Synthesis of 1,2- and 2,4-Disubstituted Adamantanes. The Protoadamantane Route[1,2]

DIETER LENOIR,[3a] ROBERT GLASER,[3b] PIERRE MISON,[3c] AND PAUL VON RAGUE SCHLEYER*

Department of Chemistry, Princeton University, Princeton, New Jersey 08540

Received October 15, 1970

A number of 1,2-disubstituted adamantanes have been prepared easily by using the facile rearrangement of 4-substituted protoadamantanes as the synthetic principle. The conversion of 4-methylprotoadamantan-4-ol (**3**) to the 1-methyladamantane 2-substituted alcohol **4**, bromide **5**, acetamide **6**, amine **7**, and ketone **8** are high-yield processes. The reaction of 4-protoadamantanone (**2**) with PCl_3-PCl_5 afforded 4-chloroprotoadamantene (**10**) as well as the 1,2-dichloroadamantane (**11**) rearrangement product. The dichloride (**11**) was also prepared by reaction of thionyl chloride on adamantane-1,2-diol (**13**). In addition, the Ritter reaction on adamanto[2,1-*d*]oxazolidin-2-one (**1**) gave 1-*N*-acetyladamantane-1,2-diamine hydrochloride (**14**) and its hydrolysis product, adamantane-1,2-diamine dihydrochloride (**15**). 2,4-Disubstituted adamantanes can also be prepared *via* protoadamantane precursors. Starting from protoadamantene (**19**), epoxidation followed by acid hydrolysis afforded adamantane-2a,4a-diol (**27**). Bromination of protoadamantene (**19**) gave a 2:1 ratio of 2a,4a-dibromoadamantane (**23**) and 2e,4a-dibromoadamantane (**25**).

In recent years the synthesis of a number of 1,2-disubstituted adamantane derivatives[1,2,4-10] has been reported. These compounds are difficult to obtain by the usual substitution procedures utilized in adamantane chemistry.[11] For example, ionic substitution of 1-adamantane derivatives tends to give bridgehead substitution exclusively to yield 1,3 products.[11] Free-radical substitution of 1-adamantane derivatives gives a difficult-to-separate mixture of products rich in 1,3 and 1,4 derivatives,[12] whereas radical bromination of adamantanone gives a mixture of all the possible monobrominated adamantanones.[13]

The most successful general approach is based on the work of Curran and Angier[4] who prepared adamanto-[2,1-*d*]oxazolidin-2-one (**1**) by an intramolecular nitrene insertion process.[14] The availability of **1** afforded an opportunity to prepare many other 1,2-difunctional derivatives.[4,7,8] While we record here the preparation of two new 1,2-difunctional derivatives *via* this versatile starting material, we wish to describe a new synthetic route based on rearrangement from protoadamantane precursors.

A second class, 2,4-disubstituted adamantanes, has been synthesized either by addition reactions to 2,4-dehydroadamantane[15] or by the π-route closures of bicyclo[3.3.1]non-3-en-7-acylium ions, generated from 4-oxohomoadamantan-5-one in sulfuric acid.[16] A new synthetic route to such compounds based on protoadamantane precursors has also been developed.

Results and Discussion

4-Protoadamantanone (**2**) is now readily available.[1a,17-19] Rearrangement of protoadamantanes to adamantanes generally occurs readily because of the greater thermodynamic stability of the adamantane skeleton.[1a,17]

This principle can be put to synthetic advantage. For example, 4-methylprotoadamantan-4-ol (**3**), an isomeric mixture obtained by the Grignard reaction on **2**, is readily converted by the action of aqueous acid to 1-methyladamantan-2-ol (**4**) (see Scheme I). If ethereal HBr is employed, the product is the corresponding bromide **5**. The Ritter reaction on **3** gives amide **6** which can be converted to amine **7**. 1-Methyladamantan-2-one (**8**) can be prepared easily in one step by chromic acid oxidation of **3**, or the rearrangement product **4** can be isolated and then oxidized.

All of these reactions proceed cleanly and with high yield and therefore offer a new pathway to the synthesis of 1-alkyl-2-adamantyl compounds. The only method reported for the preparation of 1-methyl-2-adamantanes utilizes a sulfuric acid oxidation of 1-methyladamantane.[20] 1-Methyladamantan-2-one (**8**) is obtained in very low yield (3-5%) and is very difficult to separate from the other oxidation products.[21] The nmr spectra of the rearranged products **4**–**8** are consistent with their proposed structures. Whereas the spectra of the epimeric alcohols **3** are complex and show the methyl singlets at τ 8.75 and 8.61 for the 4-exo and 4-endo epimers,

(1) Paper III of a series on protoadamantane chemistry. (a) Paper I, D. Lenoir and P. v. R. Schleyer, *Chem. Commun.*, 941 (1970). (b) Paper II reported this work in preliminary communication form, D. Lenoir, P. v. R. Schleyer, C. A. Cupas, and W. E. Heyd, *ibid.*, 26 (1971).

(2) Dr. M. A. McKervey has kindly informed us of work similar to that reported here: B. D. Cuddy, D. Grant, and M. A. McKervey, *ibid.*, 27 (1971).

(3) (a) NIH International Postdoctoral Fellow, 1969–1970; (b) NIH Postdoctoral Fellow, 1969–1970; (c) CNRS and NATO Postdoctoral Fellow, 1970–1971.

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

(5) M. A. McKervey, *Chem. Ind. (London)*, 1791 (1967).

(6) W. H. W. Lunn, W. D. Podmore, and S. S. Szinai, *J. Chem. Soc. C*, 1657 (1968).

(7) P. v. R. Schleyer and V. Buss, *J. Amer. Chem. Soc.*, **91**, 5880 (1969); V. Buss, R. Gleiter, and P. v. R. Schleyer, *ibid.*, in press.

(8) J. C. Martin and B. R. Ree, *ibid.*, **91**, 5882 (1969); B. R. Ree and J. C. Martin, *ibid.*, **92**, 1660 (1970).

(9) H. Stetter, H. G. Thomas, and K. Meyer, *Chem. Ber.*, **103**, 863 (1970).

(10) J. K. Chakrabarti, S. S. Szinai, and A. Todd, *J. Chem. Soc. C*, 1303 (1970).

(11) See reviews: (a) R. C. Fort, Jr., and P. v. R. Schleyer, *Chem. Rev.*, **64**, 277 (1964); (b) R. C. Bingham and P. v. R. Schleyer, *Fortschr. Chem. Forsch.*, in press.

(12) I. Tabushi, T. Okada, Y. Aoyama, and R. Oda, *Tetrahedron Lett.*, 4069 (1969).

(13) (a) I. Tabushi, personal communication; (b) D. Lenoir, unpublished esults.

