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REARRANGEMENTS IN THE ADAMANTANE SERIES

HYDRIDE SHIFTS OF THE 2-(1-ADAMANTYL)-2-PROPYL CATION[1]

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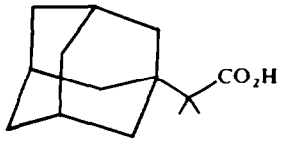
Abstract—When subjected to ordinary Koch–Haaf carboxylation conditions the tertiary alcohol, 2-(1-adamantyl)-2-propanol (**4**) yields only the rearranged carboxylic acid, 3-isopropyl-1-adamantane carboxylic acid (**5**). Mechanistic evidence is presented which indicates that the rearrangement proceeds *via* intermolecular hydride shifts. A variety of synthetic approaches to the unrearranged 2-(1-adamantyl)-2-methylpropionic acid (**1**) are described, and the successful preparation of **1** by the Koch-Haaf reaction of **4** under high dilution conditions is reported. The latter experiment confirms the role of *intermolecular* hydride shifts in the rearrangement of the 2-(1-adamantyl)-2-propyl cation (**26**) to the 3-isopropyl-1-adamantyl cation (**30**).

INTRODUCTION

SEVERAL years ago work was begun independently at Aachen and at Princeton on the synthesis of 1-t-butyladamantane (**2**). Although **2** was ultimately obtained by a different route,[4] much of the initial effort in our laboratories was directed toward the synthesis of 2-(1-adamantyl)-2-methylpropionic acid (**1**). As the latter material contains the entire carbon skeleton, it was hoped that reduction of the carboxyl group



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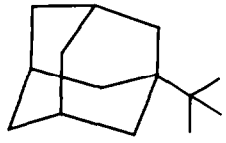


2

would lead to t-butyladamantane (**2**). This apparently simple objective, the synthesis of **1**, proved to be highly elusive, but led to investigations which provided mechanistic clues to the general behavior of adamantane derivatives under sulfuric acid conditions.

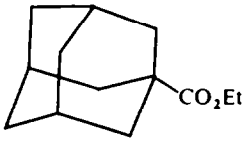
Synthetic approaches to the carboxylic acid **1**

A promising synthetic route to the carboxylic acid **1** seemed to be available from the reaction of methyl Grignard reagent with the ethyl ester (**3**) of 1-adamantanecarboxylic acid[5] followed by a Koch–Haaf carboxylation reaction[6] on the resulting tertiary alcohol **4**.

The Koch–Haaf reaction, however, led not to the desired acid **1**, but to the isomeric

3-isopropyl-1-adamantanecarboxylic acid **5** (m.p. 115–116°).[7] This report describes work we have done to elucidate the mechanism of this unexpected rearrangement.

The structure assignment of **5** was readily made on the basis of the appearance of the Me resonances in the NMR as a doublet at 9·16τ (typical of an isopropyl moiety)



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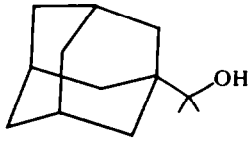

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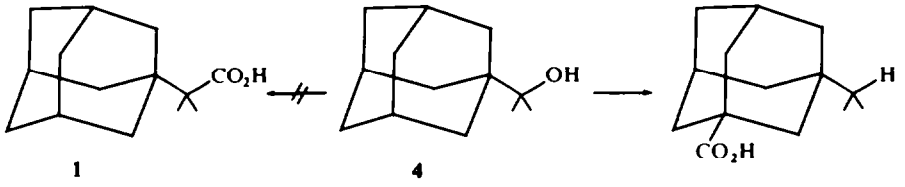
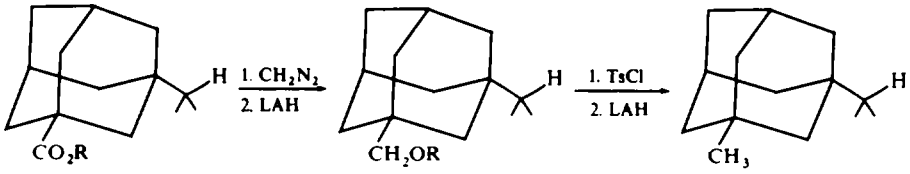


1 **4** **5**

rather than as the single absorption peak anticipated for **1**. The NMR spectrum showed in addition the other absorptions expected[8] for the 3-alkyl substituted 1-adamantanecarboxylic acid. The structure was proved by conversion of **5** to 1-methyl-3-isopropyladamantane (**9**) by the sequence shown below and comparison with a sample of **9** synthesized by an unambiguous route.

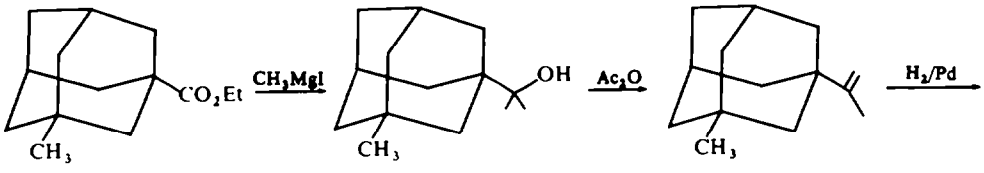


5: R = H
6: R = CH_3

7: R = H
8: R = Ts

9

The alternative synthesis of **9**, beginning with ethyl-3-methyl-1-adamantane carboxylate (**10**)[9], was accomplished by the following sequence:

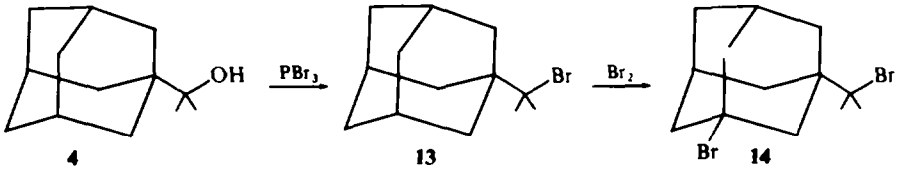


10 **11** **12**

The Koch–Haaf reaction was subsequently reported[10] in the patent literature to give a product (m.p. 75–78°) in 50% yield assigned the structure **1**. We repeated the reaction and obtained the same crude product. Sublimation of this material, however,

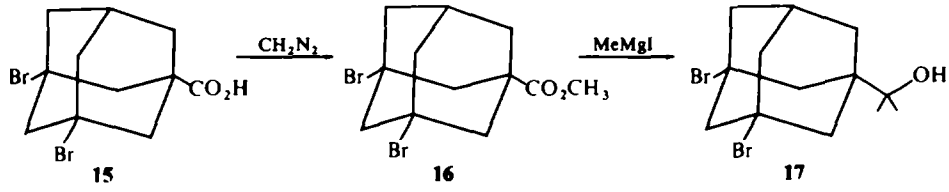
raised the m.p. to 115–116°, indicating that the structure assignment[10] was incorrect and that the product was in fact the rearranged carboxylic acid **5**.

In order to prevent the rearrangement we attempted to modify the structure of the adamantane nucleus. As the presence of electron withdrawing groups is known[11] to retard carbonium ion formation on the adamantane nucleus, we hoped that introduction of bromine substituents would permit the Koch–Haaf reaction to proceed without rearrangement. Accordingly, the mono-substituted derivative **14** was prepared from the alcohol **4**, and the disubstituted derivative **17** was synthesized from



4 **13** **14**

dibromoadamantanecarboxylic acid (**15**).[12] When **14** and **17** were subjected to the Koch–Haaf carboxylation reaction, however, no characterizable product was obtained in either instance.

