml. fractions, as follows:

| Eluting solvent | Fractions | Wt.,g. | Comments |
|---|---|---|---|
| 100% petroleum ether | 1-4 | 33.57 | 1,3-Dimethyladamantane |
| 30% ether in petroleum ether | 5-8 | 3.15 | A mixture of dimethyl-adamantanones |
| 50% ether in petroleum ether | 9-11 | 0.37 | " |
| 100% ether | 12-20 | 7.23[a] | 1-Hydroxy-3,5-dimethyl-adamantane |

a. Recrystallised from petroleum ether as needles, m.p. 96-96.5° (lit.[45] m.p. 94°).

(Found: C, 80.06; H, 11.25. Calc. for $C_{12}H_{20}O$: C, 79.94; H, 11.18%).

A second oxidation of 1,3-dimethyladamantane by air at 175-185° for 12 hours resulted in the separation of the following components after chromatography: 1,3-dimethyl-adamantane (33.5 g.), dimethyladamantanones (5.9 g.), and hydroxylic material (8.6 g.). The fractions (9.4 g.) from both oxidations containing dimethyladamantanones were chromatographed further over alumina (700 g.) taking 200 ml. fractions, as follows:

| Eluting solvent | Fractions | Wt., g. | Comments |
|---|---|---|---|
| 100% petroleum ether | 1-5 | 0.64 | 1,3-Dimethyladamantane |
| 5% ether in petroleum ether | 6-8 | - | |
| 8% ether in petroleum ether | 9 | 0.16 | |

| | | | |
|---|---|---|---|
| 8% ether in petroleum ether | 10-11 | 0.42 | 1,3-Dimethyladamtan-2-one |
| " | 12-14[a] | 1.66 | |
| 10% ether in petroleum ether | 15-20[b] | 3.42 | 1,5-Dimethyladamantan-2-one |
| 20% ether in petroleum ether | 21-23 | 0.20 | |
| " | 24-29[c] | 1.48 | 5,7-Dimethyladamantan-2-one |
| 40% ether in petroleum ether | 30-31 | 0.02 | |
| 100% ether | 32-35 | 0.60 | |
| Total material recovered | | 8.60 g. | |

a. Fractions 12-14 were added to a solution of hydroxylamine hydrochloride (20%, 8 ml.) and sodium hydroxide (1.2 g.) in ethyl alcohol (10 ml.). After 1 minute, a white precipitate (1.08 g.) which separated from the ice-cooled mixture, was collected, washed with ice-cold petroleum ether, dried and sublimed giving 1,5-dimethyladamantan-2-one oxime (1.00 g.), m.p. 178-180°. NMR spectrum (5% w./v. in $CDCl_3$) shows 1 $CH_3$, 9.17; 1 $CH_3$, 8.97; 1 CH, 7.91; 1 CH, 6.33 $\tau$.

(Found: C, 74.53; H, 9.84; N, 7.19. $C_{12}H_{19}NO$ requires C, 74.57; H, 9.91; N, 7.25%).

The petroleum ether washings were dried and distilled giving 1,3-dimethyladamantan-2-one (0.55 g.), b.p. 75-80°/0.2 mm.; m.p. 36-38°; $\nu_{max.}$ 1709 (CO) and 953 cm.$^{-1}$. (Found: C, 80.52; H, 10.26. $C_{12}H_{18}O$ requires C, 80.85; H, 10.18%).

b. Fractions 15-20 were distilled giving 1,5-dimethyladamantan-2-one (3.15 g., 3%), b.p. 62-63.5°/0.6 mm., $n_D^{18}$ = 1.4939; $\nu_{max.}$ 1715 (CO) and 1069, 1053, 1038, 1027 cm.$^{-1}$. (Found: C, 81.09; H, 10.23. $C_{12}H_{18}O$ requires C, 80.85; H, 10.18%).

c. Fractions 24-29 were recrystallised from petroleum ether at -78°, and the material recovered (1.04 g.) was sublimed (55-60°/0.2 mm.) giving 5,7-dimethyladamantan-2-one (0.99 g., 1%), m.p. 60-62°; $\nu_{max.}$ 1728 (CO) and 1067 cm.$^{-1}$.
(Found: C, 80.65; H, 10.09. $C_{12}H_{18}O$ requires C, 80.85; H, 10.18%).

5,7-Dimethyladamantan-2-one oxime

5,7-Dimethyladamantan-2-one (0.13 g., 1 mol.) was added to a solution of hydroxylamine hydrochloride (20%., 2 ml., 8 mols) and sodium hydroxide (0.3 g.) in ethyl alcohol (3 ml.) After 10 minutes, the reaction mixture was poured into water (20 ml.). 5,7-Dimethyladamantan-2-one oxime (0.12 g., 88%)

was collected, dried and recrystallised as needles, m.p. 144-145°, from petroleum ether. NMR spectrum (5% w./v. in $CDCl_3$) shows $2CH_3$, 9.14; 1 CH, 7.43; 1 CH, 6.40τ. (Found: C, 74.68; H, 9.76; N, 7.05. $C_{12}H_{19}NO$ requires C, 74.57; H, 9.91; N, 7.25%).

Ozonolysis of 1,3-dimethyladamantane[6]

Ozonised oxygen (approx. 30 l./hour) was bubbled into a solution of 1,3-dimethyladamantane (30 g.) and di-t-butyl peroxide (1 ml.) in carbon tetrachloride (450 ml.) at room temperature for 21 hours. The reaction mixture was concentrated down to 100 ml. by distillation, diluted with petroleum ether (100 ml.) and dried. Removal of the petroleum ether gave a pale yellow liquid (31 g.), which was chromatographed over alumina (1 kg.) taking 100 ml. fractions, as follows:

| Eluting solvent | Fractions | Wt.,g. | Comments |
|---|---|---|---|
| 100% petroleum ether | 1-20 | 17.70 | 1,3-Dimethyladamantane |
| 5% ether in petroleum ether | 21-40 | 0.50 | |
| 10% ether in petroleum ether | 41-46 | 0.27 | Mainly 1,3-dimethyl-adamantan-2-one |
| " | 47-50[a] | 0.33 | 1,3-Dimethyladamantan-2-one |
| " | 51-52 | 0.20 | Mainly 1,3-dimethyl-adamantan-2-one |

| | | | |
|---|---|---|---|
| 10% ether in petroleum ether | 53-58 | 0.42 | Mainly 1,5-dimethyladamantan-2-one. |
| " | 59-64[b] | 0.45 | 1,5-Dimethyladamantan-2-one |
| 20% ether in petroleum ether | 65-72[b] | 0.54 | " |
| 50% ether in petroleum ether | 73-80 | 0.25 | |
| 100% ether | 81-92 | 0.50 | |
| methanol-ether | 93-100[c] | 9.88 | Mainly 1-hydroxy-3,5-dimethyladamantane |

a. Yield 0.18 g. after distillation, b.p. 65-70°/0.1 mm., $n_D^{25}$ = 1.4946

b. Yield 0.45 g. after distillation, b.p. 62-65°/0.6 mm., $n_D^{22}$ = 1.4901

c. Yield 6.5 g., m.p. 95-96°, after recrystallisation from petroleum ether.

1,3,5-Trimethyladamantane

Technical grade fluorene (340 g., 1 mol.) was recrystallised from benzene and ethyl alcohol, and was then hydrogenated (initially 100 atm. hydrogen) over Raney nickel[46] W4 (approx. 30 g.) suspended in ethyl alcohol (60 ml.) at 140-160° for 2 days. The hydrogen absorbed was 400 l. atm. at N.T.P. (approx. 8 mols.) At this stage, further use of the hydrogen pressure decrease as a measure of the uptake of hydrogen became unreliable because of substantial leaks from the autoclave. Infrared spectral evidence showed that the reduction was incomplete. A second batch of fluorene (200 g.), partially reduced as above, was combined with the first batch and the whole hydrogenated over fresh Raney nickel (approx. 50 g.) at 140-160° for 1 day. The reaction mixture was filtered and the ethyl alcohol was removed under vacuum until the residue contained no hydroxylic material. Ten portions of sulphuric acid (98%, 50 ml.) were added to, stirred with, and separated from the residue to remove aromatic impurities by sulphonation which gave crude perhydrofluorene (347 g., 60%).

Crude perhydrofluorene (300 g., 1 mol.) was treated with anhydrous aluminium bromide (300 g., 0.3 mol.) and t-butyl bromide (8 ml.) for 1 day at 55-65°. The upper hydrocarbon layer was decanted and added to the petroleum

ether washings of the catalyst. The petroleum solution was washed with 2N hydrochloric acid and dried. Removal of the petroleum ether gave 1,3,5-trimethyladamantane (215 g., 72%), b.p. 94-95°/25 mm., $n_D^{22}$ = 1.4752 (lit.,[30] $n_D^{20}$ = 1.4751, b.p. 88-89.5°/19 mm.) The infrared spectrum (liquid film, 0.1 mm. cell) was unchanged by distillation of the product.

1-Bromo-3,5,7-trimethyladamantane

1,3,5-Trimethyladamantane (10 g., 1 mol.) was heated under reflux with bromine (20 ml., 6 mols.) for 20 hours. The reaction mixture was poured into water (250 ml.) and extracted with methylene chloride (200 ml.). Sulphur dioxide was bubbled through the solution to remove the excess of bromine. The methylene chloride solution was dried and distilled leaving 1-bromo-3,5,7-trimethyladamantane (13 g., 90%), which formed needles, m.p. 100-101.5°, from methanol (lit.,[30] m.p. 101-102°). Characteristic bands occur in the infrared spectrum at 1325, 1194, 935, and 879 $cm.^{-1}$.