(14) (a) Other intramolecular processes have already been reported that give four- and five-membered rings fused to the adamantane skeleton.[6,10,14b] (b) R. B. Gagonan, J. C. Dalton, and N. J. Turro, *J. Amer. Chem. Soc.*, **92**, 4752 (1970).

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

(16) M. A. McKervey, D. Faulkner, and H. Hamill, *ibid.*, 1971 (1970).

(17) M. L. Sinnot, H. J. Storesund, and M. C. Whiting, *Chem. Commun.*, 1000 (1969).

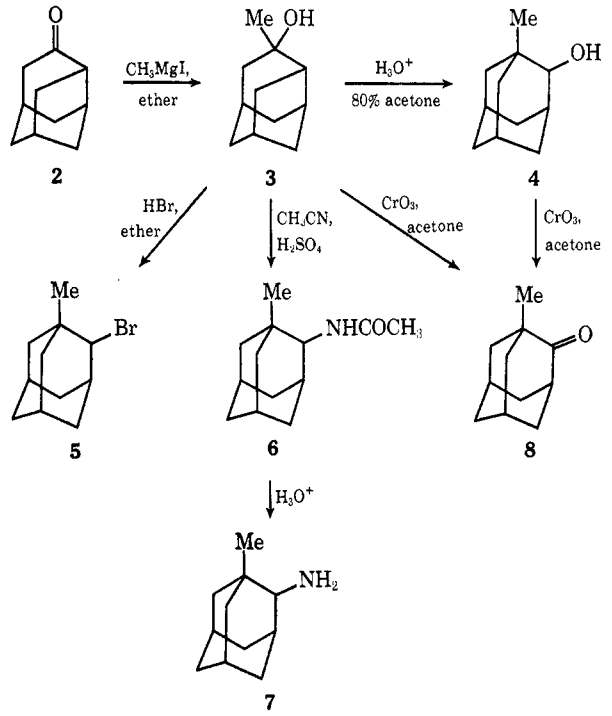
(18) R. M. Black and G. B. Gill, *ibid.*, 972 (1970).

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

(20) H. W. Geluk and J. L. M. A. Schlatmann, *Recl. Trav. Chim. Pays-Bas*, **88**, 13 (1969).

(21) (a) E. Ōsawa, unpublished results; (b) D. Lenoir and S. Pouls, unpublished results.

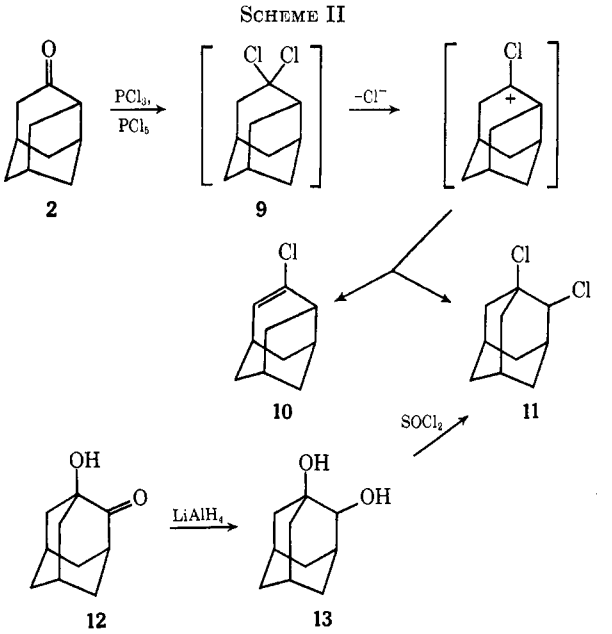
SCHEME I



respectively, the spectra of **4–8** are considerably simpler and the methyl protons are more shielded.

No synthesis of a 1,2-dihaloadamantane has been reported in the literature; the "protoadamantane route" provides a method of preparation. Reaction of 4-protoadamantanone (**2**) with a PCl_3–PCl_5 mixture at 0° gives a 2:1 mixture of the chlorinated products **10** and **11** which can be separated either by column-chromatography on silica gel or by preparative glpc (see Scheme II). This result is somewhat surprising,

SCHEME II

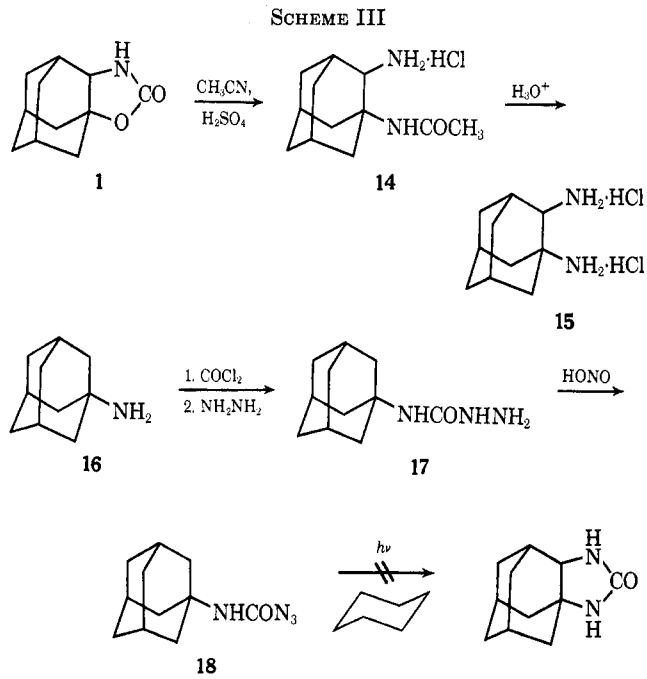


since all the other 4-protoadamantyl derivatives studied rearranged almost completely to the 2-adamantyl isomers. A possible intermediate, 4,4-dichloroprotoadamantane (**9**), could not be isolated under the conditions utilized.

Besides undergoing the usual rearrangement to product **11**, the cation arising from **9** can eliminate a proton from C-5 to give olefin **10**. The nmr spectrum of compound **10** is consistant with its proposed structure and shows a four-line pattern (A part of an AMN spectrum) of one vinylic proton centered at τ 3.79 ($J_{H\text{-}5,H\text{-}6}$ = 8 Hz and $J_{H\text{-}5,H\text{-}8}$ = 1.8 Hz). The structure of 1,2-dichloroadamantane (**11**) was proven by synthesizing this compound by an unambiguous route. 2-Ketoadamantan-1-ol (**12**)[7,8] was reduced with $LiAlH_4$ in ether to adamantane-1,2-diol (**13**). This was converted to **11** (*ca.* 45% yield) by treatment with $SOCl_2$.

