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Preparations of Some 1,2- and 1,4-Disubstituted Adamantanes

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From readily available 1-carboxyadamantan-2-one (**1**), nine 1,2-disubstituted adamantanes (**2**–**10**) were prepared. Photoacetylation of 2-acetoxyadamantane resulted in the exclusive formation of 1-acetyl-4-acetoxyadamantane (**13**), from which seven 1,4-disubstituted adamantanes (**14**–**20**) were derived. In some cases, novel dibromocarbene bromination was applied to the oxy esters (**3** and **15**). By the protoadamantane route was prepared 1-ethyl-2-bromoadamantane (**23**). Autoxidation of 1-fluoroadamantane gave the 4 and 2 ketones **26** and **27** besides the bridgehead alcohol **25**. α methine proton chemical shifts of some 1,2- and 1,4-disubstituted adamantanes are discussed from the viewpoint of additivity relationship based on the chemical shifts of monosubstituted adamantanes.

Because of its high rigidity and unique geometry, the chemistry of adamantanes has received much interest in recent years both from theoretical and synthetic viewpoints. The high symmetry of adamantane allows only two monosubstituted derivatives to exist. The situation is more complicated for disubstituted adamantanes ($C_{10}H_{14}XY$). When $X \neq Y$, 13 isomers (seven chiral and six achiral) are possible. This number is reduced to nine (six achiral and three chiral) when X = Y. Regioselective difunctionalization of adamantane may be one of the most exciting synthetic challenges for adamantane chemists.

A 1,3-disubstituted adamantane may be prepared rather easily *via* direct bridgehead substitutions such as ionic substitutions,[1] dichlorocarbene insertion,[2] and photoacetylation.[3] Some elegant procedures (based on intramolecular processes[4,5] or the protoadamantane route[6]) have been established for the preparations of 1,2-disubstituted adamantanes. A number of 2,4-disubstituted adamantanes have also been prepared by the direct substitution of adamantanone,[7] addition reactions to 2,4-dehydroadamantane,[8] the so-called π route ring closures of bicyclo[3.3.1]non-3-ene systems,[9,10] or the protoadamantane route.[6a,11] On the other hand, only limited works have been reported on the 1,4 difunctionalization of adamantane. The sulfuric[12–14] or nitric acid[15] oxidation or oxidative rearrangement of 1- or 2-adamantyl derivatives gave some 1,4-disubstituted adamantanes. The aluminum bromide catalyzed bromination of adamantanone has been reported to give 1-bromoadamantan-4-one almost exclusively.[9] A unique microbiological oxidation of 1-acetamido- or benzamidoadamantane has been reported to give the anti 4-hydroxy derivatives.[16] The present paper describes the preparations of 1,2- and 1,4-disubstituted adamantanes utilizing some novel together with known techniques.

(1) (a) H. Stetter and C. Wulff, *Chem. Ber.*, **93**, 1366 (1960); (b) H. Koch and W. Haaf, *Angew. Chem.*, **72**, 628 (1960); (c) P. Kovacic and P. D. Roskos, *J. Amer. Chem. Soc.*, **91**, 6457 (1969).

(2) I. Tabushi, Z. Yoshida, and N. Takahashi, *J. Amer. Chem. Soc.*, **92**, 6670 (1970).

(3) I. Tabushi, Z. Yoshida, and S. Kojo, *Tetrahedron Lett.*, 2329 (1973).

(4) (a) W. V. Curran and R. B. Angier, *Chem. Commun.*, 563 (1967); (b) W. V. Curran and R. B. Angier, *J. Org. Chem.*, **34**, 3668 (1969).

(5) (a) W. H. W. Lunn, W. D. Podmore, and S. S. Szinai, *J. Chem. Soc. C*, 1657 (1968); (b) J. K. Chakrabarti, S. S. Szinai, and A. Todd, *ibid.*, 1303 (1970).

(6) (a) B. D. Cuddy, D. Grant, and M. A. McKervey, *Chem. Commun.*, 27 (1971); (b) D. Lenoir, R. Glaser, P. Mison, and P. v. R. Schleyer, *J. Org. Chem.*, **36**, 1821 (1971).

(7) T. Sasaki, S. Eguchi, and T. Toru, *J. Amer. Chem. Soc.*, **91**, 3390 (1969).

(8) A. C. Udding, J. Strating, and H. Wynberg, *Tetrahedron Lett.*, 1345 (1968).

(9) M. A. McKervey, D. Faulkner, and H. Hamill, *Tetrahedron Lett.*, 1971 (1970).

(10) (a) T. Sasaki, S. Eguchi, and T. Toru, *J. Org. Chem.*, **35**, 4109 (1970); (b) T. Sasaki, S. Eguchi, and T. Toru, *Tetrahedron Lett.*, 1109 (1971).

(11) D. Lenoir, P. v. R. Schleyer, C. A. Cupas, and W. E. Heyd, *Chem. Commun.*, 26 (1971).

(12) M. A. McKervey, J. R. Alford, J. F. McGarrity, and E. J. F. Rea, *Tetrahedron Lett.*, 5165 (1968).

(13) H. W. Geluk and J. L. M. A. Schlatmann, *Recl. Trav. Chim. Pays-Bas*, **90**, 516 (1971).

(14) H. W. Geluk, and J. L. M. A. Schlatmann, *Tetrahedron*, **24**, 5369 (1968).

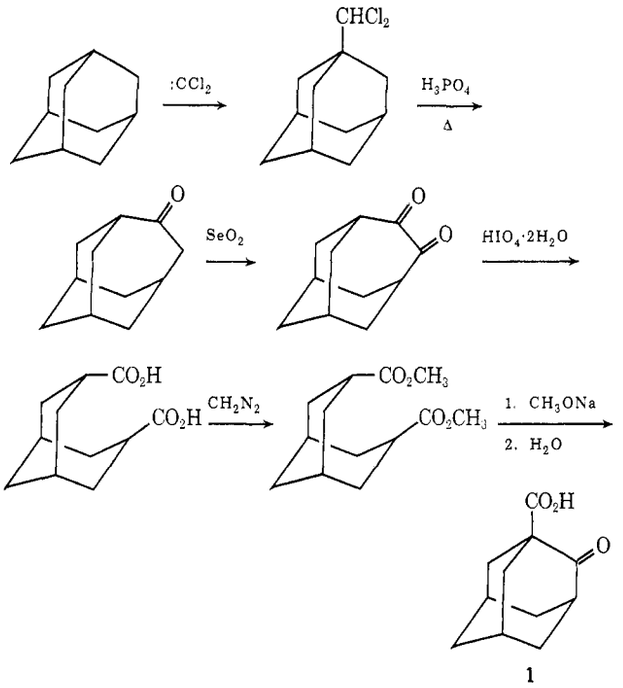
(15) (a) H. W. Geluk, *Tetrahedron Lett.*, 4473 (1971); (b) *Synthesis*, 374 (1972).