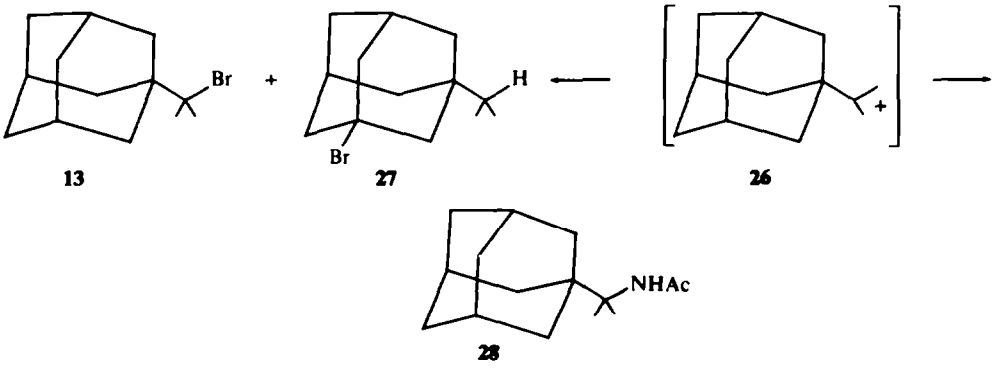


15 **16** **17**

A variety of other reactions were investigated as possible methods for the synthesis of the carboxylic acid **1** (Table 1). However, these attempts were all unsuccessful, either as a consequence of failure of the materials to give any reaction under the conditions utilized, or as a result of other undesired side reactions.

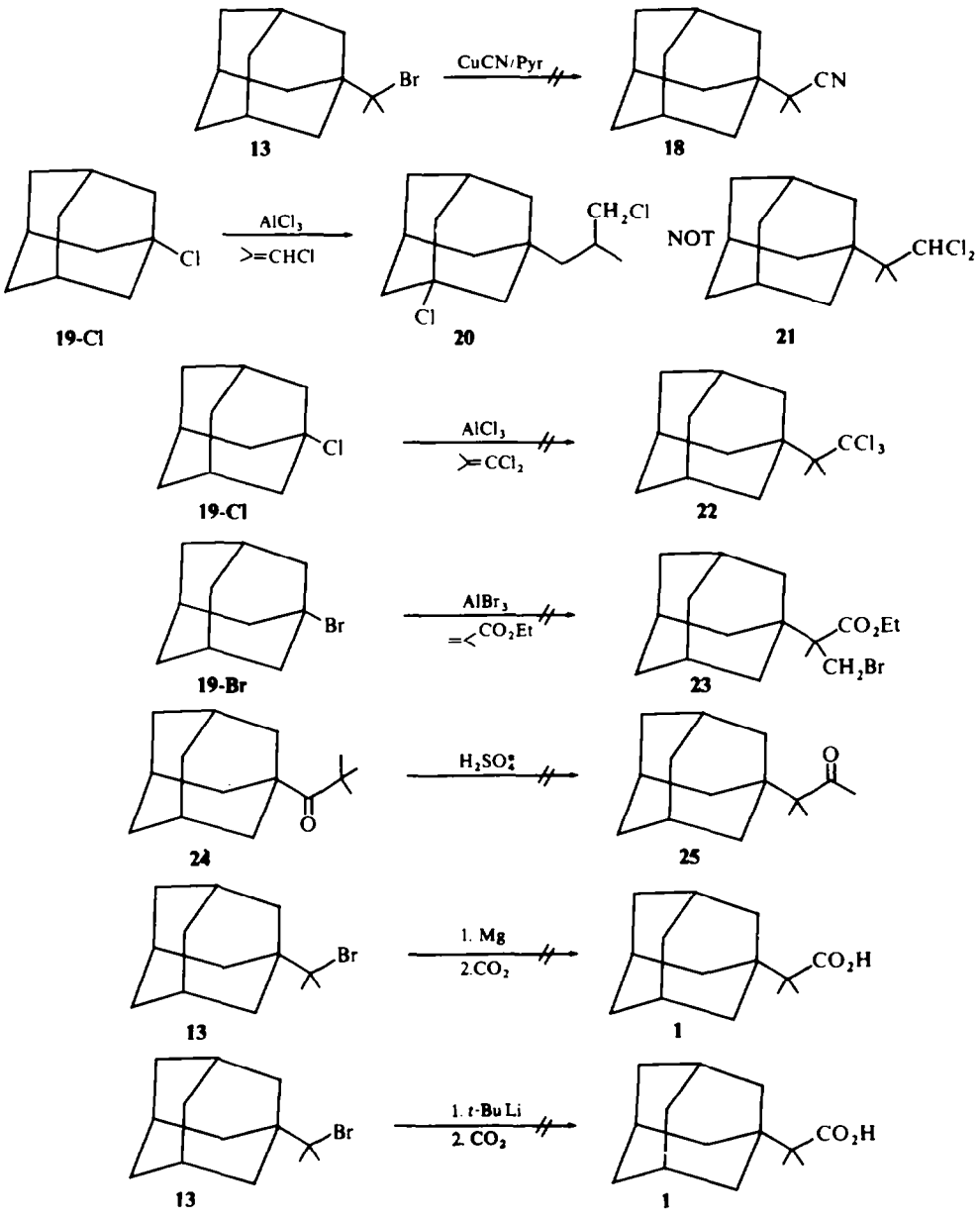
The Mechanism of the rearrangement

The failure of the Koch–Haaf reaction (**4** ⇸ **1**) is somewhat surprising in view of the successful conversion[14] of **4** to the amide **28** in the Ritter reaction.[15] Both reactions



13 **27** **26** **28**

TABLE 1. UNSUCCESSFUL ATTEMPTS DIRECTED TOWARD THE SYNTHESIS OF CARBOXYLIC ACID 1

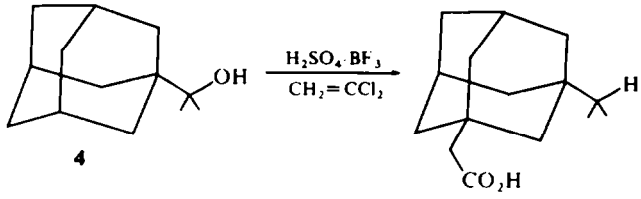


* This reaction has subsequently been accomplished by Professor J. E. Dubois (private communication). The analogous reaction with di-*t*-butyl ketone leads to methyl triptyl ketone.[13]

are carried out in concentrated sulfuric acid and presumably involve the intermediacy of the tertiary carbonium ion **26**. Similarly, the reaction of **4** with hydrobromic acid gives a product mixture in which the unrearranged bromide **13**

predominates over the rearranged bromide **27** in a ratio of about 19:1.[7] On the other hand, the Bott reaction[16] of **4** also takes place with rearrangement to yield **29**.

In order to learn if the facility of the rearrangement was simply a temperature

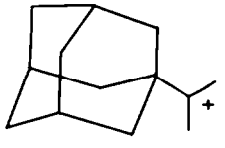


4 **29**

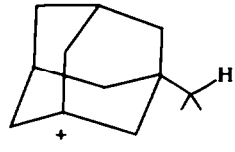
dependent phenomenon, the Koch–Haaf reaction was carried out at 50° (the conditions[14] of the Ritter reaction) rather than at 0–25° (the usual conditions for Koch–Haaf reactions[6]); again, however, the sole product was the rearranged carboxylic acid **5**.