The preparation of diamine **15** involved the reaction of **1** under Ritter conditions (Scheme III). This afforded 1-*N*-acetyladamantane-1,2-diamine isolated as the hydrochloride salt **14**. Acid hydrolysis of **14** yielded adamantane-1,2-diamine as the dihydrochloride monohydrate salt **15**. Attempts to prepare this diamine in a more direct way by the photolysis of **18** under the conditions tried (Scheme III) were not successful. Despite the obvious similarity between this route and that used to prepare **1** (as well as that used to prepare a fused five-membered ketone[10]), photolysis of **18** under similar conditions led to a mixture of products which nmr indicated chiefly to result from nitrene insertion into the cyclohexane used as solvent. Change of solvent to benzene still gave a complex mixture of photolysis products. Even the insertion reaction reported by Curran and Angier[4] gives an intermolecular nitrene insertion into the solvent (*ca.* 40%) besides the formation of **1**. The photochemical decomposition of carbamoyl azide (NH_2CON_3) in alcoholic solvents was reported to give a mixture of products arising from nitrene insertion into the solvent and from HN_3 elimination.[22] The conformation of the intermediate nitrene from **18** may be trans, precluding intramolecular attack.

SCHEME III

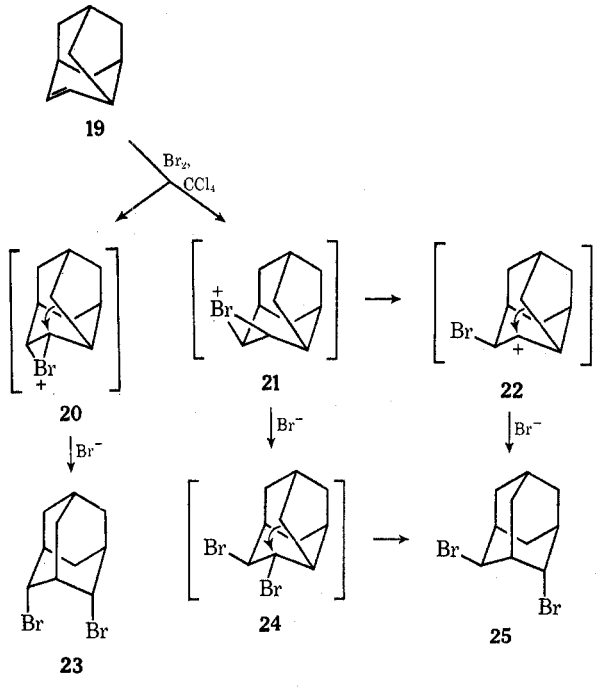


Protoadamantene (**19**)[1] is available by the Wolff–Kishner reduction of the ketone mixture arising from the thermal rearrangement of allyloxycyclohepta-

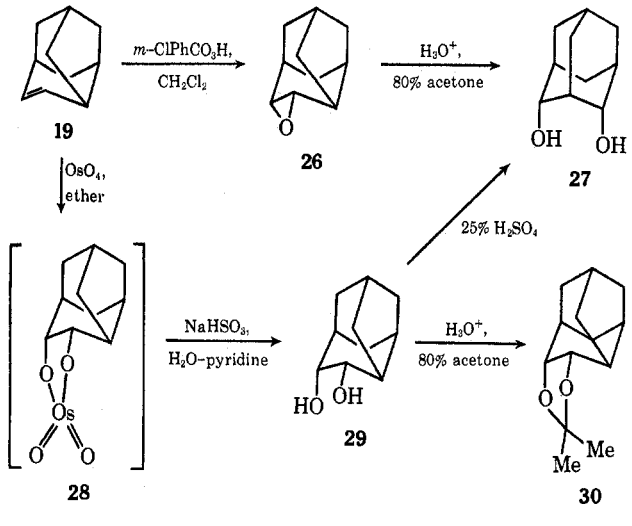
(22) R. Kreher and G. H. Berger, *Tetrahedron Lett.*, 369 (1965).

triene.[23] Recently, the synthesis of **19** in 34% yield by the pyrolysis of 4-protoadamantyl xanthate has also been reported.[18,24] Protoadamantene (**19**) proves to be a valuable starting material for the synthesis of 2,4-disubstituted adamantanes (Schemes IV and V).

SCHEME IV



SCHEME V



Treatment of **19** with 1 mol of bromine in CCl_4 gave a 2:1 mixture of the isomeric dibromides, 2a,4a-dibromoadamantane (**23**) and 2a,4e-dibromoadamantane (**25**).[1b,2] Whereas the formation of 2a,4e-dibromoadamantane (**23**) can be explained best by the ring opening of the *exo*-4,5-protoadamantyl bromonium ion **20** shown, the 2a,4e isomer **25** can be visualized as being formed by two plausible mechanistic pathways. In the first pathway, the *endo*-4,5-protoadamantane bromonium ion **21**, formed from **19** along with **20**, undergoes nucleophilic attack to give *trans*-4,5-dibromoprotoadamantane (**24**). This dibromide would be expected to be quite unstable toward rearrangement with internal return to **25**. The endo bromonium ion **21** could open to the *endo*-5-bromoprotoadamant-4-yl cation **22**; "leakage" allowing bond migration and nucleophilic bromide attack would give **25**. There is evidence for such a "leakage" mechanism in the solvolysis of *endo*-4-protoadamantyl derivatives.[1a]

m-Chloroperbenzoic acid reacts with **19** in methylene chloride to give a protoadamantane 4,5-epoxide product; the exo isomer **26** is the major constituent of this mixture, along with a minor amount of the endo isomer. The configuration of the major isomer was demonstrated by $LiAlH_4$ reduction of the epoxide mixture; the main product was *exo*-protoadamantan-4-ol. Treatment of epoxide **26** with 80% aqueous acetone containing a trace of HCl afforded adamantane-2a,4a-diol (**27**), rather cleanly. It is reasonable that diol **27** is formed by ring opening of the *exo*-4,5-protoadamantyl oxonium ion (**26** H^+) with concurrent skeletal rearrangement and nucleophilic attack by water.

Protoadamantene (**19**) reacts with OsO_4 in ether almost instantaneously to form a black osmate **28** precipitate (see Scheme V). The osmate **28** was cleaved with $NaHSO_3$ in 50% aqueous pyridine to give *exo*-protoadamantane-4,5-*cis*-diol (**29**). The configuration of the diol **29** was determined by analysis of the nmr spectral pattern of the protons at C-4 and C-5.[25] Attempted rearrangement of **29** to the more stable adamantane-2a,4a-diol (**27**) by refluxing with 80% aqueous acetone containing a trace of hydrochloric acid gave acetonide **30** instead of **27**. The rearrangement of **29** to **27** had to be carried out under more vigorous conditions: 25% sulfuric acid and a temperature of 100°. However, after 1.5 hr **29** gave a 80% crude yield of **27**.