(16) (a) M. E. Herr, R. A. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *J. Org. Chem.*, **33**, 3201 (1968); (b) M. E. Herr, R. A. Johnson W. C. Krueger, H. C. Murray, and L. M. Pschigoda, *ibid.*, **35**, 3607 (1970); (c) R. A. Johnson, M. E. Herr, H. C. Murray, and L. M. Reineke, *J. Amer. Chem. Soc.*, **93**, 4880 (1971).

Results and Discussion

Preparations of Some 1,2-Disubstituted Adamantanes Derived from 1-Carboxyadamantan-2-one (1).—1-Carboxyadamantan-2-one (1) was prepared by a modification of the procedure of Peters, *et al.*[17] (Chart I). The modification was made for the preparation

CHART I

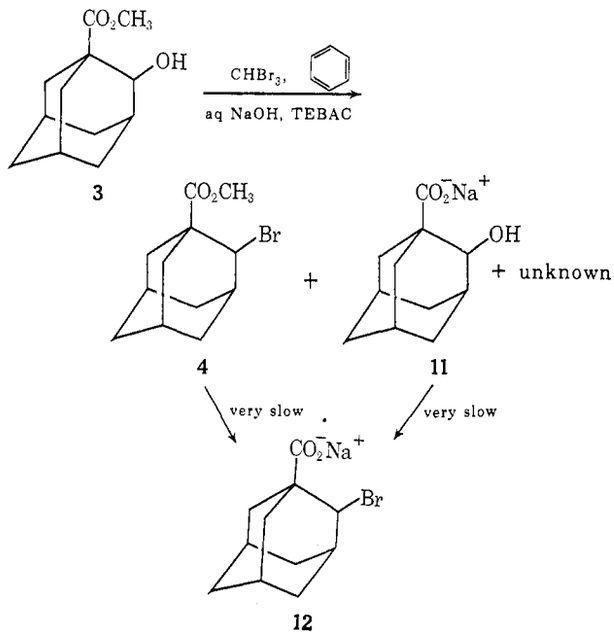


1

of homoadamantanone, which was obtained by the hydrolytic rearrangement of 1-dichloromethyladamantane[2] in our study instead of diazomethane ring homologation of adamantanone.

Some 1,2-disubstituted adamantanes derived from the keto acid **1** are summarized in Chart II. The sodium borohydride reduction of the keto acid **1** gave, in a quantitative yield, the oxy acid **2**, which was esterified with diazomethane in a quantitative yield.

Some unexpected difficulties have been encountered in the next step, the replacement of the hydroxy to bromine giving the bromo ester **4**. Common procedures such as treating the oxy ester **3** with thionyl bromide or triphenylphosphine dibromide did not give satisfactory results. In analogy with the successful chlorination of an alcohol by dichlorocarbene in an alkaline emulsion,[18] the dibromocarbene bromination of the alcohol was the final choice for this conversion.[19] Thus, the reaction of the oxy ester **3** with dibromocarbene generated from bromoform in 50% aqueous sodium hydroxide containing a small amount of benzene emulsified by triethylbenzylammonium chloride (TEBAC) gave the expected bromo ester **4** (10–15% yield) together with unknown tarry materials and the hydrolyzed oxy carboxylate **11**, which was subjected to a cycle of reesterification–dibromocarbene bromination to complete the conversion.



Interestingly, there was found no bromo carboxylate **12**, suggesting that neither the hydrolysis of the bromo ester **4** nor the bromination of the oxy carboxylate **11** took place under the present condition.

The bromo ester **4** was hydrolyzed to the bromo acid **5**, which was converted to the bromo amide **6** *via* the acid chloride in a 60% yield. Finally the bromo nitrile **7** was obtained by the triphenylphosphine–triethylamine dehydration of the bromo amide **6**.[20] Similarly the keto amide **8** in a yield of 73% and the keto nitrile **9** in a yield of 85% were obtained starting from the keto acid **1**. The sodium borohydride reduction of the keto nitrile **9** gave the oxy nitrile **10** in a yield of 99%.

Preparation of 1-Acetyl-4-acetoxyadamantane and Derived Compounds.—Principally, a 1,4-disubstituted adamantane may be prepared either by a selective γ (bridge) substitution of a 1-substituted adamantane (process a) or by a selective γ (bridgehead) substitution of a 2-substituted admantane (process b). Process a would be less accessible. Even in the simple free-radical substitution of a 1-substituted adamantane, attack at the γ (4) position was the minor reaction compared with the attack at the β (3) position.[22] In addition the stereoselectivity in the atom transfer step to the thus formed γ (4) radical was very low.[23] Process b, on the other hand, seems more promising because of a number of known examples of selective

(17) J. A. Peters, J. D. Remijnnse, A. van der Wiele, and H. van Bekkum, *Tetrahedron Lett.*, 3065 (1971).

(18) I. Tabushi, Z. Yoshida, and N. Takahashi, *J. Amer. Chem. Soc.*, **93**, 1820 (1971).

(19) Mechanistic and stereochemical details of this novel procedure for the bromination of an alcohol will be published later: I. Tabushi and Y. Aoyama.

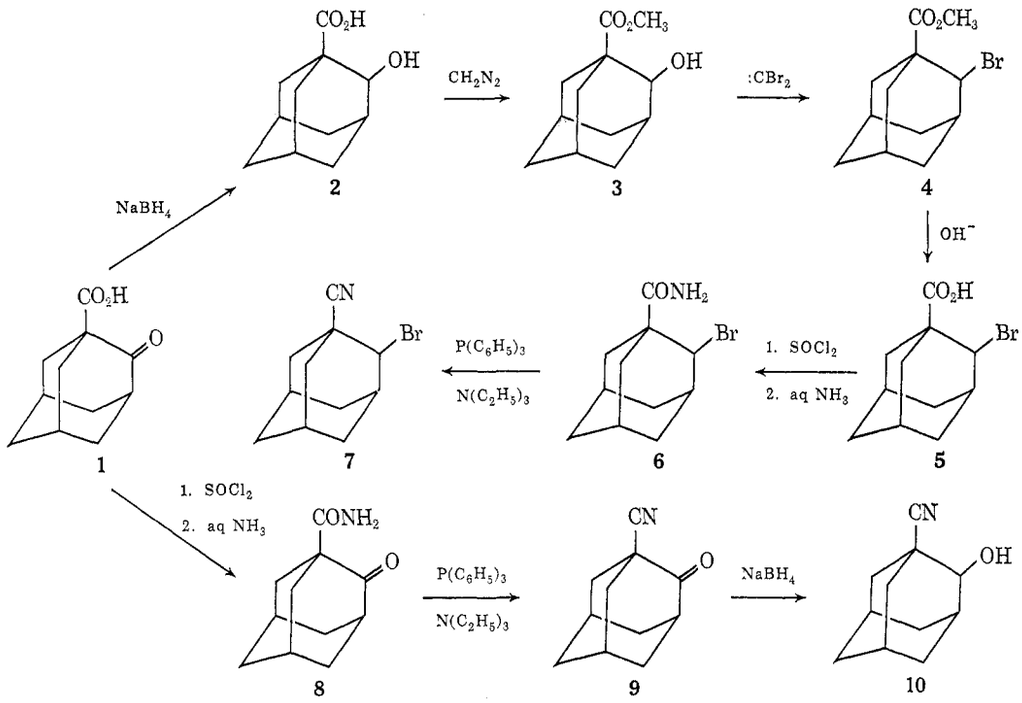
(20) The procedure was practically the same as that of Snatzke[21] for the preparation of 4-cyano-2,6-adamantanedione.