The reasons for the rearrangement of cation **26** under the conditions of the Koch–Haaf and Bott reactions, but not under the similar conditions of the hydrogen bromide and Ritter reactions are not immediately clear. The presumed greater nucleophilicity* of a bromide ion or a cyano group relative to carbon monoxide or 1,1-dichloroethylene suggests the possibility that in contrast to the former two reactions, the cation **26** is trapped by bromide ion or acetonitrile before it has the opportunity to rearrange. Alternatively, the known[18] reversibility of the Koch–Haaf reaction might simply have permitted establishment of an equilibrium between **1** and **5** in which the latter predominates.†

The relative stabilities of structures related to **1** and **5** merit discussion. The corresponding carbonium ions **26** and **30** are expected to differ substantially in stability,[7, 11] the former being considerably more stable. The energy difference is estimated at about 5·5 kcal on the basis of the 10^4 difference in the solvolysis rates of the bromides



26



30

13 and **27** (Table 2). On the other hand, a smaller energy difference between isomeric structures might be expected for neutral molecules (e.g., **1** and **5** or **13** and **27**), and steric arguments suggest that the 3-substituted adamantane (**5** or **27**) should be of lower energy. The side chain substituent of **1** or **13** suffers two skew interactions with the methylene groups of the adamantane nucleus, whereas the bridgehead substituent of **5** or **27** is equatorially disposed to all three cyclohexane rings of the adamantane moiety and has no skew interactions. Thus in the Koch–Haaf reaction, the product

* An inverse order of nucleophilicity has been suggested for reaction with highly stabilized (phenyl substituted) carbonium ions.[17]

† The Ritter reaction is also reversible,[18c] but apparently not as easily as the Koch–Haaf reaction.

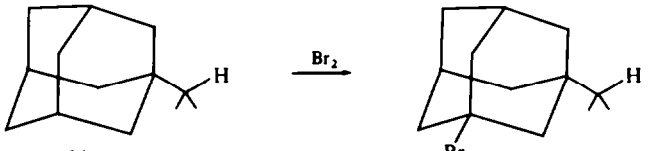
TABLE 2. RATE CONSTANTS FOR SOLVOLYSIS OF 2-(1-ADAMANTYL)-2-BROMOPROPANE (13) AND 3-ISOPROPYL-1-BROMOADAMANTANE (27) IN 80% ETHANOL

Substrate	Temp	k (sec^{-1})	$\Delta H^{\ddagger}$(kcal)	$\Delta S^{\ddagger}$(e.u.)
13[a]	25.[b]	4.37×10^{-3}	22.0	4.3
	27.2	5.78×10^{-3}		
	0.0	1.35×10^{-4}		
27[c]	25.[b]	4.39×10^{-7}	24.5	−5.5
	42.9	4.83×10^{-6}		
	70.4	1.19×10^{-4}		

[a] conductimetric [b] extrapolated from other temps [c] titrimetric

(which is derived from the cation **30**) does not appear to reflect the stability of the carbonium ion.

A similar observation may be made with regard to the bromination of 1-isopropyladamantane (**31**) which leads to substitution on the adamantane nucleus:

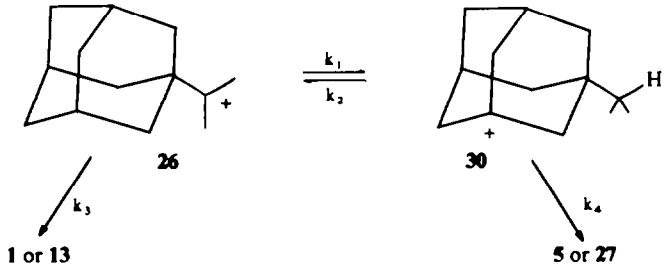


31 **27**

This type of bromination is known to proceed by a carbonium ion mechanism,[19] and the lower energy of **26** relative to **30** indicates that the former should be the first formed intermediate. Yet the product is derived from **30**, and interconversion of the two ions must occur. The possibility that **13** might be an intermediate in this reaction can be ruled out. When **13** is subjected to the bromination conditions rearrangement to **27** is not observed, and the product of the reaction is the dibromide **14**.

Although the Koch–Haaf and bromination products may in each case be the more stable isomer, the "complete" absence of the other isomer is not consistent with establishment of an equilibrium between two products which should not differ greatly in stability. A more attractive explanation (Scheme 1) involves establishment

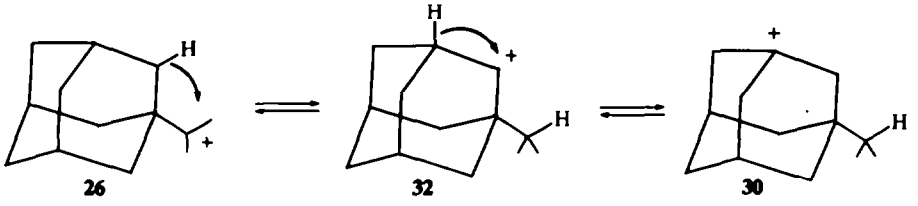
SCHEME 1



of a rapid equilibrium between isomeric cations **26** and **30**. The less stable cation (**30**) must then react to give product at a much greater rate than cation **26** (i.e., $k_3 \gg k_4$). The formation of unrearranged products in the reaction of **4** (with HBr to give **13** and

with H_2SO_4—CH_3CN to give **28**) suggests that when the attacking nucleophile is sufficiently reactive, cation **26** is trapped before it can rearrange (i.e., $k_4 > k_1$).

The interconversion of the carbonium ions **26** and **30** formally involves a 1,4-hydride shift. Although intramolecular hydride shifts are well documented[20] in carbonium ion chemistry, the geometries of **26** and **30** render the possibility of such 1,4-shifts highly unlikely in this system. Alternatively, sequential 1,3- and 1,2-hydride shifts could produce the observed rearrangement *via* the secondary 2-adamantyl cation **32**. However, this pathway is also somewhat improbable, especially since 1,2-hydride shifts (e.g., **32** ⇌ **30**) do not appear to be facile processes on the adamantane skeleton.[1, 21]

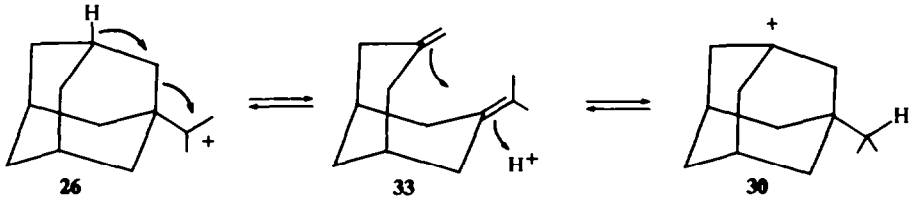


26 **32** **30**

Similarly, the 1,3-hydride shift (**26** ⇌ **32**) should also be unfavorable. The transition state for this rearrangement would resemble a protonated cyclopropane in which the cyclopropane ring is fused to the 1 and 2 positions of the adamantane moiety; such a strained intermediate is predicted to be of very high energy.

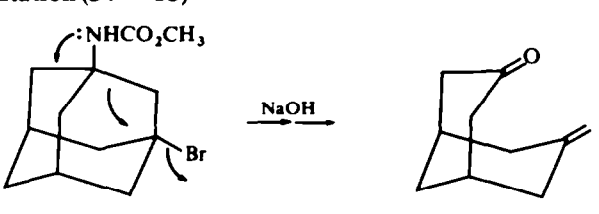
Two alternatives therefore remain: intermolecular hydride shifts[22] and a fragmentation-recombination mechanism. Although intermolecular hydride shifts may at first appear improbable, they are clearly implicated in a number of adamantane reactions.[1, 23] Furthermore, the isolation of small amounts of isopropyladamantane in the Koch–Haaf reaction of **4** indicates that at least some disproportionation *via* intermolecular hydride shifts takes place. On the other hand, the great facility of the rearrangement initially seemed better explained by another reaction pathway.