Special aspects of the spectral features of **23** and of **27** have already been commented on in the preliminary communication.[1b]

The examples we have presented in this paper demonstrate that both 1,2- and 2,4-disubstituted adamantanes can be prepared readily from protoadamantane precursors.

Experimental Section

Routine infrared spectra were taken on a Perkin-Elmer 237B spectrophotometer and were run in KBr pellets unless specified. Higher resolution infrared spectra were taken of some compounds on a Perkin-Elmer 421 double-beam spectrophotometer. Unless otherwise stated, pmr spectra were taken in $CDCl_3$ with TMS acting as internal standard and were recorded on a Varian A-60A spectrometer. Mass spectra were taken on an AEI MS-9 spectrometer at 150° and 70 eV. With $(C_4F_9)_3N$ as reference, high-resolution mass spectral analyses were performed on the parent peaks of some compounds, and the calculated values were taken from J. H. Beynon and A. E. Williams, "Mass and Abundance Tables for Use in Mass Spectrometry," Elsevier, Amsterdam, 1963. Melting points were determined on a Mettler FP1 apparatus in a sealed capillary and are uncorrected. Elemental analyses were determined by G. Robertson, Florham Park, N. J.

4-Methylprotoadamantan-4-ol (3).—Methylmagnesium iodide was prepared by reaction of 0.486 g of magnesium and 2.84 g of methyl iodide in 20 ml of absolute ether. To this solution 1.0 g (6.7 mmol) of 4-protoadamantanone (**2**),[1a,17-19] dissolved in 20 ml of ether, was added dropwise during 10 min with stirring.

(23) C. A. Cupas, W. Schuman, and W. E. Heyd, *J. Amer. Chem. Soc.*, **92**, 3237 (1970).

(24) Pyrolysis of 2-adamantyl trifluoroacetate at 350° gives a hydrocarbon fraction (*ca.* 30%) which consists of nearly equal amounts of adamantane, 2,4-dehydroadamantane, and protoadamantene: D. Raber, unpublished results.

(25) D. Lenoir and P. v. R. Schleyer, unpublished results.

The mixture was refluxed for 2 hr and worked up by addition of 10 ml of saturated ammonium chloride solution. The ether phase was separated, washed with water, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to give 1.02 g (94%) of crude 4-methylprotoadamantan-4-ol (**3**). After sublimation *in vacuo*, glpc revealed that the solid consisted of two products in the ratio of 2:1. These were shown to be the epimeric 4-exo and 4-endo alcohols, respectively.[1a] Complete experimental details on the separation and characterization of the epimeric alcohols **3** will be published elsewhere.[25] The mixture of the epimeric alcohols **3** was used without further separation. The nmr of the 4-endo alcohol showed a complex multiplet with broad peaks at τ 7.80, 7.90, 8.12, 8.20, 8.40, 8.50 (m, 15, protoadamantyl H and OH), and 8.61 (s, 3, CH_3). The nmr of the 4-exo alcohol showed a complex multiplet with broad peaks at τ 7.80, 7.93, 8.10, 8.25, 8.50, 8.68 (m, 15, protoadamantyl H and OH), and 8.75 (s, 3, CH_3).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.10; H, 10.60. Found: C, 79.46; H, 10.91.

1-Methyladamantan-2-ol (4).—To 0.50 g (3.0 mmol) of **3** dissolved in 20 ml of 80% aqueous acetone, 1 drop of concentrated hydrochloric acid was added and the mixture refluxed for 10 min. The solution was concentrated *in vacuo* to a small volume, and then the mixture was extracted with ether. After drying over anhydrous sodium sulfate and evaporation *in vacuo*, 0.48 g of crude product was obtained. Sublimation *in vacuo* gave 0.43 g (85%) of 1-methyladamantan-2-ol (**4**): mp 168.5–170.0°; nmr τ 6.52 (broad s, 1, CHOH), complex multiplet with broad peaks at 8.50, 8.40, 8.20 (m, 15, adamantyl H and OH), and 9.12 (s, 3, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 166 (27, M^+) (measured 166.1358, calcd for $C_{11}H_{18}O$ 166.1356, 151 (15), 148 (100), 133 (22), 119 (5), 107 (14), 106 (22), 105 (16), 93 (58), and 79 (24).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.10; H, 10.60. Found: C, 79.12; H, 10.50.

1-Methyladamant-2-yl Bromide (5).—To 0.20 g (1.2 mmol) of **3**, 10 ml of ether saturated with hydrogen bromide was added. The solution was refluxed for 30 min, and evaporated *in vacuo*, and the residue sublimed to give 0.21 g (76%) of 1-methyladamant-2-yl bromide (**5**): mp 99–101°; nmr τ 5.60 (broad s, 1, CHBr), 7.76 (broad s, 1, CHCHBr), complex multiplet with broad peaks at 8.25, 8.10 (m, 14, adamantyl H), and 9.10 (s, 3, CH_3).

Anal. Calcd for $C_{11}H_{17}Br$: C, 57.65; H, 7.48; Br, 34.87. Found: C, 57.58; H, 7.38; Br, 34.74.

***N*-Acetyl-1-methyladamantane-2-amine (6).**—To 4 ml of acetonitrile, cooled in an ice bath, 1.5 ml of concentrated sulfuric acid was added dropwise with stirring, followed by 0.161 g (0.96 mmol) of **3**. The reaction mixture was allowed to warm and was kept at room temperature for 3 hr. After quenching in ice, a 10% solution of potassium hydroxide was added until basic pH, causing a solid to precipitate. The mother liquor was filtered off and the solid residue washed two times with water. The wet solid was dissolved in 5 ml of absolute ethanol and evaporated *in vacuo* to remove any water present. Sublimation *in vacuo* of the residue gave 0.170 g (90%) of *N*-acetyl-1-methyladamantane-2-amine (**6**): mp 139–141°; ir 3320 (NH), 1640 (C=O), and 1550 cm^{-1} (NH, b); nmr τ 4.0 (broad s, 1, NHCOMe), 6.12 (broad d, 1, J = 10 Hz, CHNHCOMe), 7.99 (s, 3, $NHCOCH_3$), 7.9–9.0 (m, 13, adamantyl H), and 9.33 (s, 3, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 207 (100 ,M^+), 192 (6), 164 (8), 148 (43), 133 (22), 119 (5) 107 (14), 106 (22), 105 (16), 93 (58), and 79 (24).

Anal. Calcd for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.79. Found: C, 75.37; H, 10.49; N, 6.99.