(Found: C, 60.43; H, 8.27; Br, 31.55. Calc. for $C_{13}H_{21}Br$: C, 60.70; H, 8.23; Br, 31.07%).

Oxidation of 1,3,5-trimethyladamantane by air[7]

Air was bubbled slowly through 1,3,5-trimethyladamantane (50.0 g.) in the presence of cobalt naphthenate (50 mg.) as

catalyst for 12 hours at 175-185° (external oil bath). The reaction mixture was diluted with petroleum ether (100 ml.) dried and chromatographed over alumina (500 g.), taking 200 ml. fractions, as follows:

| Eluting solvent | Fractions | Wt., g. | Comments |
|---|---|---|---|
| 100% petroleum ether | 1-5 | 31.8 | 1,3,5-trimethyladamantane |
| 25% ether in petroleum ether | 6-13 | 5.8 | A mixture of 1,3,5-trimethyladamantan-2-one and 1,5,7-trimethyl-adamantan-2-one |
| 100% ether | 14-20[a] | 8.5 | 1-Hydroxy-3,5,7-trimethyl-adamantane |
| Total material recovered | | 46.1 g. | |

a. Yield 16%; recrystallised from petroleum ether, m.p. 120-121° (lit.[47] m.p. 122-123°).

(Found: C. 80.21; H, 11.41. Calc. for $C_{13}H_{22}O$: C, 80.35; H, 11.41%).

The fractions 6-13 from above were rechromatographed over alumina (300 g.) taking 150 ml. fractions as follows:

| Eluting solvent | Fractions | Wt., g. | Comments |
|---|---|---|---|
| 100% petroleum ether | 1-5 | - | |
| " | 6 | 0.30 | |
| 5% ether in petroleum ether | 7-8[a] | 0.70 | 1,3,5-Trimethyladamantan-2-one |

| | | | |
|---|---|---|---|
| 5% ether in petroleum ether | 9-11[b] | 1.76 | A mixture of both isomers |
| 10% ether in petroleum ether | 12-16[c] | 2.51 | 1,5,7-Trimethyladamantan-2-one |
| " | 17-18 | 0.08 | |
| 100% ether | 19-20 | 0.35 | |
| Total material recovered | | 5.70 g. | |

a. B.p. 62-63°/0.3 mm.; $n_D^{23}$ = 1.4880; $\nu_{max.}$ (CO) 1715 and other bands at 1160 and 1012 $cm.^{-1}$

Parent peak in the mass spectrum occurs at $^{m}/_{e}$ = 192.

(Found: C, 81.51; H, 10.42. $C_{13}H_{20}O$ requires C, 81.20; H, 10.48%).

b. Fractions 9-11 were added to a solution of 20% hydroxylamine hydrochloride (8 ml.) and sodium hydroxide (1 g.) in ethyl alcohol (6 ml.). After 10 minutes, a white precipitate (0.52 g.), which separated from the ice-cooled mixture, was collected, washed with petroleum ether, dried and recrystallised from ether-petroleum ether giving 1,5,7-trimethyladamantan-2-one oxime (0.49 g.), m.p. 175-177°; NMR spectrum (5% w./v. in $CDCl_3$) shows $2CH_3$, 9.14; 1 $CH_3$, 8.97; 1 CH 6.32 $\tau$ .

(Found: C, 75.19; H, 10.11; N, 6.80. $C_{13}H_{21}NO$ requires C, 75.31; H, 10.21; N, 6.76%).

The washings in petroleum ether were dried and distilled to give more 1,3,5-trimethyladamantan-2-one (0.87 g.), b.p. 63-65°/0.4 mm.

c. Recrystallised from petroleum ether at -78° and sublimed, m.p. 45-46°; $\nu_{max.}$ (CO) 1721 and other bands at 1121 and 1063 cm.$^{-1}$. Parent peak in the mass spectrum occurs at $^{m}/_{e}$ = 192.

(Found: C, 81.08; H, 10.57. $C_{13}H_{20}O$ requires C, 81.20; H, 10.48%).

Oxidation of 1,3,5-trimethyladamantane by chromic acid

1,3,5-Trimethyladamantane (50 g., 1 mol.) was added slowly to a stirred solution of chromium trioxide (26 g., 1 mol.) in acetic acid (85%, 150 ml.) and concentrated sulphuric acid (15 ml., 1 mol.) maintained at 70° for 20 hours. The reaction mixture was added to a dilute solution of sodium chloride (1 l.), and extracted with ether (800 ml.). The ethereal solution was washed with dilute potassium carbonate solution, dried and distilled leaving a white semi-solid residue (53 g.), from which 1-hydroxy-3,5,7-trimethyladamantane (32 g., 59%) was collected after washing with ice-cold petroleum ether. After recrystallisation from petroleum ether, the alcohol had m.p. 119.5-120.5°.

The residue (approx. 20 g.) in petroleum ether was chromatographed over alumina (250 g.) taking 150 ml. fractions, as follows:

| Eluting solvent | Fractions | Wt., g. | Comments |
|---|---|---|---|
| 100% petroleum ether | 1-5 | 14.3 | 1,3,5-Trimethyladamantane |
| 20% ether in petroleum ether | 6-7[a] | 0.15 | A mixture of 1,3,5-trimethyl-adamantan-2-one and 1-acetoxy-3,5,7-trimethyl-adamantane |
| 40% ether in petroleum ether | 8-9[b] | 1.13 | 1-Acetoxy-3,5,7-trimethyl-adamantane |
| 60% ether in petroleum ether | 10-13[c] | 0.52 | A mixture of 1,5,7-tri-methyladamantan-2-one and 1-acetoxy-3,5,7-trimethyladamantane |
| 100% ether | 14-15 | 0.06 | |
| 20% methanol in ether | 16-18 | 3.8 | 1-Hydroxy-3,5,7-trimethyl-adamantane |

a. Heated under reflux with potassium hydroxide (0.5 g. in methanol (10 ml.) for 1 hour. Material recovered filtered through alumina (1 g.) in petroleum ether giving 1,3,5-trimethyladamantan-2-one (0.11 g.), $\nu_{max.}$ (CO) 1713 cm.$^{-1}$ (see p. 852 )

b. Crystalline solid, m.p. 48-51°; NMR spectrum shows acetoxyl $CH_3$ at 8.15 $\tau$ ; $\nu_{max.}$ (CO) 1724 cm.$^{-1}$ (see p. 85 )

c. Heated under reflux with potassium hydroxide (0.6 g.) in methanol (10 ml.) for 30 minutes. Material recovered

filtered through alumina (10 g.) giving slightly impure 1,5,7-trimethyladamantan-2-one (0.32 g.), m.p. 41-43; $\nu_{max.}$(CO) 1718 $cm.^{-1}$ (see p. 83 )

1-Acetoxy-3,5,7-trimethyladamantane

1-Hydroxy-3,5,7-trimethyladamantane (0.30 g., 1 mol.) was treated with acetic anhydride (3 ml., 20 mols) and concentrated sulphuric acid (0.1 ml., 1.2 mols.) for 15 minutes at room temperature. The reaction mixture was then poured into water (100 ml.) and extracted with petroleum ether (80 ml.). The petroleum solution was washed thoroughly with dilute potassium bicarbonate solution, dried and distilled leaving 1-acetoxy-3,5,7-trimethyladamantane (0.30 g., 82%), m.p. 51-52°, after recrystallisation from petroleum ether at -78°; $\nu_{max.}$ (CO) 1726 $cm.^{-1}$.
(Found: C, 76.45; H, 10.10. $C_{15}H_{24}O_2$ requires C, 76.22; H, 10.24%).

Ozonolysis of 1,3,5-trimethyladamantane[6]

Ozonised oxygen (approx. 30 l./hour) was bubbled into a solution of 1,3,5-trimethyladamantane (10.0 g.) and di-t-butyl peroxide (0.3 ml.) in carbon tetrachloride (100 ml.) for 10 hours at room temperature. Then carbon tetrachloride was removed from the reaction mixture by distillation, and

the residue was diluted with petroleum ether, dried and chromatographed over alumina into the following components: 1,3,5-trimethyladamantane (8.0 g.) from 100% petroleum ether; ketonic material (0.6 g.) from 25% ether in petroleum ether; 1-hydroxy-3,5,7-trimethyladamantane (1.5 g., 14%) from 100% ether.

The ketonic material was further chromatographed over alumina (35 g.), by which 1,3,5-trimethyladamantan-2-one (0.26 g., 2.4%), $\nu_{max.}$ (CO) 1714 cm.$^{-1}$; $n_D^{20}$ = 1.4885., and a mixture of both isomers (0.24 g.), $\nu_{max.}$ (CO) 1717 cm.$^{-1}$ were separated.

The oxidation of 1-hydroxy-3,5,7-trimethyladamantane by sulphuric acid.