An entirely plausible alternative mechanism[7] would involve fragmentation of cation **26** to the bicyclic diene **33** followed by recombination in the opposite mode to give cation **30**.

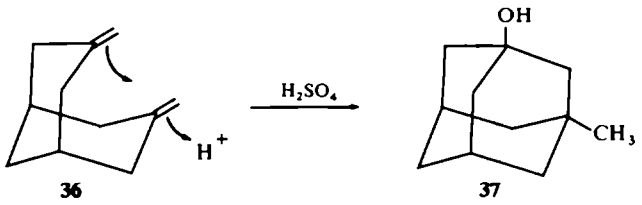


26 **33** **30**

Both the fragmentation (**34** → **35**)[24]



and recombination (**36** → **37**)[27] steps have been demonstrated in adamantane chemistry.

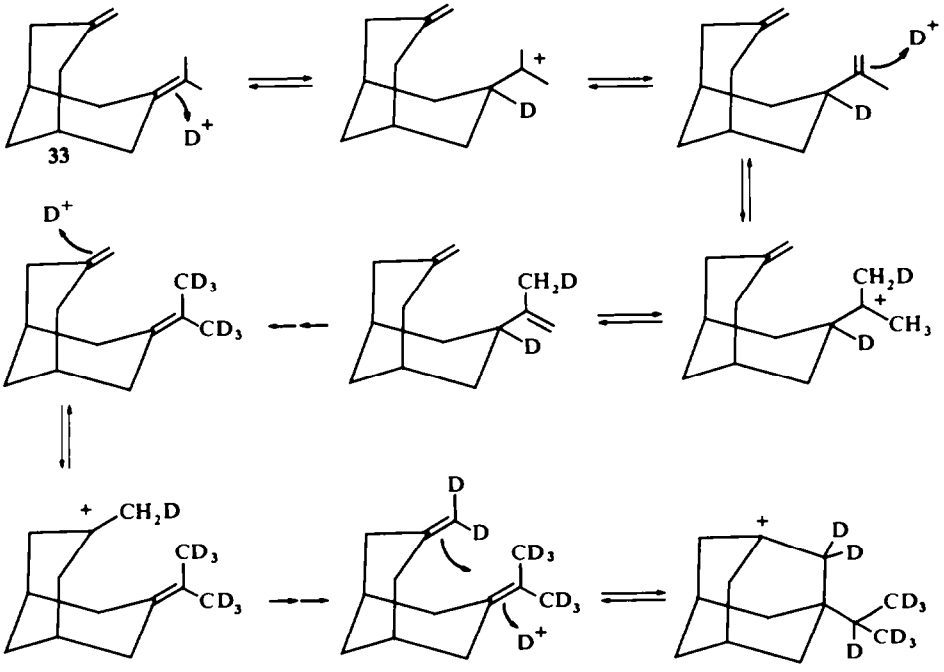


36 **37**

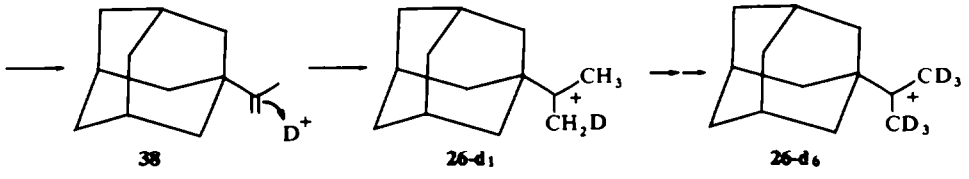
Deuterium labelling studies

The fragmentation–recombination mechanism, if it is operating, should be demonstrable by carrying out the reaction in D_2SO_4. The intermediate diene **33** should be capable of incorporating at least eight deuterium atoms by the exchange process shown in Scheme **2**. Although the cation **26** could also exchange the six protons of the

SCHEME 2. Deuterium Incorporation Anticipated for the Fragmentation–Recombination Mechanism



SCHEME 3. A Scheme for Deuterium Exchange in the Me Groups of Cation **26**.



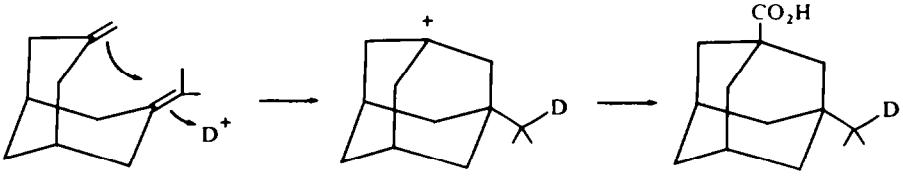
38 **26-d₁** **26-d₆**

isopropyl Me groups by the process depicted in Scheme 3, only the fragmentation-recombination mechanism would allow incorporation of deuterium into the adamantane nucleus.

When the Koch–Haaf reaction of **4** was carried out in deuterated sulfuric acid the mass spectrum of the product indicated the net incorporation of 5 to 6 D atoms. The NMR spectrum showed that most or all of the label was located in the Me groups of the isopropyl moiety. Furthermore, the mass spectra of both the deuterated and undeuterated acids (**5**) have a strong peak at 179 mass units corresponding to the loss of isopropyl (M-43). For the deuterated acid the peaks at (179 + D_n) amount to less than 2% of the peak at 179, indicating that virtually no deuterium had been incorporated into the adamantane nucleus.

Perhaps the most convincing evidence is found in the presence of the doublet at 9·16 τ in the NMR spectrum of the carboxylic acid **5** isolated from the Koch–Haaf reaction in D_2SO_4. This absorption (which is reduced in intensity as a result of deuterium incorporation) corresponds to the two Me groups of the side chain. In contrast to the case of simple exchange of the cation **26** (Scheme 3) for which no exchange of deuterium for protium at the methine position is expected,[26] Scheme **4** shows that with the fragmentation-recombination mechanism such incorporation at the methine position is imperative. Consequently, the presence of the Me group

SCHEME 4. Deuterium Incorporation into the Methine Position for the Fragmentation-Recombination Mechanism



33 30-d 5-d

resonance as a doublet with the same coupling constant as in the undeuterated compound is consistent only with protium as the substituent at the methine position.* Thus deuterium was not incorporated into the methine position, and the fragmentation-recombination pathway cannot be operating.

Dilution studies

After ruling out the fragmentation-recombination mechanism, the most reasonable alternative for the interconversion of cations **26** and **30** involves intermolecular hydride shifts. If an intermolecular mechanism is operative, then the rate of interconversion should be concentration dependent. On this assumption we subjected the alcohol **4** to the conditions of the Koch–Haaf reaction at *high dilution*. The concentration of the adamantane species was 0·01 M or less *both* in the sulfuric acid solution and in the carbon tetrachloride solution of the alcohol **4** which was added to the reaction mixture. The NMR spectrum of the product showed the presence of the unrearranged acid **1** (8·90 τ, 6H, singlet) and rearranged acid **5** (9·16 τ, 6H, doublet: J = 5 Hz) in a

* The absorption in the NMR spectrum of **5** corresponding to this methine proton is a complex multiplet and is difficult to observe; however, in the deuterated material it appears as a broad singlet at 8·72 τ.

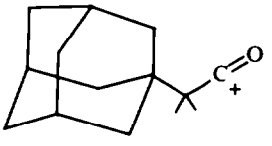
ratio of 7:1. Recrystallization from aqueous methanol afforded the pure acid, 2-(1-adamantyl)-2-methylpropionic acid (**1**), m.p. 186–188°.