1-Methyladamantane-2-amine (7).—To 84 mg (0.4 mmol) of **6**, 9 ml of concentrated hydrochloric acid and 2 ml of methanol were added. The mixture was heated to reflux with stirring for 3 days and then cooled. After addition of excess potassium hydroxide, the aqueous solution was extracted three times with chloroform (50 ml each). The combined organic layers were dried over anhydrous potassium carbonate, filtered, and evaporated to yield a solid. Sublimation of the residue gave 60 mg (90%) of 1-methyladamantyl-2-amine (**7**): mp 140–142°; ir (Nujol mull) 3400 (broad NH) and 1605 cm^{-1} (NH, b asym); nmr τ 7.37 (broad s, 1, $CHNH_2$), 7.9–9.0 (m, 15, adamantyl H and NH_2), and 9.21 (s, 3, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 165 (100, M^+), 164 (89), 148 (89), 133 (24), 119 (8), 106 (30), 105 (24), 93 (40), 92 (34), and 79 (20). The amine **7** was submitted for elemental analysis as the hydrochloride salt which was prepared in the same manner as in **15**.

Anal. Calcd for $C_{11}H_{20}NCl$: C, 65.49; H, 9.99; N, 6.94. Found: C, 65.61; H, 9.95; N, 7.06.

1-Methyladamantan-2-one (8).—To 1.0 g (6.0 mmol) of **3** dissolved in 10 ml of acetone, 3 ml of Jones-type reagent[26] was added, and the mixture was stirred for 2 hr at room temperature. To reduce the excess chromic oxide, 5 ml of methanol was added upon work-up. The solution was diluted with 50 ml of water and extracted five times with chloroform (15 ml each). The combined organic layers were washed with potassium bicarbonate solution and water, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The crude product was purified by chromatography on a 50-g silica gel column, with *n*-pentane and *n*-pentane–2% ether as eluents. Evaporation of the main fraction yielded 0.84 g of purified ketone. Sublimation of the residue gave 0.81 g (80%) of 1-methyladamantan-2-one (**8**) as a waxy, colorless solid: mp 106.5–108.5°; ir (CCl_4) 1729 cm^{-1} (C=O); nmr τ 7.76 (broad s, 1, CHC=O), a complex multiplet with broad peaks at 7.87, 8.07 (m, 12, adamantyl H), and 9.00 (s, 3, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 164 (100, M^+), 149 (9), 136 (8), 135 (7), 131 (8), and 93 (91).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.38; H, 9.80.

Compound **8** was also prepared by oxidation of the rearranged alcohol **4**. To 0.10 g (0.6 mmol) of **4** dissolved in 5 ml of acetone, 0.5 ml of Jones-type reagent[26] was added, and the mixture stirred for 1 hr at room temperature. Using the work-up described for the direct rearrangement oxidation of **3**, 0.08 g (80%) of **8** was obtained, mp 104–106°. The ketone formed by this route was shown by glpc coinjection, ir, and mixture melting point to be identical with that obtained by the direct rearrangement–oxidation of **3**.

Chlorination of 4-Protoadamantanone (2).—To 1.00 g (6.7 mmol) of **2**, 4 ml of phosphorus trichloride was added with stirring at 0°. Following the addition of 3.6 g of phosphorus pentachloride added during 5 min, the reaction mixture was stirred for 10 hr at 0° and then was allowed to warm. Stirring was continued at room temperature for 2 hr, after which the mixture was cooled to 0° and the excess Lewis acid was hydrolyzed by addition of ice. After extraction five times with ether (25 ml each), the combined organic layers were washed with 15 ml of saturated potassium bicarbonate solution and water, dried over anhydrous magnesium sulfate, and then filtered. Evaporation of the solvent gave 0.8 g of crude solid which was shown by analytical glpc (column, 10% Carbowax 20M on Chromosorb W 30–60) to consist mainly (>95%) of two products in the ratio of 2:1. Separation of the mixture on a column of 30 g of silica gel gave two main fractions when eluted with pentane. Upon evaporation of the eluent, the less polar product consisted of 0.41 g of the crude liquid **10** and the more polar product consisted of 0.24 g of the crude solid **11**.

4-Chloroprotoadamantene (10).—The less polar crude fraction of the reaction product from phosphorus trichloride–phosphorus pentachloride and 4-protoadamantanone (**2**) was purified by preparative glpc (column, 15% FFAP, Chromosorb W 60–80) to give an analytical sample of 4-chloroprotoadamantene (**10**): $n^{25}D$ 1.5331; ir (thin film) 3050 (=CH), 1640 (C=C), and 830 cm^{-1}(CH, out of plane torsion); nmr shows a four-line pattern centered at τ 3.79 (m, 1, C=CH, $J_{H\text{-}5,H\text{-}6}$ = 8 Hz and $J_{H\text{-}5,H\text{-}3}$ = 1.8 Hz) and 7.0–8.5 (m, 12, adamantyl H); mass spectrum (70 eV) *m/e* (rel intensity) 170 (13, M^+), 168 (44, M^+), 153 (3), 139 (3), 133 (88), 126 (37), 113 (28), 105 (10), and 91 (100).

Anal. Calcd for $C_{10}H_{13}Cl$: C, 71.21; H, 7.77; Cl, 21.02. Found: C, 71.31; H, 8.04; Cl, 20.99.

1,2-Dichloroadamantane (11).—The more polar crude fraction of the reaction product from phosphorus trichloride–phosphorus pentachloride and 4-protoadamantanone (**2**) was purified two times by chromatography on a 20-g silica gel column (eluted with pentane) to give an analytical sample of 0.10 g (7%) of 1,2-dichloroadamantane (**11**): mp 183–185° dec; ir 850, 780, 740, and 690 cm^{-1} (strong CCl); nmr τ 5.50 (broad s, 1, CHCl) and 7.0–8.7 (broad m, 13, adamantyl H); mass spectrum (70 eV) *m/e* (rel intensity) 208 (1, M^+), 206 (5, M^+), 204 (9, M^+), 171 (30), 169 (100), 133 (15), 127 (4), 115 (3), 113 (7), 105 (4), 91 (16), 79 (11), and 77 (8).

(26) C. Djerassi, P. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

Anal. Calcd for $C_{10}H_{14}Cl_2$: C, 58.55; H, 6.88; Cl, 34.57. Found: C, 58.29; H, 6.90; Cl, 34.51.