1-Hydroxy-3,5,7-trimethyladamantane (8.5 g., 1 mol.) was stirred vigorously with 95% sulphuric acid (60 ml., 25 mols) at 55° for 5 hours and left to cool overnight. The reaction mixture was poured into iced water (500 ml.) and extracted with ether (400 ml.) The ethereal solution was washed with dilute potassium carbonate solution, dried and distilled leaving a yellowish orange liquid (7.8 g.), which was chromatographed over alumina (250 g.) taking 150 ml. fractions, as follows:

| Eluting solvent | Fractions | Wt., g. | Comments |
|---|---|---|---|
| 100% petroleum ether | 1-4 | 3.33 | 1,3,5-Trimethyladamantane |
| 5% ether in petroleum ether | 5-9 | 0.32 | An unidentified ether |
| 10% ether in petroleum ether | 10-12 | - | |
| 40% ether in petroleum ether | 13-16 | - | |
| 100% ether | 17-22[a] | 0.30 | Mainly 1,5,7-trimethyladamantan-2-one |
| 100% methanol | 23-25 | 1.88 | Apparently polyoxygenated material. |

a. Sample sublimed, m.p. 40-42°; $\nu_{max.}$ (CO) 1719 cm.$^{-1}$

3,5,7-Trimethyladamantane-1-carboxylic acid

Concentrated sulphuric acid (30 ml., 15 mols.) was slowly added to an ice-cooled mixture of 1-hydroxy-3,5,7-trimethyladamantane (7.0 g., 1 mol.) and formic acid (98-100%, 10 ml., 7 mols.) After 3 hours at room temperature, the reaction mixture was diluted with water and 3,5,7-trimethyladamantane-1-carboxylic acid (7.7 g., 96%), was collected, dried and recrystallised, m.p. 137.5-139°, from methanol (lit.,[30] m.p. 140.5-141°).

(Found: C, 75.48; H, 9.99. Calc. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97%).

Methyl 3,5,7-trimethyladamantane-1-carboxylate

A distilled ethereal solution of diazomethane (approx. 2M., 3 ml.) was added dropwise to 3,5,7-trimethyladamantane-1-carboxylic acid (1.00 g.) in dry ether (10 ml.) until the solution remained pale yellow. Removal of the ether gave methyl 3,5,7-trimethyladamantane-1-carboxylate (1.04 g., 98%), which formed plates, m.p. 57-58°, from petroleum ether. $\nu_{max.}$ (CO) 1723 cm.$^{-1}$.
(Found: C. 76.39; H, 10.18. $C_{15}H_{24}O_2$ requires C, 76.22; H, 10.24%).

1-Cyano-3,5,7-trimethyladamantane

3,5,7-Trimethyladamantane-1-carboxylic acid (3.4 g., 1 mol.) was treated with thionyl chloride (16 ml., 14 mols.) and dimethylformade (0.5 ml.) After 15 minutes, the excess of thionyl chloride was distilled under vacuum and the residue, suspended in methylene chloride (25 ml.), was added dropwise to 0.88 ammonia (60 ml.). Removal of the methylene chloride left 3,5,7-trimethyladamantane-1-carboxamide (2.8 g., 82%), which without purification was added to thionyl chloride (15 ml.) and dimethylformamide (0.5 ml.) After 18 hours, the excess of thionyl chloride was removed from the reaction mixture by distillation under vacuum, and the residue was left overnight in aqueous pyridine and ether. Hydrochloric acid (5N) was added to remove

pyridine, and the ethereal solution was separated, washed with dilute potassium carbonate solution, and dried. Removal of the ether, and sublimation ($75^{\circ}/0.2$ mm.) of the residue (2.5 g.) gave 1-cyano-3,5,7-trimethyladamantane (2.3 g.,89%), m.p. 80-81°.

(Found: C, 82.64; H, 10.44; N, 6.83. $C_{14}H_{21}N$ requires C, 82.70; H, 10.41; N, 6.89%).

1,3,5,7-Tetramethyladamantane

Perhydrophenanthrene (Koch-Light, 300 g., 1 mol.) was treated with anhydrous aluminium bromide (400 g., 0.5 mol.) and t-butyl bromide (20 ml.) for 3 days at 55°. The upper hydrocarbon layer was decanted, and, after adding to this the catalyst washings in petroleum ether, the petroleum solution was washed with dilute hydrochloric acid and water, dried and distilled leaving crude hydrocarbon (240 g.), from which 1,3,5,7-tetramethyladamantane (135 g., 45%), m.p. 64-66°. (lit.[4] m.p. 65-67°), was obtained by recrystallization from ether- methanol at -78°.

The oxidation of 1,3,5,7-tetramethyladamantane by chromic acid.[19]

Chromium trioxide ("AnalaR", 40.0 g., 2 mols.) was added in 8 g. portions over a period of 20 minutes to a solution of 1,3,5,7-tetramethyladamantane (40.0 g., 1 mol.) in 99% acetic acid (350 ml.) at 50-55°. The temperature was maintained at 55-60° as concentrated sulphuric acid (35 ml., 3 mols.) was added slowly. The reaction mixture was stirred for 100 minutes at 60°, then poured into iced water (1500 ml.), and the resulting white precipitate (45 g.) was collected, washed with water, and added to the residue (3 g.) isolated from ethereal extraction of the acidic

filtrate after partial neutralisation by careful addition of potassium hydroxide (250 g.). The crude product (48 g.) was heated under reflux in methanol (150 ml.) with potassium hydroxide (14 g.) for 4 hours, then was cooled and poured into water (400 ml.). The resulting white precipitate was collected, washed with water and sucked dry, and dissolved in acetone ("AnalaR", 160 ml.). Jones chromic acid reagent (6 ml.) was added dropwise until the solution became orange tinted, then the slight excess of reagent was destroyed with isopropyl alcohol (1 ml.). Addition of water (400 ml.) precipitated material (29.0 g.) which was separated by alumina chromatography into 1,3,5,7- tetramethyladamantane (4.4 g.) and 1,3,5,7-tetramethyladamantan-2-one (23.8 g., 55%), m.p. 109-110° after sublimation and recrystallisation from petroleum ether (lit.,[8] m.p. 108.5-109.5°). $\nu_{max.}$ 1716 (CO) and 1159, 1027, 988, 934 $cm.^{-1}$

(Found: C, 81.31; H, 10.49. Calc. for $C_{14}H_{22}O$: C, 81.50; H, 10.75%).

The alkaline filtrate from the methanolic hydrolysis above was acidified with 5N hydrochloric acid, and the solution was left at 0° for 6 days, before filtering to obtain 1,3,5,7-tetramethyladamantan-2,4-dione (5.5 g., 13%), which was collected, washed with water, dried and recrystallised, m.p. 127-128°, from petroleum ether. $\nu_{max.}$ (CO) 1707 and 1735

$cm.^{-1}$

(Found: C, 76.01; H, 9.20. $C_{14}H_{20}O_2$ requires C, 76.32; H, 9.15%).

Oxidation of 1,3,5,7-tetramethyladamantan-2-one by chromic acid .

Chromium trioxide ("AnalaR", 1.0 g., 2 mols.) and concentrated sulphuric acid (1.1 ml., 4 mols.) were added to a stirred solution of 1,3,5,7-tetramethyladamantan-2-one (1.00 g., 1 mol.) in glacial acetic acid (20 ml.) at 20°. The mixture was stirred for 5 hours, poured into water (100 ml.) and the precipitate (0.77 g.) was collected, washed, dried, and heated under reflux in methanol (20 ml.) with potassium hydroxide (2 g.) for 4 hours. After addition of water (100 ml.), the precipitate (0.29 g.) was collected, washed and dried. A mass spectrum of this material showed it was mainly 1,3,5,7-tetramethyladamantan-2-one (M.W.206). Two small peaks attributed to molecular ions occurred at $^{m}/_{e}$ = 220 and $^{m}/_{e}$ = 222. The material (0.18 g.) was chromatographed over alumina (18 g.) taking 100 ml. fractions eluted with 20% ether in petroleum ether, as follows: (1) 1,3,5,7-tetramethyladamantan-2-one (0.13 g.); (2) (0.01 g.); (3) eluted with 100% ether was 4-oxa-1,3,6,8-tetramethyl-homoadamantan-5-one , (0.03 g.), m.p. 138-139°; $\nu_{max.}$ (CO) 1724 $cm.^{-1}$ N.M.R. spectrum shows 2 $CH_3$, 9.07; 1 $CH_3$, 8.88;

1 $CH_3$, 8.69 $\tau$ .

(Found: C, 75.77; H, 10.01. $C_{14}H_{22}O_2$ requires C, 75.63; H, 9.97%).

The alkaline solution from the methanolic hydrolysis was acidified with concentrated hydrochloric acid and left standing overnight. The resulting crystalline precipitate (0.30 g.) was collected and dried. Its NMR and infrared spectra were identical to those of 1,3,5,7-tetramethyladamantan-2,4-dione. No other compounds were identified.

1,3,5,7-Tetramethyladamantan-2-ol

1,3,5,7-Tetramethyladamantan-2-one (10.0 g., 1 mol.) was added slowly to a solution of lithium aluminium hydride (1.8 g. 1 mol.) in ether (50 ml.). The mixture was heated under reflux for 1 hour before the excess of hydride was destroyed by careful addition of water. The reaction mixture was extracted with ether (200 ml.) after addition of dilute sulphuric acid. The ethereal solution was dried, and distilled leaving 1,3,5,7-tetramethyladamantan-2-ol (9.8 g., 97%), which was recrystallised, m.p. 86.5-87.5°, from petroleum ether.

