Synthesis and Chemistry of 2,5-Dehydro-4-protoadamantanone

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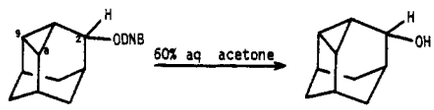
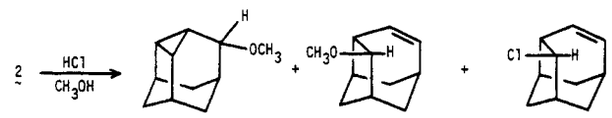
2,5-Dehydro-4-protoadamantanone (**12**) has been synthesized in a three-step reaction sequence from bicyclo[3.2.1]-oct-6-en-3-*endo*-ylacetic acid. Treatment of **12** with methyllithium gives 4-*endo*-hydroxy-4-*exo*-methyl-2,5-dehydroprotoadamantane (**13**), which reacts with Jones reagent to provide 1-methyl-8,9-dehydro-2-adamantanone (**16**). Ketone **16** has also been prepared in three steps from **13** by initial acid-catalyzed isomerization of **13** to 2-*exo*-hydroxy-4-methylprotoadamantene (**17**). Subsequent oxidation of **17** gives 4-methyl-2-protoadamantenone, which undergoes an oxa-di-π-methane photorearrangement to afford **16**. Extended treatment of alcohol **17** with dilute perchloric acid in 80% aqueous acetone gives 3-methyl-2,4-dihydroxyadamantane. Cyclobutanone **12** also offers an entry to 2-substituted noradamantanes, since treatment of **12** with potassium *tert*-butoxide in dimethyl sulfoxide gives 2-*endo*-carboxynoradamantane. Irradiation of a methanol solution of cyclobutanone **12** affords 4-methoxy-3-oxatetracyclo[5.3.1.$0^{2,6}$.$0^{5,9}$]undecane via an apparent oxacarbene intermediate.

The solvolytic behavior of 2-substituted 8,9-dehydroadamantanes has been the subject of several reports.[2-4] Baldwin and Foglesong observed that solvolysis of 8,9-dehydro-2-adamantyl 3,5-dinitrobenzoate (**1**) in 60% aqueous acetone occurs with the marked rate acceleration characteristic of cyclopropylcarbinyl derivatives to give 8,9-dehydro-2-adamantanol (**2**).[2] Labeling studies established that during the



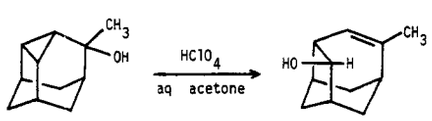
1 **2**

course of this reaction C-2, C-8, and C-9 of **1** achieve nearly complete equivalence.[2] Acid-catalyzed reactions of 2-substituted 8,9-dehydroadamantanes have also been found to give products of a homoallyl type. For example, treatment of **2** with hydrochloric acid in methanol provides a mixture of 2-methoxy-8,9-dehydroadamantane (**3**), 2-*exo*-methoxyprotoadamantene (**4**), and 2-*exo*-chloroprotoadamantene (**5**).[3] Under



3 **4** **5**

milder conditions, reaction of 2-methyl-8,9-dehydroadamantan-2-ol (**6**) with dilute perchloric acid in refluxing 80% aqueous acetone gives 2-*exo*-hydroxy-5-methylprotoadamantene (**7**).[4]



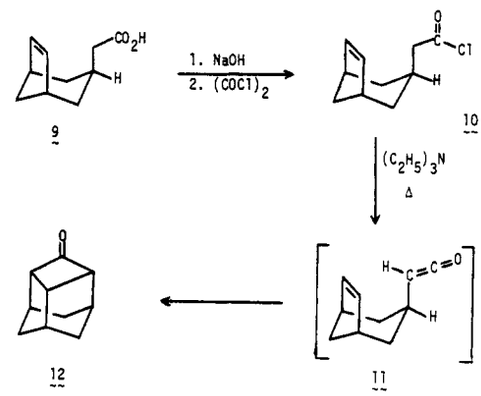
6 **7**

In view of the chemistry of other cyclopropylcarbinyl and homoallyl derivatives,[5] it is striking that in these several reactions no 4-substituted 2,5-dehydroprotoadamantane derivatives (**8**) have been obtained. We now wish to report the synthesis of a precursor to **8**, 2,5-dehydro-4-protoadamantanone[6] (**12**), and some of the aspects of its chemistry.