Adamantane-1,2-diol (13).—To a suspension of 0.08 g of lithium aluminum hydride in 5 ml of anhydrous ethyl ether, 0.12 g (0.72 mmol) of 2-ketoadamantan-1-ol (**12**)[5,6] dissolved in 7 ml of anhydrous ethyl ether was added and the mixture refluxed overnight. After the usual work-up,[27] sublimation *in vacuo* gave 0.11 g of diol **13**. An analytical sample was obtained by chromatography on a 20-g silica gel column which was eluted with ethyl ether. Evaporation of the solvent gave 0.10 g (83%) of adamantan-1,2-diol (**13**): mp 328–330°; ir (dilute CCl_4) 3644, 3627, 3607, 3585, and 3564 cm^{-1} (O-H);[28] nmr (DMSO-d_6) τ 5.71 (d, 1, 2 OH, J = 3 Hz), 5.95 (s, 1, 1 OH), 6.56 (broad s, 1, CHOH), and 7.8–9.0 (m, 13, adamantyl H); mass spectrum (70 eV) *m/e* (rel intensity) 168 (100, M^+), 152 (14), 150 (35), 137 (3), 111 (5), 110 (6), 108 (8), 107 (5), 95 (84), 94 (14), and 79 (7).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.63; H, 9.74.

Chlorination of Adamantane-1,2-diol.—To 37 mg of **13**, 2 ml of thionyl chloride was added and the reaction mixture was heated to reflux overnight. The excess thionyl chloride was distilled off and the crude product was analyzed by glpc (column, 10% Carbowax 20M on Chromosorb W 30–60). Two peaks in the ratio of 3:2 were observed, and the more polar product showed the same retention time as the 1,2-dichloride **11** (by coinjection). The crude reaction mixture was purified by chromatography on a 20-g silica gel column and pentane was used as the eluent. Evaporation of the solvent of the more polar fraction gave an analytical sample of 1,2-dichloroadamantane (**11**). The 1,2-dichloride formed by this route was shown by glpc coinjection, ir, and melting point to be identical with that obtained *via* the reaction of phosphorus trichloride–phosphorus pentachloride and **2**.

1-*N*-Acetyladamantane-1,2-diamine Hydrochloride (14).—To 8 ml of acetonitrile, cooled in an ice bath, 3 ml of concentrated sulfuric acid was added dropwise with stirring, followed by 0.50 g (2.6 mmol) of adamanto[2,1-*d*]oxazolidin-2-one (**1**).[2] The reaction mixture was allowed to warm and was kept at room temperature for 3 hr. After quenching in ice–water, potassium hydroxide solution was added until the solution was pH 9 and then the aqueous mixture was extracted three times with chloroform (75 ml each). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and evaporated to yield an oil. The oil was dissolved in 10 ml of acetone and filtered, and then concentrated hydrochloric acid was added dropwise until the solution was acidic. Upon addition of *ca.* 40 ml of ether, a small amount of amorphous solid separated. After filtration, the filtrate was cooled in a refrigerator, and a crystalline solid separated which was recrystallized from ethanol/acetone–ether to give 0.15 g (23%) of 1-*N*-acetyladamantane-1,2-diamine hydrochloride (**14**): mp >300° dec; ir 3470 (broad, NH), 3250 (NH amide), 3020 (weak, NH amide), 2010 ($\overset{+}{N}H_3$, b and torsion), 1655 (C=O), 1600 (NH amine, b asym), 1540 (NH amide, b), and 1495 cm^{-1} (NH amine, b sym); nmr (D_2O, DSS internal standard) τ 5.65 (s, 1, $CH\overset{+}{N}H_3$), 7.25–8.50 (m, 11, adamantyl H and amide H), and 7.95 (s, 3, $NHCOCH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 208 (34, M^+ of free amine) (measured 208.15775, calcd for $C_{12}H_{20}N_2O$ 208.157555), 191 (8), 165 (7), 149 (100), 136 (17), 120 (4), 107 (13), and 94 (10).

Anal. Calcd for $C_{12}H_{21}N_2OCl$: C, 58.88; H, 8.65; N, 11.44. Found: C, 58.81; H, 8.65; N, 11.18.

Adamantane-1,2-diamine Dichloride Monohydrate (15).—To 10 ml of 6 *N* hydrochloric acid, 125 mg (0.5 mmol) of **14** was added. The reaction mixture was heated to reflux for 33 hr and then cooled. After addition of excess potassium hydroxide solution, the aqueous mixture was extracted three times with chloroform (50 ml each). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and evaporated to yield a solid. The solid was dissolved in 10 ml of acetone and then filtered. Upon addition of concentrated hydrochloric acid (added dropwise until the solution was acidic), a solid separated which was recrystallized from ethanol/acetone–ether to give 75 mg (61%) of adamantane-1,2-diamine dihydrochloride monohydrate (**15**): mp >300° dec; ir 3425 (broad, NH), 1965 ($\overset{+}{N}H_3$, b and torsion), 1575 (NH, b asym), and 1500 cm^{-1} (NH, b sym); nmr (D_2O, DSS as internal standard) τ 6.22 (m, 1, $CH\overset{+}{N}H_3$, $\nu_{1/2}$ = 6 Hz) and 7.50–8.30 (m, 13, adamantyl H); mass spectrum (70 eV) *m/e* (rel intensity) 166 (100, M^+ of free diamine) (measured 166.146777, calcd for $C_{10}H_{18}N_2$ 166.146991), 149 (20), 136 (6), 123 (4), 120 (4), 110 (10), 109 (43), 108 (8), 107 (10), 106 (12), and 95 (8).

Anal. Calcd for $C_{10}H_{20}N_2Cl_2 \cdot H_2O$: C, 46.69; H, 8.62; N, 10.89. Found: C, 46.36; H, 8.81; N, 10.52.

4-(Adamant-1-yl) Semicarbazide (17).—To 18.8 g (0.1 mol) of adamantane-1-amine hydrochloride (**16**) dissolved in 100 ml of water, excess potassium hydroxide solution was added, and the solid which separated was extracted five times with chloroform (100 ml each). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and evaporated to yield a solid. The solid was dissolved in 400 ml of benzene, dried over anhydrous magnesium sulfate, filtered, and transfered to 1-l. three-neck flask having a drying tube. The reaction vessel was cooled in an ice bath, 7.9 g (0.1 mol) of pyridine was added, and then 100 ml of 12% phosgene solution in benzene was dripped in under stirring. After 30 min, the solid pyridinium hydrochloride which had precipitated was filtered off, and the filtrate was evaporated *in vacuo* to remove excess phosgene. The solid residue was dissolved in 100 ml of benzene and was dripped into a solution of 30 ml of absolute hydrazine in 100 ml of benzene at room temperature with stirring. After stirring for 4 hr, the mixture was filtered and the filtrate was evaporated *in vacuo* to yield a solid which was recrystallized from ethanol to give 4.8 g (23%) of 4-(adamant-1-yl) semicarbazide (**17**): mp 167–168.5°; ir 3280 (NH), 1650 (NH, b asym), 1620 (C=O), and 1540 cm^{-1} (NH, b sym); mass spectrum (70 eV) *m/e* 209 (M^+).