(21) G. Snatzke, *Chem. Ber.*, **105**, 244 (1972).

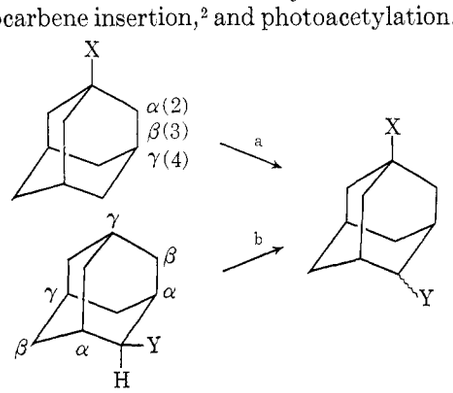
(22) (a) I. Tabushi, T. Okada, Y. Aoyama, and R. Oda, *Tetrahedron Lett.*, 1605 (1969); (b) G. J. Gleicher, T. L. Jackson, P. H. Owens, and J. D. Unruh, *ibid.*, 833 (1969); (c) P. H. Owens, G. J. Gleicher, and L. M. Smith, Jr., *J. Amer. Chem. Soc.*, **90**, 4122 (1968).

(23) Nearly a 1:1 stereoisomer ratio of 1,4 syn and 1,4 anti products was obtained in the NBS bromination of 1-*tert*-butyladamantane or the chlorocarbonylation of 1-methyladamantane: I. Tabushi, Y. Aoyama, and T. Okada, unpublished results.

CHART II

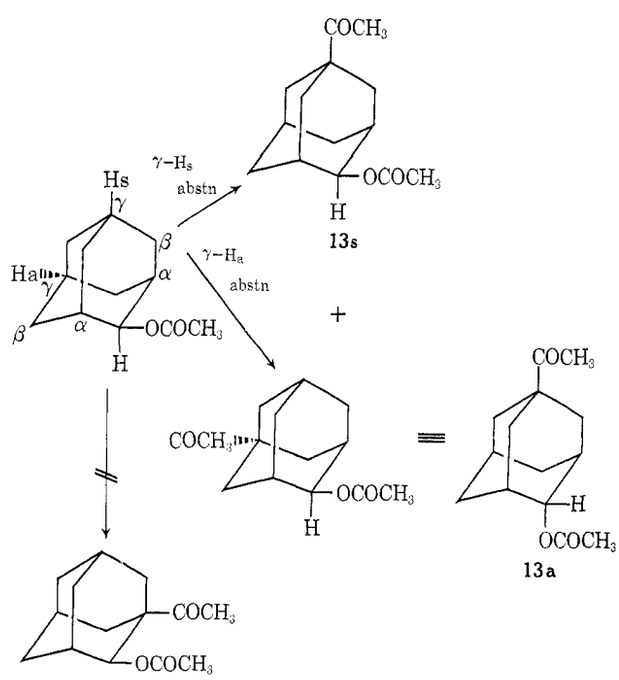


bridgehead reactions such as many ionic substitutions,[1] dichlorocarbene insertion,[2] and photoacetylation.[3]



The nonionic,[24] regioselective γ substitution of a 2-substituted adamantane was realized, for the first time, for 2-acetoxyadamantane in the photoacetylation, which was originally applied to adamantane to give rise to an exclusive formation of bridgehead acetyladamantane and was characterized by hydrogen abstraction by the photoexcited biacetyl triplet followed by the acetyl transfer from biacetyl to the thus formed adamantyl radical.[3]

High-pressure mercury lamp irradiation of a methylene chloride solution of 2-acetoxyadamantane and excess biacetyl resulted in the formation of, besides a large amount of the unreacted materials and undesired biacetyl-derived products, two bridgehead acetylated products (**13s** and **13a**) (*ca.* 10% after purification based on used 2-acetoxyadamantane, more than 40% based on consumed 2-acetoxyadamantane[26]) in a ratio of *ca* 1.7:1, although it was not yet decided which was which. That no appreciable bridge acetylation took place was confirmed by the lack of a signal assignable to the α proton of acetyl in the nmr spectra, in accord with the photoacetylation of adamantane.[3] The acetyl acetates **13s** and **13a** had by nmr (CCl_4, TMS) a sharp singlet at τ 8.00 (acetyl and acetoxy) and



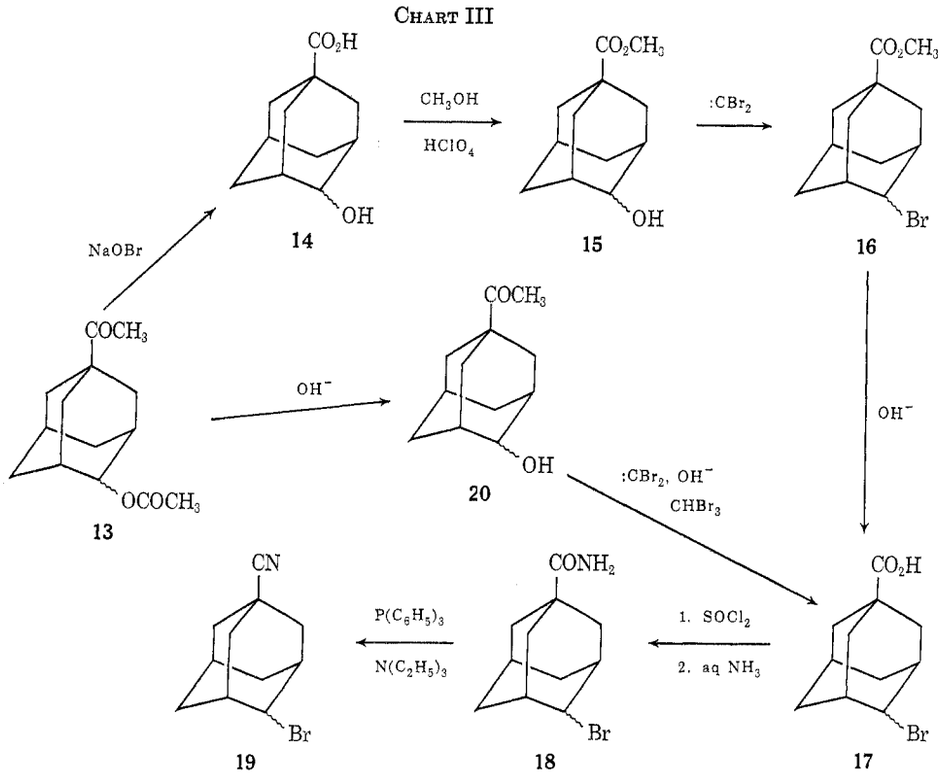
a broad singlet at τ 5.22 (acetoxy methine); ir 1705 (acetyl) and 1740 cm^{-1} (acetoxy). The acetyl acetates were converted to the oxy ester **15** (Chart III), different from the known 2-oxy-1-carbomethoxyadamantane (**3**). On this basis, it was concluded that the present photoacetylation took place exclusively at the γ bridgehead. This result may interestingly be compared with the less selective free-radical halogenation