8

Results and Discussion

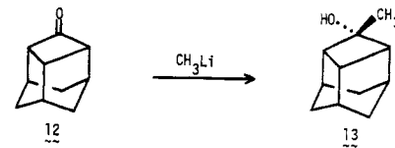
Cyclobutanone **12** is readily prepared from bicyclo[3.2.1]-oct-6-en-3-*endo*-ylacetic acid (**9**).[7] Treatment of the sodium salt of **9** with oxalyl chloride affords acid chloride **10** which when refluxed with triethylamine in benzene provides **12**. The conversion of **10** to **12** apparently proceeds by the initial



9 **10** **12** **11**

elimination of hydrogen chloride from **10** to generate ketene **11**, which then undergoes an intramolecular cycloaddition to give **12**. By this route, **12** was obtained in isolated yields of 54–76% from **9**. Consistent with the presence of a plane of symmetry in **12**, the ^{13}C NMR spectrum of **12** contains only seven signals, and three of these signals are twice as intense as the others. In addition, the infrared spectrum of **12** shows a carbonyl absorption at 1765 cm^{-1}, and no signals appear below δ 3.55 in the ^1H NMR spectrum of **12**.

Treatment of **12** with methyllithium gives a single alcohol to which we have assigned the structure of 4-*endo*-hydroxy-4-*exo*-methyl-2,5-dehydroprotoadamantane (**13**).[8] The as-

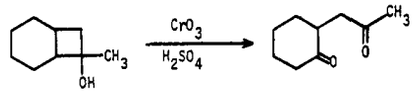


12 **13**

signment of stereochemistry at C-4 in **13** follows from an examination of molecular models, which shows that attack at the carbonyl carbon in **12** across the face of the six-membered ring (i.e., endo attack) should be significantly impeded by the equatorial hydrogen at C-7. By contrast, there is no apparent steric hindrance to attack at the carbonyl carbon in **12** across the face of the four-membered ring.[9]

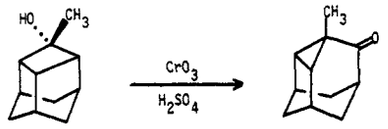
Recently Liu has reported that reaction of tertiary cyclobutanols with Jones reagent under mild conditions results in the oxidative cleavage of the cyclobutane ring to give, de-

pending on the substitution pattern of the starting alcohol, either a 1,4-ketol or a 1,4-diketone, e.g., **14** → **15**.[10] However,



14 **15**

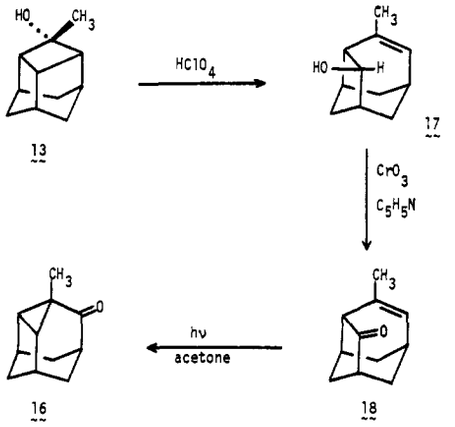
methylcyclobutanol **13** undergoes a quite different reaction under these conditions. Treatment of **13** with freshly prepared Jones reagent at 0 °C for 1 h affords 1-methyl-8,9-dehydro-2-adamantanone (**16**) in ~85% yield.[11] It would appear that



13 **16**

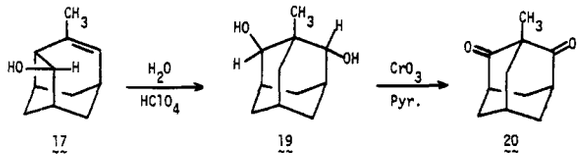
this reaction occurs by the initial formation of the 4-methyl-2,5-dehydroprotoadamantyl cation. This cation then rapidly rearranges to the 1-methyl-8,9-dehydro-2-adamantyl cation, which is trapped and irreversibly oxidized by the excess Jones reagent present to give cyclopropyl ketone **16.** Apparently none of the tertiary cyclobutanols examined by Liu[10] offered such competitive rearrangement pathways.

The structure of **16** was definitively established by means of an independent synthesis. Reaction of **13** with 0.005 M perchloric acid in 80% aqueous acetone for 12 h at 70 °C provides 2-*exo*-hydroxy-4-methylprotoadamantene (**17**) in ~75% yield.[12] Oxidation of **17** with the Sarett chromium trioxide–



pyridine complex affords 4-methyl-2-protoadamantenone (**18**) in ~75% yield. Since a variety of tertiary alcohols analogous to **13** can be prepared by the reaction of alkyllithium reagents with **12,** the sequence **13** → **17** → **18** offers a route for the synthesis of a number of 4-substituted 2-protoadamantenones. β,γ-Unsaturated ketone **18** is readily converted to **16** by an oxa-di-π-methane photorearrangement.[13] Irradiation of a solution of **18** in acetone through a Pyrex filter with a Hanovia L 450-W lamp gives **16** in ~40% yield.