Anal. Calcd for $C_{11}H_{19}N_3O$: C, 63.13; H, 9.15; N, 20.08. Found: C, 62.85; H, 8.99; N, 20.39.

1-Adamantylcarbamoyl Azide (18).—To 3.06 g (14.6 mmol) of **17** dissolved in 50 ml of glacial acetic acid, 140 ml of water was added, followed by 9 ml of concentrated hydrochloric acid. While the solution was stirred in an ice bath, a solution of 1.06 g of sodium nitrite in 15 ml of water was added and then a solid separated. After the reaction mixture stirred for 1 hr, the solution was extracted five times with chloroform (50 ml each). The combined organic layers were washed with a 5% sodium bicarbonate solution and water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* at 30° to give 2.6 g (80%) of carbamoyl azide **18**, mp 144–147°. A small amount was recrystallized from cyclohexane to give an analytical sample of 1-adamantylcarbamoyl azide (**18**): mp 145–147°; ir 3350 (NH), 3020 (weak, NH), 2150 (N=N=N, asym), 1710 (C=O), 1520 (NH, b), and 1220 cm^{-1} (N=N=N, sym).

Anal. Calcd for $C_{11}H_{16}N_4O$: C, 59.98; H, 7.32; N, 25.44. Found: C, 60.16; H, 7.65; N, 25.63.

Photolysis of 1-Adamantylcarbamoyl Azide (18).—To 2.5 g (1.1 mmol) of **18**, 800 ml of cyclohexane was added, and the solution was poured into a quartz photolysis reaction vessel having a drying tube. The solution was photolyzed using a water-jacketed mercury lamp for 24 hr. At the termination of the photolysis period, a solid was observed in the vessel. Evaporation of the solvent *in vacuo* gave an amorphous solid. Analytical glpc (10% Carbowax 20M on Chromosorb W 30–60) showed a complex mixture of at least nine products. Repeated efforts to separate this mixture by crystallization were unfruitful. The nmr spectra of the vacuum-oven dried solid mixture indicated τ 7.6–8.1 (complex m), 8.12 (broad s), and 8.56 (sharp s, cyclohexyl H). A similar uncrystallized complex reaction mixture was obtained when 3.0 g of **18** were photolyzed in 400 ml of benzene and 30 ml of ether for 20 hr. Upon hydrolysis of the amorphous photolysis residue in 3 *N* hydrochloric acid for 3 hr, no diamine **15** could be isolated.

Bromination of Protoadamantene (19).—To 134 mg (1 mmol) of protoadamantene (**19**)[22] dissolved in 100 ml of carbon tetrachloride, 0.05 ml of bromine was added at room temperature with stirring. Bromine was immediately decolorized during dropwise addition. Analytical glpc of the reaction mixture showed two peaks in a 1:2 ratio. After evaporation of the solvent, the product mixture was separated by chromatography on a column of 20 g of silica gel. Elution with *n*-pentane gave 91 mg of a less polar crude solid, the axial–equatorial dibromide **25**. Further

(27) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 584.

(28) The characterization of the free and hydrogen-bonded O–H bands will be published elsewhere: T. Gorrie and P. v. R. Schleyer, to be published.

elution with a solution of 90% *n*-pentane and 10% ether (v/v) gave 156 mg of a more polar crude solid, the diaxial isomer **23**.

2a,4a-Dibromoadamantane (23).—The more polar chromatography fraction described above was purified by crystallization from *n*-pentane to give 123 mg (42%) of 2a,4a-dibromoadamantane (**23**) as colorless needles: mp 171.8–173.0° (reported 171–172°[2]); nmr τ 5.35 (broad s, 2, CHBr, calcd 5.45[29]), 7.16 (broad downfield AB d, 1, H-9a,[30] J = 16 Hz, calcd 7.09[29]), 7.32 (broad s superimposed on right part of downfield AB d, 1, H-3, calcd 7.59[29]), 7.67 (broad s, 2, H-1 and H-5, calcd 7.86[29]), 8.05 ± 0.23 with large peak at 8.00 (m, 7, H-10a,e, calcd 7.93,[29] and H-6a,e, H-8a,e, calcd 8.07,[29] and H-7, calcd 8.15[29]), and 8.26 (upfield AB d, the left part superimposed on m, 1, H-9e, calcd 8.51[29]); mass spectrum (70 eV) *m/e* (rel intensity) 296 (8, M^+), 294 (16, M^+), 292 (9, M^+), 215 (98), 213 (100), 133 (51), 105 (16), 91 (69), and 79 (32).

Anal. Calcd for $C_{10}H_{14}Br_2$: C, 40.85; H, 4.80; Br, 54.35. Found: C, 41.00; H, 4.95; Br, 54.55.

2a,4e-Dibromoadamantane (25).—The less polar crude fraction of the reaction product from the bromination of **19** was sublimed *in vacuo* to give 85 mg (29%) of 2a,4e-dibromoadamantane (**25**): mp 119–121° (lit.[15] 120–122°); nmr τ 4.80 (s, 1, H-4a,[30] lit.[29] 4.85), 5.21 (s, 1, H-2, lit.[29] 5.27), and 7.2–8.6 (m, 12, adamantyl protons).

Anal. Calcd for $C_{10}H_{14}Br_2$: C, 40.85; H, 4.80; Br, 54.35. Found: C, 40.42; H, 4.60; Br, 53.91.

4,5-Epoxidoprotoadamantane (Mainly 26).—To a solution of 264 mg (2.0 mmol) of protoadamantene (**19**)[23] in 10 ml of methylene chloride at 0°, 364 mg of 80% *m*-chloroperoxybenzoic acid dissolved in 5 ml of methylene chloride was added carefully. The stirring was continued for 30 min at 0° and then for 2 hr at room temperature. The reaction mixture was extracted with a 5% sodium bisulfite solution, followed by shaking with 5% sodium bicarbonate solution and then water. After drying over anhydrous sodium sulfate, the organic solvent was evaporated in a rotating evaporator, and the resulting residue sublimed *in vacuo* to give 252 mg (85%) of protoadamantyl 4,5-epoxide as a waxy solid, mp 237.5–239.0°. Analytical glpc of this sublimate gave two peaks in the ratio of 6:1 taken to indicate a mixture of the exo and endo epoxides. Attempts to separate the epoxide mixture by silica gel chromatography were not fruitful. Chemical reduction of the epoxide followed by hydrolysis gave products which indicated that exo epoxide **26** was the major component. The nmr spectrum of the sublimate showed a six-line pattern of the epoxide H at τ 6.84 ± 0.25 and 7.25–9.00 (m, 12, protoadamantyl H); its mass spectrum (70 eV) was *m/e* (rel intensity) 150 (46, M^+), 136 (26), 132 (8), 121 (21), 117 (24), 106 (20), 104 (28), 93 (52), 91 (48), 81 (37), 88 (60), 79 (100), and 77 (31).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.21; H, 9.67.