(Found: C, 80.60; H, 11.35. $C_{14}H_{24}O$ requires C, 80.71; H, 11.61%).

2-Bromo-1,3,5,7-tetramethyladamantane

1,3,5,7-Tetramethyladamantan-2-ol (0.60 g., 1 mol.) was dissolved in bromine (2 ml., 9 mols.) and left standing for 3 days at room temperature. The reaction mixture was poured into dilute solution of sodium metabisulphite, and extracted with petroleum ether. The petroleum solution was dried and chromatographed over alumina (20 g.) which gave 2-bromo-1,3,5,7-tetramethyladamantane (0.46 g., 58%), b.p. 85-95°/0.2 mm., $n_D^{20}$ = 1.5169. N.M.R. spectrum shows 2 $CH_3$, 9.04; 1 $CH_3$ 9.14; 1 $CH_3$, 9.20; 1 CH, 6.15 $\tau$. GLC (Silicon oil at 150°) shows only one peak (99%, r.t. 34 mins.). Parent peaks in the mass spectrum occur at $m/_e$ = 272 and $m/_e$ = 270.

1,3,5,7-tetramethyladamantan-2-one (0.22 g., 37%) was eluted from the alumina with 100% ether.

1,3,5,7-Tetramethyladamantane-2-carboxylic acid

Concentrated sulphuric acid (50 ml., 24 mols.) was cautiously added to a solution of 1,3,5,7-tetramethyladamantan-2-ol (8.0 g., 1 mol.) in formic acid (98-100%, 20 ml., 12 mols.) at 0°. After 30 minutes, the reaction mixture was poured into water (400 ml.) and cooled to 0° before collecting 1,3,5,7-tetramethyladamantane-2-carboxylic acid (8.4 g., 92%), which was washed free from acid with water, and re-

crystallized, m.p. 185-186°, from methanol. Parent peak in the mass spectrum occurs at $^{m}/_{e}$ = 236. Loss of $CH_3$ or $H_2O$ follows, confirmed by metastable peaks at 207.0 and 201.4 respectively.

(Found: C, 76.20; H, 10.30. $C_{15}H_{24}O_2$ requires C, 76.22; H, 10.24%).

2-Cyano-1,3,5,7-tetramethyladamantane

1,3,5,7-Tetramethyladamantane-1-carboxylic acid (0.48 g., 1 mol.) was treated with thionyl chloride (5 ml., 30 mols.) and dimethylformamide (0.05 ml.). After 1 hour, the excess of thionyl chloride was removed by distillation under reduced pressure, and the residue in methylene chloride (20 ml.) was added dropwise to sodamide (from sodium, 2 g.) in liquid ammonia (100 ml.). The excess of ammonia was allowed to evaporate over 4 days, then dilute phosphoric acid was added, and extraction with ether gave material (0.39 g.), which was treated with thionyl chloride (8 ml.) and dimethylformamide (0.05 ml.). After 2 hours at room temperature, the excess of thionyl chloride was distilled leaving a residue which was extracted with petroleum ether. The petroleum solution was washed with dilute sodium bicarbonate solution, dried and distilled leaving material (0.32 g.) which was chromatographed over alumina giving 2-cyano-1,3,5,7-

tetramethyladamantane (0.17 g., 38%) m.p. 34-36°, after recrystallization from petroleum ether at -78°. The N.M.R. spectrum shows 2 $CH_3$, 8.97; 1 $CH_3$, 9.12; 1 $CH_3$, 9.17; 1 CH, 8.00 $\tau$. Parent peak in the mass spectrum occurs at $^m/_e$ = 217.

1,3,5,7-Tetramethyladamant-2-yl methyl ketone

1,3,5,7-Tetramethyladamantane-2-carboxylic acid (1.00 g., 1 mol.) was treated with thionyl chloride (10 ml., 30 mols.) and dimethylformamide (0.1 ml.). After 3 hours, the excess of thionyl chloride was removed, and the residue in dry ether (25 ml.), was added dropwise to a Grignard reagent at reflux, prepared from methyl iodide (5 ml., 20 mols) and magnesium (2 g., 20 mols) in dry ether (100 ml.). After 15 minutes, the reaction mixture was cooled to 0°, and added slowly to a saturated solution of ammonium chloride and extracted with ether. The ethereal solution was washed, dried and distilled leaving material (0.96 g.), which was chromatographed over alumina with ether-petroleum ether (1:5) to give 1,3,5,7-tetramethyladamant-2-yl methyl ketone (0.80 g., 80%), a solid, m.p. 46-49°, after distillation (b.p. 85-90°/0.04 mm.). $\nu_{max.}$ (CO) 1712 $cm.^{-1}$ Parent peak in the mass spectrum occurs at $^m/_e$ = 234. Loss of $CH_3$ ($^m/_e{}^*$ = 205.1) is followed by loss of CO ($^m/_e{}^*$ = 166.5).

The alumina was washed with ether giving a compound presumed to be 1,3,5,7-tetramethyladamant-2-yl dimethyl carbinol (0.13 g., 12%), a white solid which turned brown in air and could not be recrystallised. The infrared spectrum shows OH band at 3620 $cm.^{-1}$, but no carbonyl absorption. The NMR spectrum shows $4CH_3$, 9.17; $2\ CH_3$, 8.91 $\tau$.

2-Hydroxymethyl-1,3,5,7-tetramethyladamantane

A distilled ethereal solution of diazomethane (25 ml.) was added slowly to a solution of 1,3,5,7-tetramethyl-adamantane-2-carboxylic acid (5.00 g.) in dry ether (100 ml.) until the solution remained yellow. The ethereal solution was passed over alumina (5 g.) and distilled leaving methyl 1,3,5,7-tetramethyladamantane-2-carboxylate (5.05 g., 95%), $\nu_{max.}$(CO) 1735 $cm.^{-1}$. The NMR spectrum shows $CH_3$ singlets in 2:1:1 pattern at 9.24, 9.21 and 9.14 $\tau$, $OCH_3$ at 6.43 and 1 CH at 8.06 $\tau$.

Unpurified methyl 1,3,5,7-tetramethyladamantane-2-carboxylate (4.80 g., 1 mol.) in 1,4-dioxan (30 ml.) was added to a solution of lithium aluminium hydride (1.3 g., 2 mols) in dioxan (70 ml.) at reflux. After 40 minutes, water was added dropwise to destroy the excess of hydride, followed by more water (200 ml.). The precipitate was collected and, together with the filtrate, which had been

concentrated by distillation under reduced pressure to 40 ml. dissolved in dilute sulphuric acid and extracted with ether (150 ml.). The ethereal solution was washed, dried and distilled leaving 2-hydroxymethyl-1,3,5,7-tetramethyladamantane (4.25 g., 95%), m.p. 89.5 - 9[illegible]°, after recrystallisation from petroleum ether. The NMR spectrum shows $CH_3$ singlets at 9.09 and 9.22 $\tau$, and $CH_2$ doublet at 6.40 $\tau$ ($J_{vic}$ = 4 cps). Parent peak in the mass spectrum occurs at $^m/_e$ = 222. (Found: C, 80.19; H, 11.54. $C_{15}H_{26}O$ requires C, 81.02; H, 11.79%).

1,3,5,7-Tetramethyladamant-2-ylmethyl toluene-p-sulphonate

Toluene-p-sulphonyl chloride (2.5 g., 2 mols.) was added to a solution of 2-hydroxymethyl-1,3,5,7-tetramethyl-adamantane (0.75 g., 1 mol.) in dry pyridine (10 ml.). After 3 days at -8°, a few drops of water were added to hydrolyse the excess of toluene-p-sulphonyl chloride before the reaction mixture was poured into iced-water (50 ml.) and extracted with ether (50 ml.). The ethereal solution was washed, dried and distilled leaving 1,3,5,7-tetramethyl-adamant-2-ylmethyl toluene-p-sulphonate (1.21 g., 95%), m.p. 52-57°, which, after recrystallisation from petroleum ether at -78°, had m.p. 60-62 (with decomp$^n$.). No parent peak was found in the mass spectrum for the molecular ion $^m/_e$=376.

However, the base peak at $^{m}/_{e}$ = 221 was attributed to loss of the tosyl group, which gave rise to a peak at $^{m}/_{e}$ = 155. (Found: C, 68.84; H, 8.22; S, 8.20. $C_{22}H_{32}SO_3$ requires C, 70.17; H, 8.57; S, 8.52%).

The Solvolysis of 1,3,5,7-tetramethyladamant-2-ylmethyl toluene-p-sulphonate.[33]

A mixture of 65% (v/v) aqueous diglyme (30 ml.), 1,3,5,7-tetramethyladamant-2-ylmethyl toluene-p-sulphonate (0.75 g., 1 mol.), and anhydrous sodium bicarbonate (0.71 g., 4 mols.) was heated under reflux for 75 hours. The reaction mixture was poured into water (300 ml.) and extracted with petroleum ether (250 ml.). The petroleum solution was dried and filtered through alumina (10 g.) to remove diglyme. Removal of the solvent gave crude 2-methylene-1,3,5,7-tetramethyladamantane (0.26 g., 63%), identified by its infrared and NMR spectra (see following reaction). No other compounds were isolated or detected.