If alcohol **17** is reacted with 0.005 M perchloric acid in 80% aqueous acetone at 70 °C for an extended reaction time (8 days), further rearrangement occurs and 3-methyl-2,4-dihydroxyadamantane (**19**) is obtained in ~70% yield.[14] The



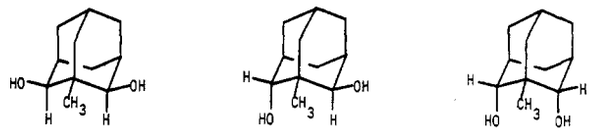
17 **19** **20**

skeletal framework of **19** and the skeletal positions of the substituents in **19** were established by oxidation of **19** with the Sarett chromium trioxide–pyridine complex to give 3-methyl-2,4-adamantanedione (**20**). Diketone **20** shows carbonyl absorptions at 1738 and 1708 cm^{-1} in its infrared spectrum. Other related 1,3-diketones show similar infrared characteristics. Thus, the carbonyl absorptions of 2,4-adamantanedione (**21**)[15] appear at 1720 and 1695 cm^{-1}, and in

21 **22**

2,6-bicyclo[2.2.2]octanedione (**22**)[16] the carbonyl absorptions occur at 1735 and 1710 cm^{-1}. Moreover, consistent with the presence of a plane of symmetry in **20,** the ^{13}C NMR spectrum of **20** consists of only eight signals, and three of these signals are twice as intense as the others.

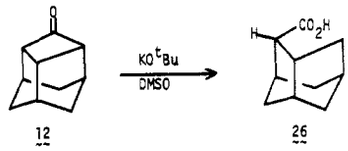
The ^1H NMR spectrum of **19** clearly shows that the acid-catalyzed addition of water to **17** proceeds to give a 55:45 mixture of stereoisomers. The major product has broad singlets for the C**H**(OH) protons at δ 3.94 and 3.64. Of the three possible 3-methyl-2,4-dihydroxyadamantanes (**23–25**) only



23 **24** **25**

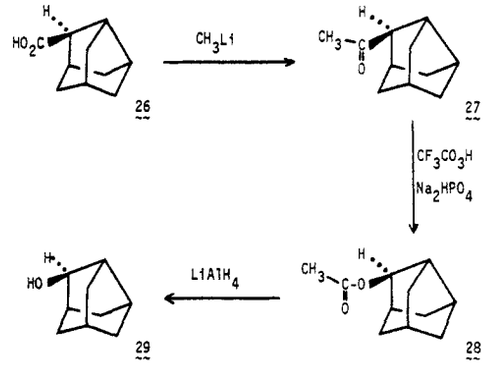
the axial–equatorial isomer **24** would be expected to show a significant difference in the chemical shifts of the C**H**(OH) protons and, consequently, **24** is assigned as the major product. The C**H**(OH) protons of the minor product appear as a broad singlet ($W_{1/2}$ = 5.3 Hz) at δ 3.4, which is consistent with either **23** or **25.** It should be noted that there is ample precedent for the reaction **17** → **19,** since protoadamantene undergoes electrophilic addition with rearrangement to give 2,4-disubstituted adamantanes.[17]

Cyclobutanone **12** also can be employed as a precursor for the synthesis of 2-substituted noradamantanes. Treatment of **12** with potassium *tert*-butoxide in dimethyl sulfoxide gives 2-*endo*-carboxynoradamantane (**26**) in nearly quantitative



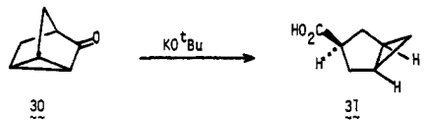
12 **26**

yield. The skeletal framework of **26** and the position and stereochemistry of the carboxy substituent in **26** follow from the conversion of **26** to the known alcohol, 2-*endo*-hydroxynoradamantane (**29**).[18] Reaction of **26** with methyllithium gives 2-*endo*-acetylnoradamantane (**27**), which can be oxi-



26 **27** **29** **28**

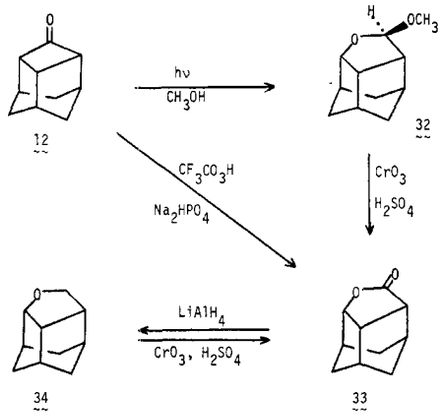
dized with trifluoroperoxyacetic acid to afford 2-*endo*-acetoxynoradamantane (**28**). Reduction of **28** with lithium aluminum hydride provides alcohol **29.** The stereochemical outcome of **12** → **26** parallels the observation of Gassman and Zalar that reaction of nortricyclanone (**30**) with potassium