Although this experiment demonstrates the intermolecular nature of the rearrangement of cations **26** and **30**, the question of thermodynamic *vs* kinetic control in the original Koch–Haaf reaction remains unresolved. In order to clarify this point we subjected the unrearranged acid **1** to the conditions of a "concentrated" (0·1 M) Koch–Haaf reaction. The rearrangement of **1** to **5** does take place, but at a rate substantially slower than the rate of conversion of **4** to **5** under the same conditions. Although exact equilibrium data were not obtained, this experiment demonstrates that at equilibrium the rearranged acid **5** is favored over **1** by at least 5:1.

CONCLUSIONS

We have shown that the Koch–Haaf reaction of 2-(1-adamantyl)-2-propanol (**4**) proceeds with rearrangement to give the acid **5** as a consequence of *intermolecular* hydride shifts. As the rearrangement is bimolecular it can be inhibited by using a lower concentration of substrate; the use of dilute conditions in the Koch–Haaf reaction of **4** has resulted in the synthesis of the elusive 2-(1-adamantyl)-2-methylpropionic acid (**1**).

Since the rearrangement of **1** to **5** under the normal conditions of a Koch–Haaf reaction is considerably slower than the conversion of the alcohol **4** to **5**, the carboxylic acid **1** cannot be an intermediate in the Koch–Haaf reaction (**4** → **5**). Although differential trapping rates of the carbonium ions **26** and **30** (Scheme 1) appears to be a likely explanation for the observed product distribution, the possibility cannot be ruled out that a thermodynamic equilibrium is established between the acylium ions **39** and **40**. The products **1** and **5** could then arise in the same ratio as that of **39**



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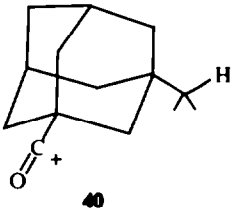

40

and **40** in the equilibrium mixture. However, data on the relative stabilities of **39** and **40** are not available, and a decision between the two alternatives to explain the product distribution is not possible.

EXPERIMENTAL

2-(1-Adamantyl)-2-propanol (**4**). To the Grignard reagent prepared from 57 g MeI and 9·6 g Mg turnings was added over 45 min a soln of 3[5] (32 g) in 100 ml ab diethyl ether. The reaction mixture was heated at reflux for 1 hr, and the Mg salts were decomposed by the addition of NH_4Cl aq while cooling the reaction mixture in an ice bath. The aqueous phase was extracted with diethyl ether, and the combined ether solns were washed with water and dried over $MgSO_4$. The ether was distilled and the residue was distilled at reduced pressure to give 29·1 g (97%) of **4** (b.p. 118/0·5 mm). After recrystallization from MeOH the material melted at 80·0–81·4°; IR: 3470 (OH), 1370 cm^{-1} (weak, gem dimethyl); NMR $\tau^{CCl_4}_{ppm}$ 7·92 (2H), 8·45–8·55 (12H), ~ 8·9 (1H, m), 9·19 (6H, d). (Found: C, 80·55; H, 11·50. Calc. for $C_{13}H_{22}O$: C, 80·35; H, 11·41).

3-Isopropyl-1-adamantanecarboxylic acid (**5**). The alcohol **4** (37·9 g) was dissolved in 120 ml anhy formic

acid and, after a short time, the soln separated into two layers. The layers were separated and added simultaneously to a stirred mixture of 2 l of 96% H_2SO_4 and 150 ml cyclohexane over a period of 5 hr. When the addition was complete the mixture was poured onto crushed ice, and the aqueous phase was extracted with three portions diethyl ether. The combined ether solns were washed with water until neutral, dried over $CaCl_2$, and evaporated at reduced pressure. The residue was dissolved in 750 ml benzene containing 26 ml EtOH and 2 g *p*-toluenesulfonic acid. The mixture was heated at reflux using a Dean–Stark trap until no more water was formed. After cooling to room temp, the mixture was washed with $NaHCO_3$ aq and water, and was dried over $CaCl_2$. The solvent was distilled off, and the residue was fractionally distilled at reduced pressure. The fraction boiling at 120–130°/3 mm (34·7 g, 71%) was redistilled to give 21·6 g (44%) of ethyl-3-isopropyl-1-adamantanecarboxylate, b.p. 126°/3 mm.

A 20 g portion of the purified ester was added to a soln of KOH (8 g) in EtOH (150 ml), and the mixture was heated at reflux for 15 hr. Most of the EtOH was distilled off, and the residue was taken up in water. The aqueous soln was extracted with light petroleum and acidified with conc HCl. The ppt was collected by filtration and recrystallized from aqueous MeOH to give 13·3 g (33%, 75% based on the ester) of *3-isopropyl-1-adamantanecarboxylic acid* (**5**), m.p. 116°; NMR: $\tau_{ppm}^{CDCl_3}$ −1·55 (1H), 7·91 (2H), 8·17 (4H), 8·36 (4H), 9·16 (6H, d); *Mass spectrum*: *m/e* 222 (13%, M^+); 179 (100%, $-C_3H_7$); 161 (10%, $-C_3H_7$, $-CO_2$); 135 (7·5%); 133 (17%); 44 (1·7%); 43 (4·8%); 41 (7·8%). (Found: C, 75·29; H, 10·00. Calc for $C_{14}H_{22}O_2$: C, 75·63; H, 9·97%).

Methyl-3-isopropyl-1-adamantanecarboxylate (**6**). To a soln of **5** (10 g) in 80% aqueous MeOH (50 ml) was added a soln of diazomethane in diethyl ether until a weak yellow colour persisted. The mixture was poured into water, and the aqueous mixture was extracted with diethyl ether. The ether soln was washed with water and dried over $MgSO_4$. The solvent was distilled off, and the residue was distilled at reduced pressure to give 9·5 g (89%) of *methyl-3-isopropyl-1-adamantanecarboxylate* (**6**), b.p. 160·5°/15 mm. (Found: C, 75·87; H, 10·09. Calc for $C_{15}H_{24}O_2$: C, 76·22; H, 10·24%).

1-Hydroxymethyl-3-isopropyladamantane (**7**). To a suspension of LAH (1·2 g) diethyl ether (50 ml) was added dropwise with stirring a soln of **6** (11·5 g) in diethyl ether (100 ml). The mixture was heated at reflux for 45 min, and after it had cooled to room temp the excess LAH was destroyed by the addition of water. The inorganic solid was removed by filtration and washed with ether. The ether solns were evaporated, and the residue was distilled at reduced pressure to give 7·0 g (69%) of *1-hydroxymethyl-3-isopropyladamantane* (**7**), b.p. 105°/2 mm.

1-Tosyloxymethyl-3-isopropyladamantane (**8**). To a soln of **7** (6·8 g) pyridine (100 ml) which was cooled in an ice bath was added *p*-toluenesulfonyl chloride (6·8 g). The mixture was allowed to stand at room temp for 20 hr, and was then poured into cold, dil HCl. The oily ppt soon solidified and was collected by filtration and washed well with water. The solid was dried under vacuum and recrystallized from MeOH to give 10·1 g (86%) of *1-tosyloxy-3-isopropyladamantane* (**8**), m.p. 58°. (Found: C, 69·47; H, 8·27. Calc for $C_{21}H_{30}O_3S$: C, 69·58; H, 8·34%).