2-Methylene-1,3,5,7-tetramethyladamantane

A solution of 1,3,5,7-tetramethyladamantan-2-one (5.5.g., 1 mol.) in dry ether (40 ml.) was added to a Grignard reagent prepared from magnesium (8.0 g., 13 mols.) and methyl iodide (20 ml., 12 mols.) in dry ether (60 ml.). The reaction mixture was heated under reflux for 3 hours, cooled and

poured into a saturated solution of ammonium chloride (500 ml.), and extracted with ether (200 ml.). The ethereal solution was dried and distilled leaving 2-hydroxy-1,2,3,5,7-pentamethyladamantane (5.8 g., 97%). The NMR spectrum shows 4 $CH_3$, 9.20; 1 $CH_3$, 8.90 $\tau$. Unpurified 2-hydroxy-1,2,3,5,7-pentamethyladamantane (5.6 g.) was treated with phosphoric acid (85%, 150 ml.) for 6 hours at 80-90°. The reaction mixture was diluted with water (400 ml.), and extracted with petroleum ether (300 ml.). The petroleum solution was dried, filtered through alumina (10 g.), and distilled leaving 2-methylene-1,3,5,7-tetramethyladamantane (4.9 g., 95%), m.p. 33-34°, after crystallisation from petroleum ether at -78° (lit.,[8] m.p. 32-33°). The NMR spectrum shows $2CH_3$, 9.18; 2 $CH_3$, 9.02; 5 $CH_2$, 8.82; 2 CH (vinyl), 5.49 $\tau$.

(Found: C, 87.89; H, 11.61. Calc. for $C_{15}H_{24}$: C, 88.16; H, 11.84%).

1,3,5,7-Tetramethyladamantane-2-aldehyde.

A mixture of 90% hydrogen peroxide (1.7 ml., 2 mols.) trifluoroacetic anhydride (10 ml., 3 mols.) and methylene chloride (10 ml.) at 0° was added dropwise to a stirred solution of 2-methylene-1,3,5,7-tetramethyladamantane (4.7 g., 1 mol.) in methylene chloride (25 ml.) with anhydrous sodium carbonate (18 g.) in suspension providing a buffer for tri-

fluoroacetic acid generated during the reaction. The reaction mixture was stirred for 15 minutes at 0°, heated under reflux for 15 minutes, cooled and filtered. The filtrate was distilled leaving crude 2-methylene-1,3,5,7-tetramethyladamantane oxide (4.5 g.) (NMR spectrum shows $CH_2$-O singlet at 7.47 $\tau$ ), which was treated with boron trifluoride etherate (6 ml.) in benzene (20 ml.) at -8° for 18 hours. Dilute sodium carbonate solution was added to the reaction mixture, before extraction with ether (100 ml.). The ethereal solution was dried and distilled leaving material (4.4 g.) which was chromatographed over alumina (150 g.) to give 1,3,5,7-tetramethyladamantane-2-aldehyde (2.60 g., 51%), m.p. 41-44°, eluted with 50% ether in petroleum ether. $\nu_{max.}$ (CO) 1730 $cm.^{-1}$ The NMR spectrum shows 1 $CH_3$, 9.18; 2 $CH_3$, 9.15; 1 $CH_3$, 9.10; 1 CH (aldehydic) 0.12 $\tau$ ($J_{vic}$ = 5.1 cps.) Parent peak in the mass spectrum occurs at $^{m}/e$ = 220.

1,3,5,7-Tetramethyladamantane-2-(O-methyl)aldoxime

A mixture of 1,3,5,7-tetramethyladamantane-2-aldehyde (0.30 g., 1 mol.), methoxylamine hydrochloride (0.46 g., 4 mols), pyridine (0.8 ml.), water (0.2 ml.) and ethanol (3 ml.) was heated under reflux for 5 hours. Water was added to the reaction mixture, before extraction with

petroleum ether (40 ml.). The petroleum solution was washed, dried and distilled leaving 1,3,5,7-tetramethyladamantane-2-(O-methyl)aldoxime (0.32 g., 94%), m.p.51-53°. (Found: C, 77.29; H, 11.07; N, 5.24. $C_{16}H_{27}NO$ requires C, 77.06; H, 10.91; N, 5.62%).

The action of diazomethane on 1,3,5,7-tetramethyladamantan-2-one

A distilled ethereal solution of diazomethane (approx. 2.0 M, 5 ml., 2.5 mols.) was added dropwise to a stirred solution of 1,3,5,7-tetramethyladamantan-2-one (0.8 g., 1 mol.) and anhydrous aluminium chloride (0.2 g.) in dry ether (10 ml.). The reaction mixture was diluted with ether and washed with dilute hydrochloric acid. The ethereal solution was dried and distilled leaving a white solid (0.9 g.) which contained three major components (GLC, silicon oil at 175°), whose retention times were A, 8 mins.; B, 15 mins.; C, 22.5 mins. The material was chromatographed over alumina (40 g.), taking 100 ml. fractions, as follows:

| Eluting solvent | Fractions | Wt., g. | Comments | | |
|---|---|---|---|---|---|
| 100% petroleum ether | 1 | 0.25[a] | A:96% | B: 0% | C: 2% |
| " | 2 | 0.18 | A:50 | B:14 | C:34 |
| " | 3 | 0.09[b] | A:24 | B:39 | C:36 |
| " | 4 | 0.07 | A: 9 | B:76 | C:14 |
| " | 5 | 0.06 | A: 0 | B:93 | C: 7 |
| 10% ether in petroleum ether | 6 | 0.16[c] | A: 0 | B:95 | C: 2 |
| " | 7 | 0.00 | | | |
| 100% ether | 8 | 0.00 | | | |

a. Fraction 1 contained 96% A, which was identified as 1,3,5,7-tetramethyladamantan-2-one by its infrared spectrum.

b. Fraction 3 contained 36% C, a bishomoderivative identified as 1,3,7,9-tetramethyltricyclo$[5,3,1,1^{7,9}]$dodecan-5-one. Peaks in the mass spectrum occur for the three expected molecular ions at $^{m}/e$ = 206, 220 and 234. After deuterium exchange, peaks were found at $^{m}/e$ = 206, 222 and 234, 235, 236.

c. Fraction 6 contained 95% B, <u>1,3,6,8-tetramethylhomoadamantan-4-one</u>, m.p. 36-37° after sublimation. $\nu_{max.}$ (CO) 1696 $cm.^{-1}$ The NMR spectrum (7% w/v in $CCl_4$) shows a singlet $CH_2$ at 7.70 $\tau$ corresponding to the methylene

group at C(5). Parent peak in the mass spectrum occurs at $m/e$ = 220. Initial loss of CHO or $CH_3CO$ follows, confirmed by metastable peaks at 166.1 and 142.6, respectively. After deuterium exchange, (sealed tube with potassium deuteroxide in aqueous dioxan at 100° for 12 hours), the parent peak occurs at $m/e$ = 222. Similarly, initial loss of CHO and $CH_3CO$ follows, confirmed by metastable peaks at 168.0 and 144.4.

Reaction between methyl magnesium iodide and 1,3,5,7-tetramethyladamantan-2,4-dione

A solution of 1,3,5,7-tetramethyladamantan-2,4-dione (2.0 g., 1 mol.) in dry ether (40 ml.) was added slowly to a Grignard reagent prepared from methyl iodide (8 ml., 14 mols) and magnesium (3 g., 14 mols.) in ether (100 ml.). The reaction mixture was heated under reflux for 4½ hours, cooled and poured into a saturated solution of ammonium chloride, then extracted with more ether (50 ml.). The ethereal solution was washed, dried with anhydrous potassium carbonate and distilled leaving material (2.25 g.), which was chromatographed over 5% deactivated alumina (100 g.) taking 100 ml. fractions as follows:

| Eluting solvent | Fractions | Wt., g. | Comments |
|---|---|---|---|
| 100% petroleum ether | 1-3 | - | |
| 10% ether in petroleum ether | 4-6 | - | |
| 25% ether in petroleum ether | 7-12 | 0.89[a] | |
| 50% ether in petroleum ether | 13-16 | 0.15 | An unidentified hydroxy compound |
| 60% ether in petroleum ether | 17-22 | 0.70[b] | |
| 100% ether | 23-26 | 0.18[c] | Syn-cis-2,4-dihydroxy-1,2,3,4,5,7-hexamethyladamantane |

a. A viscous liquid, thought to be (±)-trans-2,4-dihydroxy-1,2,3,4,5,7-hexamethyladamantane. The NMR spectrum shows $CH_3$ singlets at 8.75 and 8.85 $\tau$, and 1 $CH_3$, 9.15; 2 $CH_3$, 9.21; 1 $CH_3$, 9.25. No intramolecular hydrogen bonding is seen in the infrared spectrum (1 cm. cells).

b. Recrystallisation from petroleum ether gave <u>syn-cis-2,4-dihydroxy-1,2,3,4,5,7-hexamethyladamantane</u> (0.42 g.), m.p. 198-199.5°. Infrared spectrum in carbon tetrachloride (1 cm. cells, $\Delta\nu$ = 144 $cm.^{-1}$ between OH ('free') 3620 and OH (int.) 3476 $cm.^{-1}$ The NMR spectrum (5% w/v in $CHCl_3$) shows 1 $CH_3$, 9.22; 2 $CH_3$, 9.14; 1 $CH_3$, 9.00; 2 $CH_3$, 8.83 $\tau$. Parent peak in the mass spectrum occurs at $^{m}/e$ = 234, which corresponds to the (M-18) molecular

ion.