(24) Almost regioselective γ-bromination (ionic) of adamantanone was reported.[9] Free-radical bromination of adamantanone, however, was less selective, giving all possible monobromoadamantanones.[25]

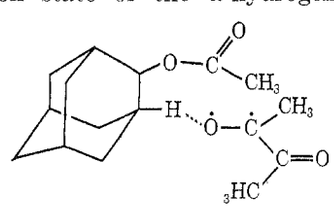
(25) I. Tabushi, Y. Aoyama, and Z. Yoshida, *J. Amer. Chem. Soc.*, **93**, 2077 (1971).

(26) Although a large amount of 2-acetoxyadamantane still remained at the end of the reaction, prolonged irradiation coupled with additional supply of biacetyl did not cause an appreciable improvement of the yield of **13**, presumably because of the accumulation of a biacetyl-derived product which had readily abstractable hydrogens.

CHART III



of adamantanone ethylene ketal,[27] 1,2-dimethyladamantane,[27] or adamantanone,[25] where the γ to α reactivity ratio ranged from 4 to 9. Although the electronic effect of the acetoxy group can never be neglected, the steric repulsion between the acetoxy group and the bulky photoexcited biacetyl in the hypothetical transition state of the α-hydrogen abstraction

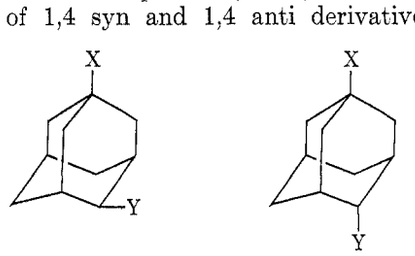


may be the best candidate for the origin of the observed high selectivity of γ-acetylation. This viewpoint is in accord with the conclusion drawn about the photoacetylation of adamantane derivatives, including diamantane.[28]

Contrary to the above-described high regioselectivity, a modest selectivity was observed for the abstraction of two kinds of γ hydrogens, one (H_s) which was syn to the acetoxy and the other (H_a) which was anti to the acetoxy. Abstraction of H_s or H_a would lead to the syn (**13s**) or anti (**13a**) acetylacetoxy derivative, respectively. This kind of "stereoselectivity"[29] will be discussed after the structural assignment is completed.

Some 1,4-disubstituted adamantanes derived from the acetylacetoxyadamantane (**13**) are summarized in Chart III.

Because an attempt to separate the two stereoisomers **13s** and **13a** in a preparative scale was not successful, all of the derived compounds (**14**–**20**) were obtained as mixtures of 1,4 syn and 1,4 anti derivatives. The



1,4 syn 1,4 anti

bromoform reaction of acetylacetoxyadamantane (**13**) in dioxane–water gave the oxy acid **14** in a 50% yield, which was quantitatively esterified to the oxy ester **15** and then converted to the bromo ester **16** *via* the dibromocarbene bromination in a yield of *ca.* 20%. The dibromocarbene bromination was accompanied with appreciable hydrolysis of the starting ester. The bromo acid **17**, bromo amide **18**, and bromo nitrile **19** were obtained in similar ways as their 1,2 counterparts (**5**, **6**, and **7**).

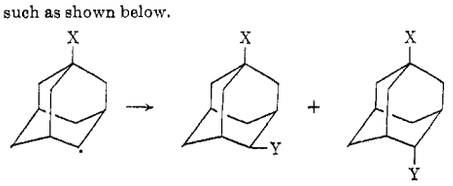
Interestingly, the dibromocarbene bromination of 4-oxy-1-acetyladamantane (**20**), obtained in a yield of 84% by the hydrolysis of acetylacetoxyadamantane (**13**), gave the bromo acid **17** in a yield of 37%. The observed conversion of acetyl to carboxyl seems to be the result of the bromoform reaction or some unknown reaction of that kind.

Glpc separation of 1,4 syn and 1,4 anti isomers was satisfactory for the bromo ester **16** and bromo nitrile

(27) I. Tabushi, Z. Yoshida, A. Togashi, M. Ozawa, and Y. Aoyama, unpublished results.

(28) I. Tabushi, Z. Yoshida, S. Kojo, and O. Fukunishi, unpublished results.

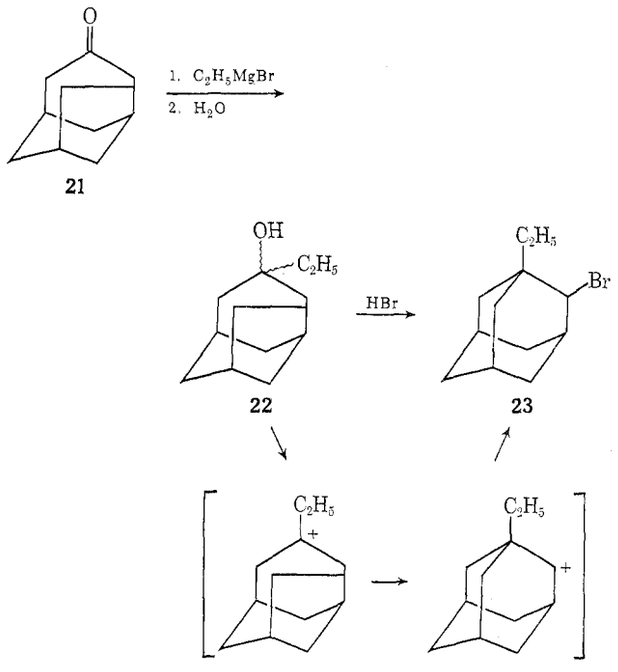
(29) It should be emphasized that this kind of "stereoselectivity" is essentially different from the more familiar stereoselectivity of an atom transfer process such as shown below.



19, where the observed stereoisomer ratios were *ca.* 2:1 and *ca.* 1:1, respectively, which were somewhat larger or smaller than the stereoisomer ratio of 1.7:1 of acetylacetoxyadamantane (**13**).