1-Methyl-3-isopropyladamantane (**9**). To a stirred suspension of LAH (2·5 g) in anhyd THF (50 ml) was added a soln of **8** (8 g) in anhyd THF (50 ml), and the mixture was heated at reflux for 16 hr. The excess LAH was destroyed by the cautious addition of water, and the inorganic salts were removed by filtration and washed well with diethyl ether. After removal of the solvent from the combined organic solns, the residue was fractionally distilled at reduced pressure to give 3·3 g (78%) of *1-methyl-3-isopropyladamantane* (**9**), b.p. 112°/13 mm; NMR: $\tau_{pp}^{CCl_4}$ 8·00 (2H), 8·60 (8H), 8·81 (2H), 9·15 (6H, d), 9·16 (3H, s). (Found: C, 87·32, H, 12·55. Calc. for $C_{14}H_{24}$: C, 87·42; H, 12·58%).

2-(3-Methyl-1-adamantyl)-2-propanol (**11**). To the Grignard reagent prepared from 5·35 g Mg turnings and 32 g MeI in 50 ml anhyd diethyl ether was added dropwise with stirring a soln of **1** (19·8 g).[9] The mixture was heated at reflux for 1 hr and was then neutralized by the addition of conc NH_4Cl aq. The aqueous phase was extracted with diethyl ether, and the combined ether solns were washed with water and dried over $MgSO_4$. The solvent was distilled off to give 18·2 g (98%) of *2-(3-methyl-1-adamantyl)-2-propanol* (**11**) as an oil. As decomposition was observed to begin when at attempt was made to distill the product under vacuum, the material was carried on to the next step without further purification.

1-Methyl-3-isopropenyladamantane (**12**). A soln of **11** (18·2 g) in Ac_2O (150 ml) was heated at reflux for 12 hr, and after the mixture had cooled it was poured into ice water. The aqueous mixture was extracted with pentane, and the combined pentane extracts were washed with water and dried over $MgSO_4$. The pentane was distilled off, and the residue was distilled at reduced pressure to give 12·5 g (75%) of *1-methyl-3-isopropenyladamantane* (**12**), b.p. 109°/11 mm. (Found: C, 88·30; H, 11·70. Calc. for $C_{14}H_{22}$: C, 88·35; H, 11·65%).

Hydrogenation of 1-*methyl*-3-*isopropenyladamantane* (**12**). A soln of **12** (11 g) abs EtOH (100 ml) containing 10% Pd-C (1 g) was hydrogenated at atm pressure. The uptake of H_2 ceased after 1 hr, and the catalyst was removed by filtration. The EtOH was distilled off and the residue was distilled at reduced pressure (water aspirator) to give 10 g (90%) of 1-*methyl*-3-*isopropyladamantane* (**9**) which was identical with the sample prepared by reduction of **8** (gas chromatography).

2-(1-*Adamantyl*)-2-*bromopropane* (**13**). To a stirred soln of carefully dried **4** (16 g) in benzene (100 ml) which was cooled in an ice bath was added a soln of freshly distilled PBr_3 (4·65 g) in benzene (50 ml) over a period of 2 hr. The mixture was stirred at 0° for an additional hr and was permitted to stand at room temp for 12 hr. The mixture was heated just to the b.p. and was then cooled in an ice bath. The phosphoric acid layer was separated, and the benzene soln was washed with cold water and dried over $CaCl_2$. The benzene was distilled off, and the residue was recrystallized from hexane and sublimed to give 10·7 g (86%) of 2-(1-*adamantyl*)-2-*bromopropane* (**13**), m.p. 124°; NMR: $\tau_{ppm}^{CCl_4}$ 8·0 (3H, broad s), 8·15–8·45 (12H m), 8·29 (6H, sharp s). (Found: C, 61·01; H, 8·34. Calc. for $C_{13}H_{21}Br$: C, 60·68; H, 8·23%).

2-(3-*Bromo*-1-*adamantyl*)-2-*bromopropane* (**14**). A mixture of **13** (12 g) and Br_2 (80 ml) was heated at 70–80° for 2 hr. The cooled mixture was added to 300 ml chloroform, and the excess Br_2 was destroyed by the addition of $NaHSO_3$. The organic phase was washed with water and dried over $CaCl_2$, and the chloroform was distilled off. The residue was recrystallized from dioxan to give 13 g (82%) of 2-(3-*bromo*-1-*adamantyl*)-2-*bromopropane* (**14**), m.p. 147°. (Found: C, 46·27; H, 5·80. Calc. for $C_{13}H_{20}Br_2$: C, 46·45; H, 6·00%).

Attempted Koch–Haaf reaction of **14**. To a suspension of **14** (10·0 g) in 96% H_2SO_4 (500 ml) was added dropwise over 4 hr 50 ml of anhyd formic acid. The insoluble material was removed by filtration, washed thoroughly with water, and dried to give 9·6 g of unreacted **14**. Repetition of this procedure with the addition of 9·3 g dry silver sulfate afforded tars as the only products.

Methyl 3,5-*dibromo*-1-*adamantylcarboxylate* (**16**). To a methanolic soln of 3,5-dibromo-1-adamantanecarboxylic acid[12] (7 g) was added a soln to diaziomethane in diethyl ether until a weak yellow color persisted. The solvent was distilled off, and the residue was recrystallized from aqueous MeOH to give 6·5 g (89%) of **16** m.p. 46°. (Found: C, 41·20; H, 4·71. Calc. for $C_{12}H_{16}Br_2O_2$: C, 40·93; H, 4·58%).

2-(3,5-*Dibromo*-1-*adamantyl*)-2-*propanol* (**17**). To the Grignard reagent prepared from 1·15 g Mg turnings and 4·1 g MeI was added dropwise a soln of **16** (5·5 g) in 30 ml of anhyd diethyl ether (59 ml), and the mixture was heated at reflux for 1 hr. The mixture was neutralized by the addition of conc NH_4Claq and worked up in the usual manner to give 5·3 g (96%) of **17**.

Attempted Koch–Haaf reaction of **17**. To a mixture of **17** (5·3 g) and 96% H_2SO_4 (200 ml) was added dropwise over 2 hr 20 ml of anhyd formic acid. After about 30 min the evolution of HBr was observed. The mixture was poured onto ice, and extraction of the H_2SO_4 mixture afforded a tar from which no characterizable product could be isolated.

Reaction of 2-(1-*adamantyl*)-2-*bromopropane* (**13**) *with cuprous cyanide*. To dry cuprous cyanide (4 g) was added anhyd pyridine (40 ml) and an exothermic reaction resulted. To the pyridine soln was added **13** (12 g) and the mixture was heated in an oil bath. The temp of the oil bath was raised slowly over 2 hr at 220°, and most of the pyridine was distilled over. The residue was heated for an additional 5 min and was cooled to room temp. The tarry residue was treated with several portions hot benzene, and removal of the solvent afforded a dark oil. From this oil could be obtained neither a homogeneous crystalline solid nor a liquid of definite m.p.

1-*Chloro*-2-*methyl*-3-(3-*chloroadamantyl*)-*propane* (**20**). A soln of 1-adamantyl chloride[27] (**19-Cl**, 29 g) in freshly distilled 1-chloro-2-methylpropane[28] (70 ml) was cooled to −50°, and $AlCl_3$ (5 g) was added with stirring over a period of 1 hr. After 4 hr the resulting thick slurry was mixed with ice-conc HCl and the mixture was extracted with diethyl ether. The ether solns were washed with $NaHCO_3$aq and water, and dried over $MgSO_4$. The ether was distilled off, and the residue was crystallized with scratching in the presence of a small amount of light petroleum. Recrystallization from MeOH afforded **20** (29·75 g; 67%), m.p. 52·5°; NMR: $\tau_{ppm}^{CCl_4}$ 6·20 (2H, m), 8·22 (3H, sharp d), 8·6 (2H, m). (Found: C, 64·06; H, 8·46. Calc. for $C_{14}H_{22}Cl_2$: C, 64·37; H, 8·49%).