(Found: C, 76.13; H, 11.27. $C_{16}H_{28}O_2$ requires C, 76.14; H, 11.18%).

c. M.p. 199-200°; total yield of diaxial alcohol 27%.

Reaction between phenyl lithium and 1,3,5,7-tetramethyl-adamantan-2,4-dione.

An ethereal solution (approx. 0.8 M) of phenyl lithium (20 ml., 3 mols.) was added to a solution of 1,3,5,7-tetramethyladamantan-2,4-dione (1.10 g., 1 mol.) in dry ether (25 ml.) in a nitrogen atmosphere. After standing overnight, the reaction mixture was poured into saturated ammonium chloride solution and extracted with ether. The ethereal solution was washed, dried with anhydrous potassium carbonate, and distilled leaving a viscous residue (2.0 g.) which was chromatographed over alumina (30 g.) taking 100 ml. fractions as follows:

| Eluting solvent | Fractions | Wt., g. | Comments |
|---|---|---|---|
| 100% petroleum ether | 1 | 0.25 | Mainly biphenyl |
| 50% ether in petroleum ether | 2-3 | 1.40[a] | |
| 100% ether | 4-6 | 0.11 | Mainly phenol |

a. Rechromatographed over alumina (42 g.) into two major components: fractions (0.75 g.) eluted with 20% ether in

petroleum ether, containing only hydroxylic functionality, and fractions (0.60 g.) eluted with 40% ether in petroleum ether, containing both ketonic and hydroxylic functionality from infrared spectral evidence.

Syn-cis-2,4-dihydroxy-2,4-diphenyl-1,3,5,7-tetramethyl adamantane (0.39 g., 21%), m.p. 163-164°, was recrystallised from the former in petroleum ether. Infrared spectrum in carbon tetrachloride (1 cm. cells), $\Delta\nu$ = 172 cm.$^{-1}$ between OH ('free') 3608 and OH (int.) 3436 cm.$^{-1}$ The NMR spectrum (10% w/v in $CCl_4$) shows 10 CH (aromatic) between 2.0 and 2.9, 2 OH at 5.11, and 1:2:1 pattern of $CH_3$ singlets at 8.92, 9.29 and 9.60 $\tau$.

(Found: C, 82.35; H, 8.75. $C_{26}H_{32}O_2$ requires C, 82.93; H, 8.57%).

4-Axial-hydroxy-4-phenyl-1,3,5,7-tetramethyladamantan-2-one (0.31 g., 23%), m.p. 138-138.5°, was recrystallised from the latter in petroleum ether. $\nu_{max.}$ (CO) 1710 cm.$^{-1}$ The NMR spectrum shows 5 CH (aromatic) between 2.2 and 2.9, and 1:1:1:1 pattern of $CH_3$ singlets at 8.97, 9.03, 9.35 and 9.44 $\tau$.

(Found: C, 80.68; H, 8.86. $C_{20}H_{26}O_2$ requires C, 80.49; H, 8.78%).

Syn-cis-2,4-dihydroxy-2-phenyl-1,3,5,7-tetramethyladamantane

Lithium aluminium hydride (0.2 g.) was added to a solution of 4-axial-hydroxy-4-phenyl-1,3,5,7-tetramethyladamantan-2-one

(0.10 g.) in dry ether (10 ml.). The mixture was heated under reflux for 2 hours, then poured into dilute sulphuric acid and extracted with ether. The ethereal solution was dried with anhydrous potassium carbonate and distilled leaving a white solid residue (0.10 g.) from which syn-cis-2,4-dihydroxy-2-phenyl-1,3,5,7-tetramethyladamantane (80 mg., 80%), m.p. 153-154°, was recrystallised from petroleum ether. Infrared spectrum ($CCl_4$, 1 cm. cells), $\Delta\nu$ = 160 cm.$^{-1}$ between OH ('free') 3614 and OH (int.) 3454 cm.$^{-1}$

(Found: 79.73; H, 9.43. $C_{20}H_{28}O_2$ requires C, 79.95; H, 9.39%).

Reduction and carbonylation of 1,3,5,7-tetramethyladamantan-2,4-dione.

Lithium aluminium hydride (0.7 g., 3 mols.) was added to a solution of 1,3,5,7-tetramethyladamantan-2,4-dione (1.46 g., 1 mol.) in dry ether (25 ml.) and the mixture was heated under reflux for 20 minutes. The excess of hydride was decomposed by dropwise addition of water, before work up with dilute sulphuric acid and extraction with ether (100 ml.). The ethereal solution was washed, dried and distilled leaving material (1.40 g.), which showed no carbonyl bands in the infrared spectrum. This product, presumably a mixture of isomeric 1,3,-diols, was treated with formic acid (98-100%, 7 ml.) and concentrated sulphuric acid (20 ml.) for 3 days

at room temperature. The reaction mixture was poured into water (100 ml.) and extracted with ether (100 ml.) The ethereal solution was washed with dilute sodium carbonate solution, and water, then dried and distilled giving the lactone of (±)-syn-cis-4-hydroxy-1,3,5,7-tetramethyladamantane-2-carboxylic acid (1.00 g., 65%), m.p. 128-129°, after sublimation and recrystallisation from petroleum ether. $\nu_{max.}$(CO) 1790 cm.$^{-1}$. The NMR spectrum shows 1 CH, 6.38; 1 CH, 8.32; 4 $CH_3$ singlets at 8.96, 9.02, 9.05, 9.11 $\tau$ . Parent peak in the mass spectrum occurs at $^{m}/e$ = 234. Initial loss of $CO_2$ occurs ($^{m}/e^{*}$ = 156.7), followed by loss of $CH_3$ ($^{m}/e^{*}$ = 161.2). (Found: C, 76.80; H, 9.59. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46%).

The alkaline washings were acidified with hydrochloric acid and extracted with ether (50 ml.). The ethereal solution was dried and distilled leaving a solid residue (0.30g.) presumably a mixture of dicarboxylic acids, which was heated under reflux in acetic anhydride (25 ml.) with anhydrous sodium acetate (0.3 g.) for 16 hours. The acetic anhydride was removed by distillation in vacuum, and the residue was sublimed to give a sticky solid (0.2 g.), from which 1,3,5,7-tetramethyladamantane-2,4-dicarboxylic anhydride (25 mg., 1.5%), m.p. 180-181°, was recovered by washing with ether. $\nu$ max. (CO) 1760 and 1807 cm.$^{-1}$. The NMR

spectrum shows a narrow unresolved multiplet at 7.89, and 1:2:1 pattern of $CH_3$ singlets at 8.97, 9.02 and 9.12 $\tau$. Parent peak in the mass spectrum occurs at $^m/_e$ = 218, which corresponds to the (M-44) molecular ion. Loss of CO ($^m/_e^*$ = 166.0) is followed by loss of $CH_3$ ($^m/_e^*$ = 161.2).

Oxidation of 2-acetoxy-1,3,5,7-tetramethyladamantane

Acetyl chloride (2 ml., 3.5 mols.) was added dropwise to a solution of 1,3,5,7-tetramethyladamantan-2-ol (2.0 g., 1 mol.) in pyridine (12 ml.). After standing for 30 minutes, the reaction mixture was poured into water, and extracted with ether (100 ml.). The ethereal solution was washed with dilute hydrochloric acid, dried and distilled leaving material (2.3 g.), which was chromatographed over alumina (100 g.) in ether-petroleum ether (2:3) giving 2-acetoxy-1,3,5,7-tetramethyladamantane (1.80 g., 76%), m.p. 45-47°: $\nu_{max.}$ (CO) 1735 $cm.^{-1}$ The NMR spectrum shows 1 CH, 5.54; acetoxyl $CH_3$, 8.00; 1 $CH_3$, 9.16; 1 $CH_3$, 9.18; 2 $CH_3$, 9.29 $\tau$.
(Found: C,76.81; H, 10.55. $C_{16}H_{26}O_2$ requires C, 76.75; H, 10.47%).

A solution of concentrated sulphuric acid (1.0 ml., 2.7 mols.) in glacial acetic acid (5 ml.) was added slowly to a stirred mixture of 2-acetoxy 1,3,5,7-tetramethyladamantane (1.70 g., 1 mol.), chromium trioxide (1.1 g., 1.6 mols.)

and glacial acetic acid (25 ml.). After 1 hour at 45-50°, a dense green precipitate of chromium sulphate had formed, but the reaction mixture was left standing overnight at room temperature, then poured into water (200 ml.) and extracted thoroughly with ether (200 ml.). The ethereal solution was washed with dilute sodium carbonate solution, dried and distilled leaving a liquid residue (1.60 g.), which was chromatographed over alumina (150 g.), taking 100 ml. fractions, as follows:

| Eluting solvent | Fractions | Wt.,g. | Comments |
|---|---|---|---|
| 10% ether in petroleum ether | 1-2 | - | |
| " | 3-4 | 0.65 | Mainly 1,3,5,7-tetramethyladamantan-2-one |
| " | 5-7 | 0.39 | Mainly 2-acetoxy-1,3,5,7-tetramethyladamantane |
| " | 8-12 | - | |
| 20% ether in petroleum ether | 13-14 | 0.12[a] | A mixture of isomeric acetoxy monoketones |
| " | 15-16 | 0.11[b] | |
| 50% ether in petroleum ether | 17-21 | 0.17[b] | Other acetoxylated material |
| Total material recovered | | 1.44 g. | |

a. Infrared spectrum shows two carbonyl bands at 1720 (ketone) and 1742 cm.$^{-1}$ (acetoxy). The NMR spectrum shows two, possibly three, acetoxyl methyl singlets. Fractions

13-14 (90 mg.) were heated under reflux in methanol (5 ml.) with potassium hydroxide (0.3 g.) for 40 minutes, then added to water and extracted with ether. Removal of the solvent gave a solid (65 mg.,)which was treated with Jones reagent 0.1 ml.) in acetone (2 ml.), and work up gave 1,3,5,7-tetramethyladamantan-2,6-dione (60 mg., 4%), m.p. 143-145°. $\nu_{max.}$ 1718 (CO) and 1381, 1150, 1017, 931, and 879 $cm.^{-1}$ The NMR spectrum shows two singlets 4 $CH_3$, 9.01; 4 $CH_2$, 8.14 $\tau$. (Found: C, 75.32; H, 8.92. $C_{14}H_{20}O_2$ requires C, 76.32; H, 9.15%).

b. Fractions 15-21 were combined, hydrolysed and oxidised as described above, leaving material (175 mg.), which after further methanolic alkaline hydrolysis to remove the isomeric $\beta$-diketone, gave more 1,3,5,7-tetramethyladamantan-2,6-dione (60 mg., 4%), m.p. 145-146°, after recrystallisation from petroleum ether and sublimation.