Preparation of 1-Ethyl-2-bromoadamantane *via* the Protoadamantane Route.—1-Ethyl-2-bromoadamantane (**23**) was prepared *via* the protoadamantane route[6] (Chart IV). Thus, readily available 4-proto-

CHART IV

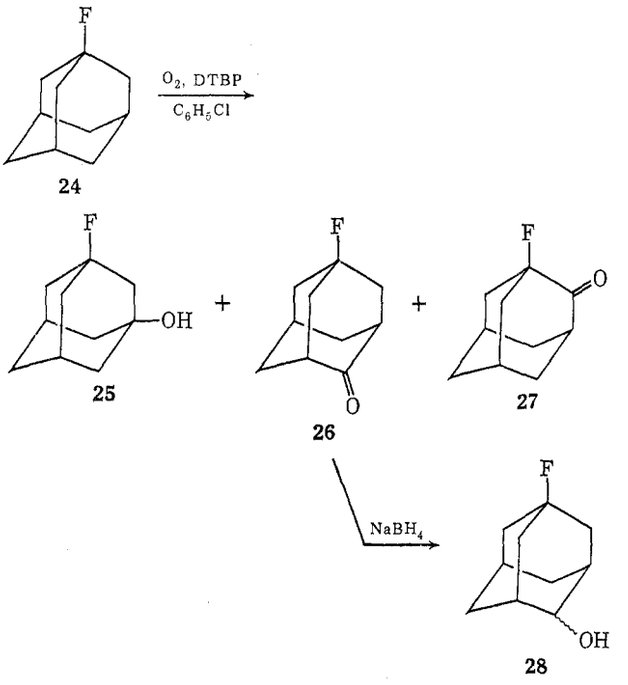


adamantanone (**21**)[30] was converted in 91% yield to the ethylhydroxy derivative **22** by reaction with ethylmagnesium bromide. Treatment of **22** with ethereal hydrogen bromide resulted in the formation of 1-ethyl-2-bromoadamantane (**23**) (61%).

Di-*tert*-butyl Peroxide Initiated Autoxidation of 1-Fluoroadamantane.—Autoxidation of 1-fluoroadamantane (**24**) in chlorobenzene was carried out using di-*tert*-butyl peroxide as an initiator under the vigorous flow of oxygen at 110–120°. As oxidates, there were obtained 1-fluoroadamantan-3-ol (**25**), 1-fluoroadamantan-4-one (**26**), and 1-fluoroadamantan-2-one (**27**) (in the order of glpc elution from a silicone column) in a ratio of *ca.* 6:2:1 (Chart V), which were readily separated by means of silica gel column chromatography. The order of glpc elution of the two ketones **26** and **27** was as expected from that of the corresponding 1,2- and 1,4-bromoadamantanones.[25] The expected upfield shift of the carbonyl stretching frequency of the 2 ketone **27** (1750 cm^{-1}) compared with that of the 4 ketone **26** (1740 cm^{-1}) was a further support for these structural assignments. From the major ketone **26** was obtained the oxy fluoride **28** by the sodium borohydride reduction in DMF (87%).

Except for some regioselective substitutions such as dichlorocarbene insertion or photoacetylation, more common free-radical substitutions are not recommendable for the second (or further) functionalization because of the low selectivities of attacking radicals re-

CHART V



sulting in the formation of tedious-to-separate mixtures of isomers.[22,31] A synthetic merit of the oxidation of a 1-substituted adamantane lies in the ease with which the products (an alcohol from the bridgehead attack and ketones from the bridge attack) are separated. Thus, despite low selectivity, autoxidation may sometimes still be an effective procedure for the preparation of adamantane derivatives such as fluoroadamantanones which otherwise are less accessible.

α Methine Proton Chemical Shifts of 1,2- and 1,4-Disubstituted Adamantanes.—Because of its rigidity, adamantane may be one of the most ideal models for the investigation of the effects of a substituent on the chemical shifts of protons which are fixed at definite angle and distance from a substituent. An especially interesting problem would be whether or not the effects of substituents are additive in di- or polysubstituted adamantanes. The nmr spectra of bridgehead-polysubstituted adamantanes[32] and 2,4-disubstituted adamantanes[33] have been studied along this line.

For a 1,2 or 1,4 derivative, a characteristic absorption of the α methine (geminal to the 2 or 4 substituent) proton was easily detected and is shown in Table I. The nmr spectrum of a 1,4 derivative (mixture of 1,4 syn and 1,4 anti isomers) except the oxy fluoride **28** showed single α proton absorption with some broadening, indicating that syn or anti orientation had little effect on the chemical shift. This result was in accord with the fact that no appreciable difference was observed in the chemical shifts of 4-axial and 4-equatorial protons of a 1-substituted adamantane.[32] In Table I are also shown the chemical shifts predicted from the additivity relationship based on the chemical

(30) W. H. W. Lunn, *J. Chem. Soc. C*, 2124 (1970).

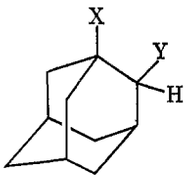
(31) Perfect determination of the product distribution of the free-radical bromination of 1-substituted adamantanes will be published soon: I. Tabushi and Y. Aoyama.

(32) R. C. Fort, Jr., and P. v. R. Schleyer, *J. Org. Chem.*, **30**, 789 (1965).

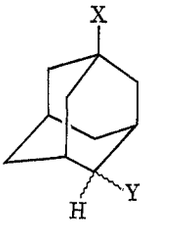
(33) F. W. van Deursen and P. K. Korver, *Tetrahedron Lett.*, 3923 (1967); (b) F. W. van Deursen and A. C. Udding, *Recl. Trav. Chim. Pays-Bas*, **87**, 1243 (1968); (c) F. W. van Deursen and J. Bakker, *Tetrahedron*, **27**, 4593 (1971).

TABLE I

CHEMICAL SHIFTS OF THE α METHINE PROTONS OF SOME 1,2- AND 1,4-DISUBSTITUTED ADAMANTANES[a]



X	CH_3	CH_3	C_2H_5	CO_2H	CO_2CH_3	CO_2CH_3	Cl	CN	CN
Y	OH	Br	Br	OH	OH	Br	Cl	OH	Br
Chemical shift, τ									
Obsd	6.52[b,c]	5.60[b,c]	5.67	5.90[b]	6.02	5.33	5.50[b,c] 5.65[b,e]	6.10	5.50
Calcd	6.42[d]	5.63[d]	5.72	5.96[d]	6.10	5.34	5.23[d]	5.90	5.15



X	$COCH_3$	$COCH_3$	CO_2CH_3	CO_2CH_3	Cl	F	CN
Y	$OCOCH_3$	OH	OH	Br	Cl	OH	Br
Chemical shift, τ							
Obsd	5.22	6.23	6.23	5.51	5.72[b,f,g]	6.32[f]	5.47
Calcd	5.26	6.18	6.27	5.51	5.69[d]	6.36	5.45

[a] In carbon tetrachloride with TMS as a standard. [b] In deuteriochloroform. [c] Reference 6b. [d] Calculated from the substituent shifts in deuteriochloroform. [e] Reference 6a. [f] Average of the chemical shifts of 1,4 syn and 1,4 anti isomers. [g] Reference 14.

shifts of monosubstituted adamantanes.[32] A marked difference in 1,2- and 1,4-disubstituted adamantanes may easily be seen in Table I. Without exception, the α methine proton chemical shifts of all of the 1,4-disubstituted adamantanes examined could be reproducible within 0.05 ppm by the additivity relationship, whereas such an additivity rule no longer held for 1,2-disubstituted derivatives, especially for 1-cyano-2-bromoadamantane, where a deviation as large as 0.35 ppm was observed. 1,2-Disubstituted derivatives having less electron-withdrawing groups such as alkyl or carbomethoxy had the α methine proton chemical shifts predictable from the additivity rule. Although only a limited set of substituents allows no decisive conclusion, a success or a failure of the additivity rule prediction about the α methine proton chemical shift of a 1,2-disubstituted adamantane may be dependent on the nature of the 1 substituent (alkyl, carbomethoxy, halo, or cyano) rather than on that of the 2 substituent (hydroxy or bromine).