Reduction of 4,5-Epoxidoprotoadamantane (Mainly 26).—To a suspension of 30 mg of lithium aluminum hydride in 5 ml of anhydrous ethyl ether was added 100 mg (0.7 mmol) of epoxide sublimate (above) dissolved in 10 ml of anhydrous ethyl ether. The usual work-up[27] gave 92 mg of a mixture of products. Analytical glc indicated that this mixture consisted of one major product and three minor products. The major component could be separated by chromatography on a silica gel column with benzene–2% ether as eluent. This gave 48 mg (48%) of *exo*-protoadamantan-4-ol.[1a] The structure was established by comparison with an authentic sample by glc coinjection, as well as by the identity of their ir and nmr spectra.

Adamantane-2a,4a-diol (27).—To 300 mg (2 mmol) of the epoxide sublimate (mostly **26**) dissolved in 10 ml of 80% aqueous acetone, 1 drop of concentrated hydrochloric acid was added and the mixture refluxed for 2 hr. The solution was first concentrated *in vacuo* to a small volume (*ca.* 2 ml) and then extracted five times with ether (10 ml each). After drying over anhydrous sodium sulfate and evaporation *in vacuo*, a solid was obtained. Sublimation *in vacuo* gave 265 mg (79%) of adamantane-2a,4a-diol (**27**): mp 305–310° dec; ir 3619 (free) and 3553 cm^{-1} (bonded OH peaks); nmr τ 5.93 (t, 2, CHOH, J = 2.5 Hz, $\Delta\nu_{1/2}$ = 7.5 Hz), 6.5 (broad s, 2, OH, signal disappears when sample is shaken with D_2O), and 7.75–8.67 (m, 12, adamantyl H).

The diol **27** was also prepared for comparison purposes by the lithium aluminum hydride reduction of 4a-hydroxyadamantan-2-one.[11] The identity of the two samples was confirmed by glpc coinjection, and nmr spectra comparison.

***exo*-Protoadamantane-4,5-*cis*-diol (29).**—To a solution of 130 mg (1 mmol) of **19** in 5 ml of absolute ether, 250 mg of osmium tetroxide dissolved in 3 ml of absolute ether was added; black osmate **28** precipitated instantaneously. After standing for 2 days at room temperature, evaporation of the solvent gave a black residue. To this 5 ml of pyridine, 5 ml of water, and 250 mg of sodium bisulfite were added, and the resulting mixture was stirred for 1 hr. The mixture was extracted five times with chloroform (10 ml each), and the combined organic layers were washed two times with cold 15% hydrochloric acid, once with saturated potassium bicarbonate solution, and then with water. The solvent was dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo* to give 138 mg (82%) of *exo*-protoadamantane-4,5-*cis*-diol (**29**) as a waxy solid: mp 212–216°; ir $\Delta\nu_{OH}$ 80 cm^{-1}; nmr τ 5.82 (d of d, 1, CHOH, C-4, $J_{4,5}$ = 7.5 Hz, $J_{3,4}$ = 3.5 Hz), 6.06 (d of d, 1, CHOH, C-5, $J_{4,5}$ = 7.5 Hz, $J_{5,6}$ = 1.5 Hz), 6.8 (broad s, 2, OH), 7.2–8.9 (m, 12, protoadamantyl H); mass spectrum (70 eV) *m/e* (rel intensity) 168 (50, M^+), 150 (100), 137 (68), 132 (19), 121 (13), 119 (12), 117 (15), 106 (17), 104 (26), 93 (27), 91 (21), 80 (21), and 79 (34).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.12; H, 9.70.

***exo*-Protoadamantane-4,5-*cis*-diol Acetonide (30).**—To 40 mg (0.2 mmol) of **29** dissolved in 5 ml of 80% aqueous acetone, 2 drops of concentrated hydrochloric acid was added, and the mixture refluxed for 2 hr. After evaporation of the solvent to a small volume *in vacuo*, the remaining solution was extracted with ether. The combined ether extract was dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo*. The solid residue which resulted was sublimed *in vacuo* to give 32 mg (65%) of *exo*-protoadamantane-4,5-*cis*-diol acetonide (**30**) as needles: mp 39.5–41.0°; ir spectrum showed no OH or C=O bands; nmr τ 5.32 (d of d, 1, CHOH, C-4, $J_{4,5}$ = 7.5 Hz, $J_{3,4}$ = 3.5 Hz), 5.63 (broad d, CHOH, C-5, $J_{4,5}$ = 7.5 Hz), 7.2–8.9 (m, 12, protoadamantyl H), 8.45 (s, 3, CH_3), and 8.61 (s, 3, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 208 (0.5, M^+), 193 (100), 151 (20), 133 (20), 91 (45), and 79 (19).

Acid-Catalyzed Rearrangement of Diol 29.—A solution of 50 mg of **29** in 5 ml of 25% aqueous sulfuric acid was heated at 100° for 1.5 hr. After cooling, ice was added and the reaction product was extracted five times with 10 ml of ether. The usual work-up gave 38 mg of a crude product whose nmr spectrum was identical with that from the authentic diol **27**. Attempted rearrangement of **29** by refluxing in an HCl-catalyzed 50% aqueous ethanol solution was unsuccessful.

Registry No.—*endo*-**3**, 28995-98-4; *exo*-**3**, 28840-89-3; **4**, 28786-69-8; **5**, 28996-01-2; **6**, 28996-02-3; **7**, 28996-03-4; **8**, 26832-19-9; **10**, 28996-05-6; **11**, 29038-91-3; **13**, 28996-06-7; **14**, 29038-92-4; **15**, 28996-07-8; **17**, 26496-36-6; **18**, 28996-09-0; **23**, 28989-82-4; **25**, 19288-33-6; *endo*-**26**, 28989-84-6; *exo*-**26**, 28989-85-7; **27**, 28644-55-5; **29**, 28989-87-9; **30**, 28989-88-0.

Acknowledgments.—This work was supported by Grant AI-07766, National Institutes of Health. We would like to thank Professor C. A Cupas and Mr. W. E. Heyd for providing a sample of protoadamantene used in this work. The technical assistance of Mr. T. Gorrie is gratefully acknowledged.

(29) F. W. Van Deursen and A. C. Udding, *Recl. Trav. Chim. Pays-Bas*, **87**, 1243 (1968).

(30) Notation adopted for 2,4-disubstituted adamantanes by G. Snatzke and D. Marquarding, *Chem. Ber.*, **100**, 1710 (1967).