4-Acetoxy-1,3,5,7-tetramethyladamantan-2-one

A mixture of 1,3,5,7-tetramethyladamantan-2,4-dione (1.10 g., 1 mol.), lithium aluminium hydride (0.4 g., 2 mols.), and ether (50 ml.) was heated under reflux for 1 hour. Work up with dilute sulphuric acid and ether gave material (1.10g.), presumably a mixture of isomeric 1,3-diols, which showed no carbonyl bands in the infrared spectrum. The diol mixture

(1.10 g., 1 mol.) was dissolved in acetone (10 ml.) and Jones reagent (1.2 ml., 0.67 mol.) was added. Work up with water and ether gave a semi-crystalline solid (1.02 g.), which was left overnight in acetic anhydride (10 ml.) and concentrated sulphuric acid (1 ml.). Further work up with ice and ether left a liquid (1.2 g.), which was chromatographed over alumina (100 g.), taking 200 ml. fractions as follows:

| Eluting solvent | Fractions | Wt.,g. | Comments |
|---|---|---|---|
| 10% ether in petroleum ether | 1-2 | 0.05 | |
| 20% ether in petroleum ether | 3-4 | 0.31 | Mainly 4-axial-acetoxy-1,3,5,7-tetramethyl-adamantan-2-one |
| " | 5-7 | 0.30 | Mainly 4-equatorial-acetoxy-1,3,5,7-tetra-methyladamantan-2-one |
| 50% ether in petroleum ether | 8-10 | 0.11 | |

a. Recrystallisation of fraction 4 from petroleum ether gave 4-axial-acetoxy-1,3,5,7-tetramethyladamantan-2-one (0.22 g., 17%), m.p. 110.5-111.5°. The NMR spectrum shows one acetoxyl $CH_3$, 7.99; 1 CH, 5.14; 2 $CH_3$, 9.07; 1 $CH_3$, 9.17; 1 $CH_3$, 9.20 $\tau$ . Parent peak in the mass spectrum occurs at $^m/e$ = 264. Loss of $CH_2CO$ or $CH_3CO_2H$ follows, confirmed by metastable peaks at 187.4 and 157.8.

(Found: C, 72.97; ..., 8.96. $C_{16}H_{24}O_3$ requires C, 72.69; H, 9.15%).

b. Recrystallisation of fraction 6 from petroleum ether gave 4-equatorial-acetoxy-1,3,5,7-tetramethyladamantan-2-one (0.14 g., 11%), m.p. 76-78°. The NMR spectrum shows one acetoxyl $CH_3$, 7.95; 1 CH, 5.45; 2 $CH_3$, 9.08; 1 $CH_3$, 9.17; 1 $CH_3$, 9.18 $\tau$ . Parent peak in the mass spectrum occurs at $^m/_e$ = 264, followed by initial loss of $CH_3CO$ or $CH_3CO_2H$.

(Found: C, 71.39; H, 8.97. $C_{16}H_{24}O_3$ requires C, 72.69; H, 9.15%).

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## ABSTRACT

Adamantane and related ring systems

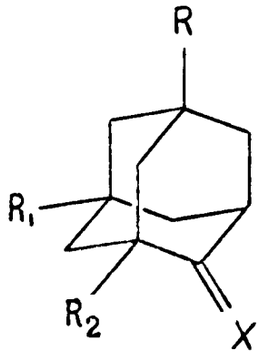
The thesis is an account of

(a) the synthesis of derivatives of adamantane and an exploratory investigation of the chemistry of some of these compounds,

(b) their use as models for correlating structure and nuclear magnetic resonance (NMR) chemical shifts and for determining values of coupling constants needed when estimating conformational equilibria in certain acylic compounds, and

(c) their use in determining the magnitude and sign of the electric dipole moment of a C-methyl group relative to a C-H group in a saturated system.

Section (a) was described in four parts. Firstly, the oxidation of adamantane and its bridgehead methyl derivatives was studied. Adamantane (1), 1,3-dimethyl-(2), and 1,3,5-trimethyladamantane (3) were oxidised with concentrated sulphuric acid.[1] Adamantane gave 2-adamantanone (4), but no products were isolated from (2) and (3). The monohydroxy bridgehead derivatives of (2) and (3), however, gave the 6-oxo- and the 4-oxo-derivatives,

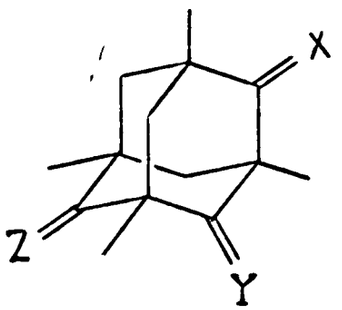



(1) $R=R_1=R_2=H$; $X=H_2$.

(2) $R=R_1=Me$; $R_2=H$; $X=H_2$.

(3) $R=R_1=R_2=Me$; $X=H_2$.

(4) $R=R_1=R_2=H$; $X=O$.




(5) $X=H_2$; $Y=H_2$; $Z=H_2$.

(6) X=H,OAc; $Y=H_2$; $Z=H_2$.

(7) X=O; $Y=H_2$; $Z=H_2$.

(8) X=O; Y=O; $Z=H_2$.

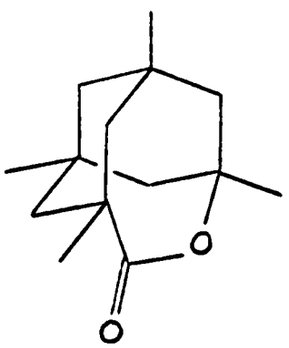
(9) X=O; $Y=H_2$; Z=O.

(11) X=O; Y=H,OAc(ax.); $Z=H_2$.

(12) X=O; Y=H,OAc(eq.); $Z=H_2$.

(13) X=O; $Y=H_2$; Z=H,OAc.

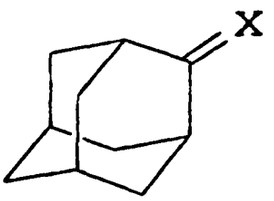
(10)



respectively, after treatment with sulphuric acid. Ozonolysis[2] of (2) gave the 2-oxo-, 4-oxo-, and 5-hydroxy derivatives, and of (3) gave the 4-oxo and 7-hydroxy derivatives. Aerial oxidation[3] gave the highest yields of monoketones, and the 2-oxo-, 4-oxo-, 6-oxo- (total 11%), and 5-hydroxy derivatives of (2), and the 2-oxo-, 4-oxo- (total 10%), and 7-hydroxy derivatives of (3) were obtained. Separation of these ketones was achieved by alumina chromatography, and their structures were established from studies of their infrared, mass and NMR spectra. The oxidation of (3) with chromic acid produced mainly the 7-hydroxy derivative and its acetate.

1,3,5,7-Tetramethyladamantane (5) gave the 2-acetoxy-(6), 2-oxo-(7), and 2,4-dioxo-(8) (but not the 2,6-dioxo-(9)). derivatives with chromic acid.[4] Oxidation of the ketone (7) with chromic acid gave the 2,4-dione (8) and 4-oxa-1,3,6,8-tetramethylhomoadamantan-5-one (10), whereas the acetate (6) gave material, which was hydrolysed and oxidised to give the 2,6-dione (9) among other products. The ketone (7) and the three possible monoacetoxyketones, (11) (12) and (13), were identified in the product of oxidation of the acetate (6).

Secondly, some derivatives of adamantane (1) were prepared to provide compounds suitable for the studies described in sections (b) and (c). Adamantanone (4) was

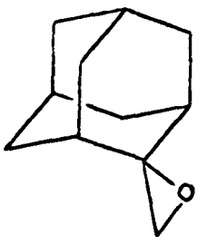


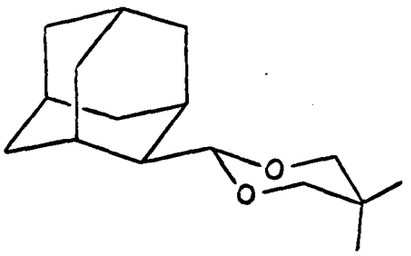

(14) X=$CH_2$.