Contrary to the bridgehead-polysubstituted adamantanes,[32] it was reported[33] that the α methine proton chemical shifts of some 2,4-disubstituted adamantanes were not predictable from the substituent shift additivity. No reasonable explanation, however, was made anywhere. Although we also hesitate to present a full interpretation of the present results, some specific interaction (steric or electronic) between the 1 and 2 substituents may be responsible for the failure of the additivity rule prediction about the α methine proton chemical shifts of some 1,2-disubstituted adamantanes.

Experimental Section

General.—Melting points (sealed capillary) and boiling points were uncorrected. Ir spectra were obtained with a Hitachi 215 spectrophotometer. Unless otherwise indicated, nmr spectra were taken in carbon tetrachloride with TMS and were recorded with a Varian T-60 spectrometer. Mass spectra were obtained with a Hitachi mass spectrometer. Microanalyses were performed either at the Microanalysis Center of Kyoto University or at the Faculty of Pharmaceutical Science of Kyushu University.

1-Carboxyadamantan-2-one (1).—According to the procedure of Peters, *et al.*,[17] **1** was prepared from homoadamantanone *via* four steps (selenium dioxide oxidation, periodic acid oxidative cleavage, esterification, and ester condensation followed by hydrolysis). Homoadamantanone was obtained by the hydrolytic rearrangement in polyphosphoric acid of 1-dichloromethyladamantane,[2] which was prepared by the dichlorocarbene insertion into adamantane in an emulsifying system.[2]

1-Carboxyadamantan-2-ol (2).—A mixture of 2.93 g of **1** and 320 mg of sodium borohydride in 10 ml of DMF was stirred for 1 hr in an ice bath and then for 18 hr at room temperature. Most of the DMF was removed *in vacuo* (140 mm) and, after acidification with hydrochloric acid, the mixture was extracted with three portions of 100 ml of ether. The combined ether extract was washed with water and dried over sodium sulfate. Evaporation of ether gave 2.96 g (quantitative) of **2** as a white solid: mp 125.5–126.5° (from 30% aqueous methanol); ir (KBr) 3345, 1705, 1280, 1252, 1208, and 1046 cm^{-1}; nmr ($CDCl_3$) τ 2.43 (broad s, 2 H, CO_2H and OH, disappeared on deuteration), 5.90 (broad s, 1 H, CHOH), and 7.6–8.6 (m, 13 H, remaining adamantyl protons).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.21. Found: C, 67.31; H, 8.19.

1-Carbomethoxyadamantan-2-ol (3).—To 800 mg of **2** was added an ether solution of excess diazomethane. The solution was stirred for 1 hr at room temperature. Evaporation of ether and excess diazomethane gave an oil which was distilled at 114–115° (0.4 mm) to give **3** in an almost quantitative yield: ir (neat) 3500, 1735, 1245, 1105, 1080, and 1053 cm^{-1}; nmr τ 6.02

(broad s, 1 H, CHOH), 6.33 (s, 3 H, CH_3), *ca.* 6.4 (broad s, 1 H, OH, disappeared on deuteration), and 7.7–8.6 (m, 13 H, remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 210 (M^+, 3.5), 192 (4.3), 182 (36), 151 (36), and 150 (100).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.61; H, 8.84.

1-Carbomethoxy-2-bromoadamantane (4).—To a vigorously stirred mixture of 2.7 g of **3**, 7 ml of benzene, 60 ml of 50% (w/w) aqueous sodium hydroxide, and 400 mg of triethylbenzylammonium chloride was added at room temperature 25 ml of bromoform in a period of 2 hr. The mixture was stirred for a further 2 hr, then 30 ml of water was added and the mixture was extracted with five portions of 70 ml of ether. Usual work-up (washing, drying, and evaporation) on the ether extract gave a brown, tarry material (1.9 g), which was chromatographed on a silica gel column. Elution with benzene–hexane (1:1) gave a yellow oil (0.96 g) which was distilled at 115–120° (0.3 mm) to give 360 mg (10%) of **4**: ir (neat) 1750, 1255, and 1092 cm^{-1}; nmr τ 5.33 (broad s, 1 H, CHBr), 6.36 (s, 3 H, CH_3), and 7.4–8.4 (complex m with peaks at 7.60, 7.77, 8.03, and 8.30, 13 H, remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 272 and 274 (M^+, 27.6), 241 and 243 (3.5), 213 (11), and 193 (100).

Anal. Calcd for $C_{12}H_{17}O_2Br$: C, 52.77; H, 6.27. Found: C, 52.63; H, 6.04.

Further elution with benzene gave a tarry material (*ca.* 1 g), the nmr spectrum of which showed no methyl signal. The structure was not further investigated.

The aqueous layer was acidified with hydrochloric acid and then extracted with three portions of 30 ml of methylene chloride. After evaporation of methylene chloride, the residue was esterified as above. Glpc analysis showed a single peak which was identified as the starting material **3** by means of glpc coinjection and spectral behavior. Thus recovered oxy ester **3** was further subjected to the dibromocarbene bromination.

1-Cyano-2-bromoadamantane (7).—A mixture of 159 mg of **4** and 80 mg of powdered sodium hydroxide in 20 ml of methanol containing 1 ml of water was refluxed for 5 hr. At the end of the reaction, 70 ml of water was added and the mixture was extracted with ether. From the ether extract was recovered a small amount of the unreacted ester. The alkaline layer was acidified with hydrochloric acid and extracted with methylene chloride. Drying and evaporation gave 100 mg (69%) of 1-carboxy-2-bromoadamantane (**5**) as an oil, which was dissolved in 2 ml of thionyl chloride. The mixture was refluxed for 2 hr, then thionyl chloride was evaporated *in vacuo* and the residue was dissolved in 0.5 ml of dry tetrahydrofuran. The tetrahydrofuran solution was added to 3 ml of 28% aqueous ammonia with stirring. The mixture was stirred at room temperature for 1 hr and extracted with methylene chloride. From the methylene chloride extract was obtained 61 mg (61% from **5**) of 1-carbamoyl-2-bromoadamantane (**6**), ir 1680 cm^{-1}. A solution of 30 mg of crude **6**, 60 mg of triphenylphosphine, 0.046 ml of triethylamine, and 35 mg of carbon tetrachloride in 3 ml of methylene chloride was refluxed for 15 hr. Water was added and the mixture was shaken. The organic layer was dried over sodium sulfate and evaporated to dryness and the residue was chromatographed on a silica gel column. After elution with hexane, **7** was eluted with hexane–benzene (1:1). Pure **7** was obtained by means of preparative glpc (silicone DC 550): ir (KBr) 2250, 970, and 735 cm^{-1}; nmr τ 5.50 (broad s, 1 H, CHCN), 7.5–8.5 (complex m with peaks at 7.60, 7.79, 8.05, and 8.30, 13 H, remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 239 and 241 (M^+, 2.35) and 161 (100).