A sample of **20** (24·5 g) was dissolved in MeOH (250 ml) containing NaOH (8·5 g), and Raney Ni catalyst was added. The soln was maintained at room temp under an atmosphere of H_2 until uptake of H_2 ceased (3 days). The catalyst was removed by filtration, the MeOH was distilled off, and the residue was fractionated at reduced pressure to give 15·7 g (84%) of 1-(1-*adamantyl*)-2-*methylpropane*, b.p. 114°/12 mm; NMR: $\tau_{ppm}^{CCl_4}$ 7·98 (3H), 8·22 (6H), 8·40 (6H), 9·00 (9H). (Found: C, 87·33; H, 12·57. Calc. for $C_{14}H_{24}$: C, 87·42; H, 12·58%).

Attempted preparation of 1,1,1-*trichloro*-2-(1-*adamantyl*)-2-*methylpropane* (**22**). A soln of 1-adamantyl

chloride[27] (**19-Cl**; 15 g) in 1,1-dichloro-2-methylpropene[29] (35 ml) was cooled to −45°, and $AlCl_3$ (2·5 g) was added in small portions with stirring over a period of 1 hr. After 4 hr the reaction was quenched by the addition of ice–conc HCl. The mixture was extracted with diethyl ether, and the ether soln was washed with water and dried $MgSO_4$. Distillation of the solvent afforded 14·3 g of 1-adamantyl chloride (**19-Cl**) as the only product.

Reaction of 1-*adamantyl bromide* (**19**) *with ethyl methacrylate.* A soln of 1-adamantyl bromide (10 g) in ethyl methacrylate (15 g) containing a trace of hydroquinone was heated at 80° for 15 hr. After distillation of the excess ester, the residue was crystallized from MeOH to give only the unreacted bromide (**19-Br**).

An identical mixture was heated in a bomb for 8 hr at 140°, but again no reaction occurred. Elevation of the temp resulted only in polymer formation.

A mixture of $AlBr_3$ (15 g) and CS_2 (50 ml) was cooled to −20°, and a soln of **19-Br** (10 g) and ethyl methacrylate (5·1 g) in CS_2 (50 ml) was added dropwise over 2 hr while the temp was maintained at −20°. The mixture was quenched by the addition of ice–conc HCl, and worked up to give **19-Br** as the only product.

1-*Adamantyl* t-butyl ketone (**24**). Into anhyd diethyl ether (100 ml) cooled to −70° in a dry ice–acetone bath was injected 85 ml of commercial soln of t-BuLi (1·54M = 0·115 mol) under an atmosphere of N_2. To the cold soln was added 1-adamantanecarboxylic acid (10 g; 0·005 mol) in anhyd diethyl ether (100 ml) dropwise with stirring. After the addition was complete, the mixture was stirred at −70° for 3 hr and was then allowed to warm to room temp for 12 hr and was then poured into 500 ml ice water. The mixture was acidified and extracted with diethyl ether. The combined ether solns were washed with 10% NaOH aq and with water, and were dried over $MgSO_4$. The ether was distilled at reduced pressure, and the residue was distilled under vacuum to give 3·5 g (30%) of 1-*adamantyl* t-*butyl ketone* (**24**), b.p. 117–120°/0·05 mm; NMR: $\tau^{CCl_4}_{ppm}$ 8·8 (9H, s); broad absorptions at 8·25 (12H) and 8·0 (3H); IR: $\bar{\nu}$ cm^{-1} 1675 (C=O).

Attempts to prepare 3-(1-*adamantyl*)-3-*methyl*-2-*butanone* (**25**). The general method employed was to place **24** (1·0 g) in H_2SO_4 (35 ml) at 0° and then allow the mixture to stir at room temp for the desired time. The mixture was then poured into water and extracted with diethyl ether. The ether extracts were washed with water, dried over $MgSO_4$ and evaporated at reduced pressure to yield the products as residue. The results are summarized below:

Reaction time	*Results*
13 hr	No reaction. IR same as starting material.
38 hr	Some reaction. IR showed some loss of starting material and some new peaks, but no new carbonyl absorption. Still mostly starting ketone **24**.
86 hr	Reaction complete. No starting material in IR. Little or no carbonyl absorption. Product identified as 1-adamantanol.

As indicated in the chart, the only product observed from the reaction was 1-adamantanol (identified by comparison of IR and NMR spectra with an authentic sample). No methyl isopropyl ketone was observed in the products, but this may have been lost in the aqueous work up or during the distillation of the solvent; alternatively it may have been degraded by the sulfuric acid.

Attempted carboxylation of the Grignard reagent derived from 2-(1-*adamantyl*)-2-*bromopropane* (**13**). To 2·4 g Mg turnings in 50 ml anhyd diethyl ether was added dropwise a soln of **13** (12·8 g) MeI (7·1 g) in diethyl ether (100 ml). After the addition of about 3 ml of this soln an exothermic reaction began, and the remainder of the soln was added at a rate which maintained gentle reflux. After the addition was complete, the mixture was heated at reflux for an additional 2 hr. Only a small amount of unreacted metal remained, and the ether soln was decanted from this under a N_2 atmosphere.

The ether soln of organometallic reagent was cooled to −18°, taking care to exclude moisture. A stream of dry CO_2 was passed through the soln for 2 hr, and the mixture was allowed to warm to room temp. The mixture was neutralized by the addition of dil HCl. Extraction of the ether soln with $NaHCO_3$ aq and with dil NaOH aq followed by acidification of the aqueous phase afforded no organic product.

Attempted carboxylation of the organolithium reagent derived from 2-(1-*adamantyl*)-2-*bromopropane* (**13**). To pentane (10 ml) and diethyl ether (10 ml) under N_2 atmosphere was injected a commercial solution of t-BuLi in pentane (10 ml; 1·5M = 0·015 mol), and the resulting soln was cooled to −70° in a dry ice–acetone bath. To the cold soln was added dropwise **13** (1·0 g; 0·0004 mol) in ether (5 ml). The mixture was stirred for 45 min at −70°, and dry CO_2 was passed through the soln forming a white ppt. The mixture was poured over dry ice and was allowed to warm to room temp. The mixture was extracted with 20% NaOH aq, and the basic soln was dried over $MgSO_4$ and evaporated at reduced pressure to give pivalic acid as the only product.

Reaction of 2-(1-*adamantyl*)-2-*propanol* (**4**) *with hydrobromic acid.* A mixture of **4** (10·0 g; 0·0515 mol) and

48% HBr (150 ml) was heated at reflux for 48 hr. The mixture was cooled, diluted to 500 ml with water, and extracted with diethyl ether. The combined ether extracts were washed with cold $NaHCO_3$ aq and cold sat NaCl aq, and were dried over $MgSO_4$. Removal of solvent afforded 9·7 g (74%) of a pale brown solid. The NMR spectrum showed the presence of about 95% of the unrearranged bromide **13** and 5% of the rearranged bromide **27** (see below).

N-Acetyl-2-(1-adamantyl)-2-propylamine (**28**).[14] NMR. $\tau_{ppm}^{CHCl_3}$ 4·3–4·7 (1H), 8·03 (3H), 8·07 (3H, s) 8·35 (12H, m)), 8·69 (6H, s).