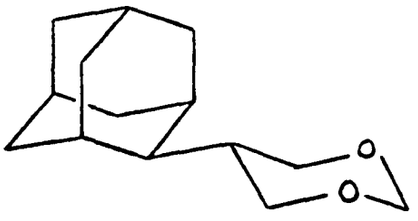
(16) X=H,CHO.

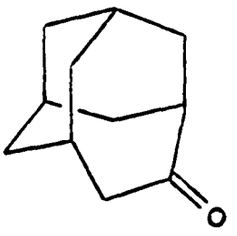
(18) X=H,$CH(COOEt)_2$.

(19) X=H,$CH(CH_2OH)_2$.

(15) 

(17) 

(20) 

(21) 

converted via 2-methyleneadamantane (14) into the epoxide (15), and thence into the 2-aldehyde (16). A previously described preparation[5] of (14) gave mainly a dimer. The 1,3-dioxane (17) was made from the 2-aldehyde [see section (b)]. Reduction of the ketone (4) gave 2-adamantanol, which was converted via the tosylate into diethyl 2-adamantylmalonate (18), which was reduced to the propan-1,3-diol (19). The 1,3-dioxane (20) was prepared from the diol (19) with paraformaldehyde. Treatment of the ketone (4) in methanol with an excess of diazomethane gave almost exclusively 4-homoadamantanone (21) with traces of higher homologues, which were formed in much larger amounts when the reaction was catalysed by aluminium chloride in ether. The 1,3-dibromide of (1) was converted into the 1,3-dicarboxylic acid, which was used to make the 1,3-dinitrile [see section (c)].

Thirdly, some bridgehead derivatives of (3) were prepared providing further examples[6] of the correlation between substituents and changes in chemical shift. The hydrocarbon (3) was used for the synthesis of the 7-bromide, the 7-acetate, the 7-carboxylic acid and its methyl ester, and the 7-nitrile [see section (c)].

Fourthly, exploratory studies of the chemistry of the 2-oxo-(7) and 2,4-dioxo-(8) derivatives of (5) were made.

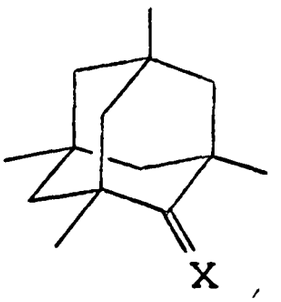
(22) X=H,OH.

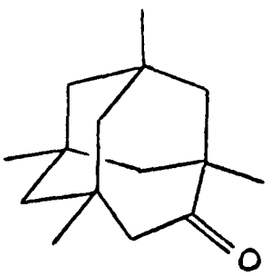
(23) X=H,COOMe.

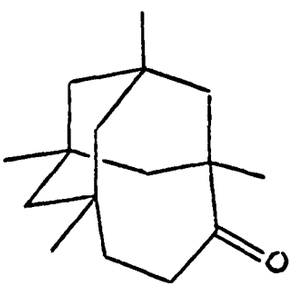
(24) X=$CH_2$.

(25) X=H,CHO.

(26) X=$CH_2OH$,H.

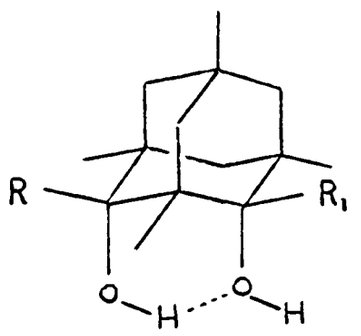



(27) 


(28) 

The monoketone (7) was reduced to the alcohol (22), which was converted into the 2-acetate (6), the 2-bromide, the 2-carboxylic acid and its methyl ester (23), the 2-methyl ketone and the 2-nitrile. The ketone (7) was converted via the 2-methylene derivative (24) into the epoxide, and thence to the 2-aldehyde (25), from which the O-methyl oxime was made [see section (b)]. The methyl ester (23) was reduced to the primary alcohol (26), and the solvolysis of its tosylate gave the olefin (24), but not homoadamantanoid derivatives. The ketone (7) was treated with diazomethane, and the product mixture was analysed by gas liquid chromatography. 1,3,6,8-Tetramethylhomoadamantan-4-one (27) was isolated and a bishomologue (28) was detected.

The 2,4-dione (8) was treated with (i) methyl magnesium iodide giving syn-cis-2,4-dihydroxy-1,2,3,4,5,7-hexamethyladamantane (29), (ii) phenyl lithium giving syn-cis-2,4-dihydroxy-2,4-diphenyl-1,3,5,7-tetramethyladamantane (30) and 4-axial-hydroxy-4-phenyl-1,3,5,7-tetramethyladamantan-2-one (31), and (iii) lithium aluminium hydride giving a mixture of isomeric diols, which was carbonylated with formic acid and converted into the lactone (32), and into an acid or acids which by treatment with acetic anhydride gave the cyclic anhydride (33) in low yield. The hydroxy-ketone (31)

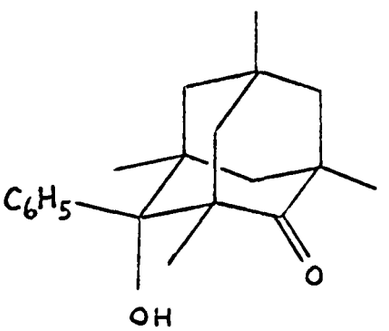



(29) $R=R_1=Me$.

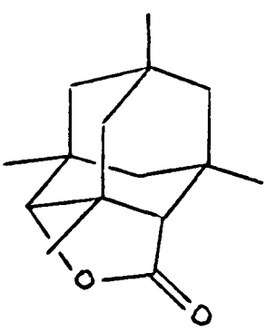
(30) $R=R_1=C_6H_5$.

(34) $R=C_6H_5$; $R_1=H$.

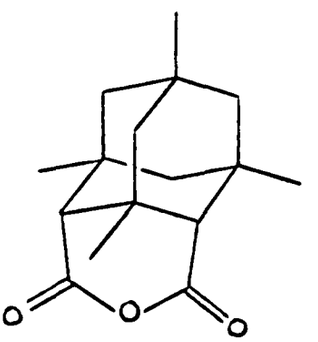
(31)




(32)




(33)



was reduced to syn-cis-2,4-dihydroxy-2-phenyl-1,3,5,7-tetramethyladamantane (34), which had a most unusual NMR spectrum, which included one hydroxyl singlet resonance, and another hydroxyl signal coupled to the secondary alcohol proton in a well resolved AB quartet. Very large intramolecular hydrogen-bonded spectral shifts were observed for the diols, (29), (30) and (34), the value for (30) being 172 $cm.^{-1}$

Section (b) was described in 3 parts. Firstly, derivatives of adamantane were used as models for correlating structure and NMR chemical shifts. NMR spectra were run on hydrocarbons (2) (3) and (5), and on all their monoketone derivatives, in carbon tetrachloride and tetramethylsilane as solvent. Assignments of protons were mostly straightforward, and in other cases, solvent shifts in benzene were used. The effects on the chemical shifts of other protons in the molecule of changing a methylene group to a carbonyl group were tabulated and compared with the chemical shift differences calculated due to magnetic anisotropy using a modified form of McConnell's equation.[7] The values of carbonyl anisotropies used had been derived from a series of steroids and the calculated shifts were found to be much smaller than those measured experimentally for the adamantanes,

which was explained by the flattened geometry of the steroids leading to overestimates in the 'geometric factor', and consequently underestimates in the anisotropies derived. More importantly, however, it was found the effect on the chemical shift of a C-H bond caused by changing a C-H bond or bonds by other groups (e.g. carbonyl or bromide) at a point distant from the first C-H bond is also dependent on the environment of that C-H bond.

Secondly, NMR chemical shifts were used to determine the conformation of the carbonyl group in 1,3,5,7-tetramethyl-adamantane-2-carboxylic acid and related compounds. In all cases except the 2-aldehyde (25), it was found that the carbonyl group pointed into the ring. The reverse conformation was predominant for the aldehyde (25).

Thirdly, variable temperature studies of vicinal coupling constants and chemical shifts were carried out for some 1,3-dioxanes, 2-substituted aldehydes and O-methyl oximes. The work has not been concluded, but preliminary results have indicated that better values of $J_{trans}$ can be estimated than has been generally possible with the systems studied[8] previously, which should lead to more confident predictions about conformation equilibria in such systems.

Section (c) described the use of adamantane derivatives in determining the magnitude and sign of the electric dipole movement of a C-$CH_3$ group relative to a C-H group in a saturated system. Previous studies[9], which were not unambiguous, had suggested that a methyl group is electron-withdrawing relative to hydrogen when attached to ($sp^3$) carbon. The dipole moments of two pairs of bromides, nitriles, and monoketones were measured. The structure of the molecules in each pair was identical except for the substitution in one at bridgehead positions of two or three methyl groups. The moments induced in the methyl groups by the polar group or groups were taken into account giving a 'corrected' dipole moment for the methyl substituted compounds. A comparison between the 'corrected' moments and the dipole moments of the non-methyl analogues led directly to values of the dipole moment of a methyl group relative to hydrogen in a saturated system. The average value obtained was $0.082 \pm 0.02$ D, the negative end of the dipole being on the methyl group.

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