1-Carbamoyladamantan-2-one (8).—A solution of 850 mg of **1** in 10 ml of thionyl chloride was refluxed for 2 hr, then excess thionyl chloride was removed *in vacuo*. The residue was dissolved in 6 ml of dry tetrahydrofuran and the tetrahydrofuran solution was added dropwise at 0° to 12 ml of 28% aqueous ammonia with stirring. Stirring was continued for 3 hr at room temperature. Water was added and the mixture was extracted with methylene chloride. The extract was dried over sodium sulfate and evaporated to dryness to give 620 mg (73%) of **8**: mp 177–177.5° (from cyclohexane); ir (KBr) 3425, 3345, 3293, 3195, 1713, 1663, 1619, and 1056 cm^{-1}; nmr ($CDCl_3$) τ 2.0–2.5 and 3.8–4.6 (very broad, each corresponded to 1 H, NH_2, disappeared on deuteration), and 7.2–8.3 (m with peaks at 7.38, 7.60, and 7.90, 13 H, adamantyl protons); mass spectrum *m/e* (rel intensity) 193 (M^+, 8.0), 164 (27.0), and 150 (100).

Anal. Calcd for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.14; H, 8.01; N, 7.23.

1-Cyanoadamantan-2-one (9).—Practically the same procedure for the preparation of **7** was applied to **8** to give **9** in a yield of 85%: mp 199.5–200.5° (from cyclohexane); ir (KBr) 2250, 1730, and 1062 cm^{-1}; nmr ($CDCl_3$ + CCl_4) τ 7.32 (broad s, 1 H, bridgehead proton vicinal to C=O), 7.67 (broad s, 4 H, methylene protons vicinal to CN), and 7.7–8.2 (m, 8 H, remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 175 (M^+, 51.8), 149 (22), 147 (100), and 146 (23.2).

Anal. Calcd for $C_{11}H_{13}ON$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.50; H, 7.23; N, 7.75.

1-Cyanoadamantan-2-ol (10).—A mixture of 300 mg of **9** and 35 mg of sodium borohydride in 10 ml of DMF was stirred at room temperature for 20 hr. Usual work-up gave 300 mg (99%) of **10** as a white crystal: mp 215.5–216° (from cyclohexane); ir (KBr) 2234, 1102, 1056, and 1031 cm^{-1}; nmr τ 6.10 (broad s, 1 H, CHOH) and 7.4–8.5 (complex m with peaks at 7.43, 7.70, 7.99, 8.20, and 8.27, 14 H, OH and remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 177 (M^+, 6.6), 150 (14.7), and 149 (100).

Anal. Calcd for $C_{11}H_{15}ON$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.68; H, 8.62; N, 7.81.

1-Acetyl-4-acetoxyadamantane (13).—A solution of 6.3 g of 2-acetoxyadamantane and 40 ml of biacetyl in 400 ml of methylene chloride was irradiated by a 450-W high-pressure mercury lamp for 35 hr in an ice bath. The methylene chloride was removed *in vacuo* and the residue was distilled. Distillation at *ca.* 90° (3 mm) gave a yellow to brown oil (*ca.* 13 g), which consisted mainly of 2-acetoxyadamantane and the pinacol derived from reductive dimerization of biacetyl.[34] About 5 g of 2-acetoxyadamantane was recovered by distillation after the removal of the pinacol *via* washing with water followed by adsorption on powdered calcium chloride. Further distillation at *ca.* 200° (3 mm) gave an oil (4 g), which was washed with water. A large amount of powdered calcium chloride was added and the mixture was allowed to stand for 3 days. Distillation at 130–150° (0.4 mm) gave a yellow oil (1.4 g), which was chromatographed on a silica gel column. About 600 mg of crude **13** was obtained by elution with benzene. A pure sample for analytical purposes was obtained by preparative glpc followed by distillation: ir (neat) 1740 ($OCOCH_3$), 1705 ($COCH_3$), and 1260 cm^{-1}; nmr τ 5.22 (broad s, 1 H, $CHOCOCH_3$), 8.00 (s, 6 H, $COCH_3$ and $OCOCH_3$), and 7.8–8.4 (m, 13 H, remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 236 (M^+, 5.3), 193 (85.6), 151 (100), and 133 (100).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.06; H, 8.39.

1-Carboxyadamantan-4-ol (14).—To a vigorously stirred solution of 2 g of sodium hydroxide and 1 ml of bromine in 12 ml of water was added a solution of 250 mg of **13** dissolved in 12 ml of dioxane in a period of 1 hr at 0°. The mixture was stirred at room temperature for 4 hr. Water (200 ml) was added and the mixture was extracted with ether. The alkaline layer was acidified with hydrochloric acid and extracted with methylene chloride. From the extract was obtained 110 mg (45%) of **14**, ir 1705 cm^{-1} (broad).

1-Carbomethoxyadamantan-4-ol (15), 1-Carbomethoxy-4-bromoadamantane (16), 1-Carboxy-4-bromoadamantane (17), 1-Carbamoyl-4-bromoadamantane (18), and 1-Cyano-4-bromoadamantane (19).—These compounds were prepared by similar procedures to those described for the preparations of their 1,2 counterparts (**3**, **4**, **5**, **6**, and **7**).

15 had ir (neat) 1737, 1250, and 1085 cm^{-1}; nmr τ 6.23 (broad s, 1 H, CHOH), 6.40 (s, 3 H, CH_3), and 7.7–8.4 (m, 14 H, OH and remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 210 (M^+, 4.3), 192 (34), 151 (100), and 133 (81).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.32; H, 8.60.

16 had ir (neat) 1735, 1250, 1080, and 733 cm^{-1}; nmr τ 5.51 (broad s, 1 H, CHBr), 6.40 (s, 3 H, CH_3), and 7.3–8.2 (m, 13 H, remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 213 and 215 (12.5) and 193 (100).

Anal. Calcd for $C_{12}H_{17}O_2Br$: C, 52.77; H, 6.27. Found: C, 52.93; H, 6.14.

19 had ir (KBr) 2270, 2250 (shoulder), 978, 925, and 740 cm^{-1}; nmr τ 5.47 (broad s, 1 H, CHCN) and 7.3–8.5 (m with peaks at 7.7 and 8.1, 13 H, remaining adamantyl protons), mass spectrum *m/e* (rel intensity) 239 and 241 (M^+, 0.2) and 161 (100).