(3-Isopropyl-1-adamantyl)-acetic acid (**29**). To a soln of BF_3 (6 g) in 96% H_2SO_4 (30 ml) which had been cooled to 10° was added dropwise over the course of 1·5 hr a soln of **4** (6 g) in 1.1 : dichloroethylene (25 g) After an additional 2 hr the mixture was poured onto ice and extracted with ether. The ether extracts were in turn extracted with 1M NaOH, and the basic soln was neutralized with conc H_2SO_4 with cooling in an ice bath. The aqueous mixture was extracted with ether, and the ether soln was dried over $MgSO_4$. Distillation of the ether afforded 3·7 g (51%) of *(3-isopropyl-1-adamantyl)-acetic acid* (**29**), which crystallized on standing. After several sublimations the product exhibited a m.p. of 78–79°; NMR: $\tau_{ppm}^{CDCl_3}$ – 1·15 (1H), 7·88 (2H, s) 7·97 (2H), 8·41 (6H), 8·59 (6H), 8·7–9·1 (1H), 9·20 (6H, d); *Mass spectrum*: *m/e* 236 (2%, M^+), 193 (20%, $-C_3H_7$), 170 (15%, $-CH_2CO_2H$), 135 (100%, $C_{10}H_{15}^+$). (Found: C, 76·86; H, 10·29. Calc. for $C_{15}H_{24}O_2$: C, 76·22; H, 10·24%).

1-Isopropyladamantane (**31**).[30] To a soln of **38** (9·5 g) in diethyl ether was added PtO_2 catalyst (0·2 g). The mixture was hydrogenated at 45 psi using Paar apparatus. When H_2 uptake ceased, the catalyst was removed by filtration, and the solvent was removed at reduced pressure. The residue was distilled at reduced pressure to give 9·5 g (98%) of *1-isopropyladamantane* (**31**), b.p. 108°/11 mm; NMR: $\tau_{ppm}^{CCl_4}$ 8·00 (3H), 8·31 (6H), 8·48 (6H), 8·9 (1H), 9·20 (6H, d).

1-Bromo-3-isopropyladamantane (**27**). A mixture of **31** (5·0 g; 0·028 mol) and Br_2 (25 ml; large excess) was heated at reflux for 12 hr. The mixture was cooled, CCl_4 (50 ml) was added, and the soln was poured into ice water (100 ml) in a separatory funnel. Excess Br_2 was destroyed by cautious addition of Na_2SO_3, and the aqueous phase was extracted with CCl_4. The combined organic extracts were washed with water and sat NaCl aq and dried over $MgSO_4$. Removal of the solvent at reduced pressure afforded a dark oil which was dissolved in hexane and passed through a 25 cm column of alumina. Evaporation of the hexane gave 4·5 g (60%) of *1-bromo-3-isopropyladamanane* (**27**) as a colourless oil; IR: $\bar{\nu}$ cm^{-1} 716, 672; NMR: $\tau_{ppm}^{CCl_4}$ 7·69 (6H), 7·88 (2H), 8·31 (2H), 8·46 (4H), 8·9 (1H), 9·14 (6H, d).

The Koch–Haaf reaction of 2-(1-adamantyl)-2-propanol (**4**) *in* D_2SO_4. In a 3-neck flask equipped with a gas inlet tube, dropping funnel, thermometer and drying tube was placed 100%-d_2 H_2SO_4 (15 ml). The temp of the mixture was maintained at 19–20° while a soln of **4** (1·0 g) in 99% HCOOD (2 ml) was added dropwise over 1 hr under an atmosphere of He. The mixture was stirred for an additional 12 hr, and was then poured onto 100 g ice. The aqueous mixture was extracted with diethyl ether, and the ether extracts were dried over Na_2SO_4. Distillation of the ether afforded 0·9 g (80%) of crude product, which was purified by repeated sublimation to give deuterated **5**, m.p. 105–108°; NMR: $\tau_{ppm}^{CDCl_3}$ – 1·92 (H), 7·92 (2H), 8·16 (4H), 8·34 (4H), 8·51 (4H), 8·72 (1H broad s), 9·18 (0·8H, broad d); *Mass spectrum*: *m/e* [229 (1%), 228 (6%), 227 (3·6%), 226 (1·7%), M^+]; 179 (100%, $-C_3H_7$); 161 (14%); 135 (9%, $-C_3H_7$, $-CO_2$); 133 (21%); 49 (5·5%); 48 (3·5%); 47 (1·5%); 45 (2%); 44 (2%); 43 (1·5%); 41 (5%).

2-(1-Adamantyl)-2-methylpropionic acid (**1**). A 5-liter 3-neck flask equipped with a Hirshberg stirrer was charged with 97% H_2SO_4 (1·5 l) and cooled in an ice salt bath. When the temp of the acid decreased to – 3° 90% formic acid (50 ml) was added causing the temp to rise to 5°. After several mins (when the reaction mixture became foamy) a soln of **4** (2·0 g) in CCl_4 (1·0 l) was added rapidly. At the same time additional formic acid (50 ml) was added dropwise. The addition took 10 min, and after an additional 5 min the mixture was poured onto 3 kg crushed ice.

The layers were separated, and the aqueous layer was separated into two parts. Each of the aqueous parts was extracted with three 100 ml portions CCl_4. The combined CCl_4 solns were washed with two 1·5 liter portions water, and were then mixed with 15 ml conc NH_4OH aq. The resulting ppt was collected by filtration.

The solid ammonium salt was washed with two 5 ml portions cold acetone and was suspended in 30 ml water. To this was added 3N HCl (20 ml), and the mixture was extracted with three 25 ml portions chloroform. The chloroform extracts were washed with NaCl aq (25 ml) and dried over Na_2SO_4. Evaporation of the chloroform at reduced pressure afforded 1·58 g (68%) of a white solid, m.p. 170–180°. The NMR spectrum of the crude product indicated the presence of 88% of **2** and 12% or the rearranged acid **4**.

Five recrystallizations from aqueous MeOH provided 2-(1-*adamantyl*)-2-*methylpropionic acid* (**1**), m.p. 186–188° (sealed capillary); NMR: $\tau_{ppm}^{CDCl_3}$ −4·33 (1H), 8·05 (3H), 8·33 (12H), 8·90 (6H, sharp s).

Rearrangement of 2-(1-*adamantyl*)-2-*methylpropionic acid* (**1**) *to* 3-*isopropyl*-1-*adamantanecarboxylic acid* (**5**) *under Koch–Haaf conditions.* In a 100 ml 3-neck flask equipped with a Hirshberg stirrer was placed 97% H_2SO_4 (10 ml). The flask was cooled in an ice bath, and 90% formic acid (0·5 ml) was added. After 5 min 0·20 g of a mixture of the carboxylic acids (88% **1** and 12% **5**) in 10 ml cold CCl_4 was added in a single portion. The mixture was stirred for 6 hr (the ice bath melted, and the temp rose to 15° at the end of the reaction).

The mixture was poured onto 25 g crushed ice, and the layers were separated. The aqueous layer was extracted with three 10 ml portions CCl_4. The combined CCl_4 solns were washed with three 20 ml portions water and were mixed with 1·0 ml conc NH_4OH aq. The resulting ammonium salts of the carboxylic acids were collected by filtration and washed with 5 ml CCl_4.

The ammonium salt was mixed with 3N HCl (20 ml) and chloroform (20 ml). The layers were separated, and the aqueous layer was extracted with two 10 ml portions chloroform. The combined chloroform solns were dried over Na_2SO_4, and the solvent was evaporated at reduced pressure to give 0·11 g white solid.

Analysis of the product by NMR spectroscopy showed that it consisted of 17% **1** and 83% **5**.

A similar experiment, but with a reaction time of only 2 hr, effected a conversion of pure **1** into a mixture of the acids **1** and **5** in the ratio of 1 : 1.

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