1-Acetyladamantan-4-ol (20).—A solution of 700 mg of **13** and

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500 mg of powdered sodium hydroxide in 50 ml of methanol containing 1.5 ml of water was refluxed for 0.5 hr. Water (300 ml) was added and the mixture was extracted with four portions of 30 ml of ether. The ether extract was washed with water and dried over sodium sulfate. Glpc analysis showed that the yield of **20** was 84%. The ether was evaporated and the residue was distilled at 114–115° (0.4 mm) to give **20**: ir (neat) 3450, 1703, 1070, and 1040 cm^{-1}; nmr τ 6.23 (broad s, 1 H, CHOH), 7.94 (s, 3 H, CH_3), and 7.6–8.9 (complex m with peaks at 7.70, 8.23, 8.45, and 8.68, 14 H, OH and remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 194 (M^+, 6.7), 151 (100), and 133 (52).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.33. Found: C, 73.83; H, 9.37.

Dibromocarbene Bromination of 20.—The reaction of **20** (270 mg) with dibromocarbene was carried out in a similar way as described for the preparation of **4**. From the alkaline layer was obtained 130 mg (37%) of **17**.

1-Ethyl-2-bromoadamantane (23).—To 10 ml of ether solution of ethylmagnesium bromide prepared from 146 mg of magnesium and 670 mg of ethyl bromide was added a solution of 308 mg of 4-protoadamantanone (**21**)[30] in 10 ml of ether. The mixture was refluxed for 2 hr. A saturated ammonium chloride solution (10 ml) was added and the ether layer was separated. The aqueous layer was extracted with 20 ml of ether. The combined ether extract was washed with water, dried over sodium sulfate, and evaporated to give 335 mg (91%) of 4-ethyl-4-hydroxyprotoadamantane (**22**) as an oil. No further purification was attempted on **22**. A solution of 115 mg of **22** in 10 ml of ether saturated with hydrogen bromide was refluxed for 0.5 hr. Evaporation of ether gave an oil, which was distilled to give 100 mg (61%) of **23**: ir (CCl_4) 962, 924, 890, 648, and 617 cm^{-1}; nmr τ 5.67 (broad s, 1 H, CHBr), 7.58 (broad s, 1 H, bridgehead proton adjacent to Br), 7.74 (broad s, 2 H, other bridgehead protons), 8.17, 8.27 (m, 10 H, remaining adamantyl protons), 8.4–9.0 (2 H, CH_2CH_3), and 9.0–9.4 (3 H, CH_2CH_3); mass spectrum *m/e* (rel intensity) 242 and 244 (M^+, 2.5), 213 and 215 (3.0), and 163 (100).

Anal. Calcd for $C_{12}H_{19}Br$: C, 59.27; H, 7.87. Found: C, 59.50; H, 8.04.

Autoxidation of 1-Fluoroadamantane.—A solution of 2.6 g of 1-fluoroadamantane (**24**) in 18 ml of chlorobenzene was heated at 120°. To this solution was added, under vigorous flow of oxygen, a mixture of 20 ml of di-*tert*-butyl peroxide and 8 ml of chlorobenzene in a period of 7 hr. The mixture was heated at the same temperature for 6 hr. After cooling, a small amount of ferrous oxide was added and the mixture was allowed to stand overnight. Chlorobenzene was distilled *in vacuo* (50 mm) and the residue was chromatographed on a silica gel column. Elution with pentane (300 ml) gave 343 mg of the recovered 1-fluoroadamantane. Elution with benzene (200 ml) gave white solid (350 mg), which consisted of 1-fluoroadamantan-4-one (**26**), 1-fluoroadamantan-2-one (**27**), and 1-fluoroadamantan-3-ol (**25**). Further elution with benzene (1000 ml) gave **25** (490 mg). The ketone fraction was rechromatographed on a silica gel column to complete the separation of **26** and **27** using hexane–benzene (1:1) as an eluent. By a controlled elution, there were obtained 27 mg of pure **27**, 90 mg of pure **26**, 80 mg of a mixture of these, and 150 mg of **25**.

26 had mp 170–171° (after sublimation *in vacuo*); ir (KBr) 1740, 1090, 1065, 1055, 965, and 920 cm^{-1}; nmr τ 7.40 (broad s, 2 H, bridgehead protons adjacent to C=O) and 7.4–8.6 (m with peaks at 7.83, 8.06, and 8.30, 11 H, remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 168 (M^+, 100), 149 (16.7), 140 (11.7), and 97 (100).

Anal. Calcd for $C_{10}H_{13}OF$: C, 71.40; H, 7.79. Found: C, 71.57; H, 8.06.

27 had mp 213–216° (after sublimation *in vacuo*); ir (KBr) 1750, 1123, 1097, 1060, 970, 880, and 838 cm^{-1}; mass spectrum *m/e* (rel intensity) 168 (M^+, 55.0), 149 (28.6), 140 (28.6), and 97 (100).

Anal. Calcd for $C_{10}H_{13}OF$: C, 71.40; H, 7.79. Found: C, 71.11; H, 7.75.

1-Fluoroadamantan-4-ol (28).—A mixture of 153 mg of **26** and 17 mg of sodium borohydride in 3 ml of DMF was stirred at room temperature for 15 hr, then 3 ml of water was added and the mixture was stirred for 10 min. Water was added and the product was extracted into three portions of 50 ml of ether. Washing, drying, and evaporation of the combined ether extract gave 133 mg (87%) of **28**: ir (KBr) 1103, 1078, 1057, and 910 cm^{-1}; nmr τ 6.23, 6.40 (broad s, 1 H, CHOH), and 7.4–8.6 (m with peaks at 7.87, 8.20, and 8.36, 14 H, OH and remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 170 (M^+, 8.7) and 151 (100).

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Registry No.—**1**, 40556-86-3; **2**, 40556-88-5; **3**, 41171-74-8; **4**, 41171-75-9; **7**, 41171-76-0; **8**, 41171-77-1; **9**, 41171-78-2; **10**, 41171-79-3; *syn*-**13**, 41163-62-6; *anti*-**13**, 41163-63-7; *syn*-**14**, 41163-64-8; *anti*-**14**, 41163-65-9; *syn*-**15**, 41163-66-0; *anti*-**15**, 41163-67-1; *syn*-**16**, 41163-68-2; *anti*-**16**, 41163-69-3; *syn*-**20**, 41163-70-6; *anti*-**20**, 41163-71-7; **21**, 27567-85-7; **23**, 41171-81-7; **24**, 768-92-3; **26**, 41171-83-9; **27**, 41171-84-0; *syn*-**28**, 41163-72-8; *anti*-**28**, 41163-73-9; homoadamantanone, 24669-56-5; 1-dichloromethyladamantane, 41171-86-2; bromoform, 75-25-2; 2-acetoxyadamantane, 19066-22-9; biacetyl, 431-03-8; ethyl bromide, 74-96-4.