30 31

tert-butoxide in dimethyl sulfoxide leads to stereospecific ring cleavage and the formation of 3-*endo*-carboxybicyclo[3.1.0]-hexane (**31**) with complete retention of configuration at C-3.[19]

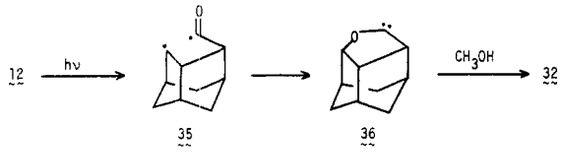
We have also examined the photochemistry of cyclobutanone **12**. Irradiation of a solution of **12** in pentane through a Corex filter leads to a gradual disappearance of the starting material, but no volatile products could be detected by gas–liquid chromatography. By contrast, irradiation of a solution of **12** in methanol through a quartz filter with a Hanovia L 450-W lamp affords acetal **32** in 90% yield. Jones oxidation of **32** provides 3-oxatetracyclo[5.3.1.$0^{2,6}$.$0^{5,9}$]undecan-4-one (**33**),



12 32 34 33

which shows carbonyl absorptions at 1795 and 1782 cm^{-1} in its infrared spectrum. The structure of **33** was readily established, since Baeyer–Villiger oxidation of **12** with trifluoroperoxyacetic acid gives lactone **33** in 95% yield. Moreover, treatment of **33** with lithium aluminum hydride provides the parent ether **34** in quantitative yield. Lactone **33** can be regenerated from **34** by Jones oxidation.

The photochemical formation of ketal **32** from cyclobutanone **12** can be rationalized as proceeding by initial Norrish type I bond cleavage to give diradical **35**, which undergoes



12 35 36 32

subsequent or concerted rearrangement and rebonding to provide oxacarbene **36**, which is then trapped by methanol to afford acetal **32**. An examination of molecular models suggests that attack at the endo face of **36** should be sterically hindered, and thus the methoxy substituent in **32** is presumed to be exo to the seven-membered ring. The photochemistry of **12** parallels that reported by Turro[20] and Yates[21] for a number of variously substituted cyclobutanones.

Experimental Section

Melting points were obtained in sealed capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained on Perkin-Elmer 180 or 337 spectrophotometers. Proton magnetic resonance spectra were recorded with Varian A-60A or Perkin-Elmer R-12B 60-MHz spectrometers and are referenced to an internal standard of tetramethylsilane. Apparent splittings are reported in all cases. Carbon magnetic resonance spectra were taken at an operating frequency of 22.63 MHz on a Brüker HFX-90 spectrometer equipped for Fourier transform pulsed nmr with a Nicolet 1085 data acquisition system and are referenced to an internal standard of tetramethylsilane. Unless noted otherwise, yields were obtained by integration of appropriate signals in the ^1H NMR spectrum of the product(s) vs. the signal of a predetermined amount of an added standard (generally chloroform or trichloroethylene) and are regarded as being accurate to ~±10%. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, Del.

2,5-Dehydro-4-protoadamantanone (12). A stirred mixture of 5.0 g (30 mmol) of bicyclo[3.2.1]oct-6-en-3-*endo*-ylacetic acid[7] (**9**) in 50% aqueous methanol (300 mL) was titrated to a phenolphthalein end point with 10% aqueous sodium hydroxide and then stirred at room temperature for 1 h. The solvent was evaporated at reduced pressure and the residue was heated at 80 °C (0.1 mm) for 24 h. The resulting dry sodium salt of **9** was treated with anhydrous benzene (200 mL) and anhydrous pyridine (4.35 mL), cooled to 0 °C, and stirred as oxalyl chloride (8.0 mL, 93 mmol) was added dropwise. After the addition was complete, the reaction mixture was stirred at 0 °C for 30 min and at room temperature for 30 min. The reaction mixture was then filtered and the collected precipitates were washed several times with anhydrous benzene. Evaporation under reduced pressure of the solvent from the combined filtrate and washings afforded 5.8 g of bicyclo[3.2.1]oct-6-en-3-*endo*-ylacetyl chloride (**10**) as a pale yellow oil: ν (C=O) 1785 cm^{-1}.

A solution of **10** (5.8 g) in anhydrous benzene (150 mL) was subsequently added over ~45 min to a stirred refluxing mixture of triethylamine (3.15 g, 31 mmol) and anhydrous benzene (450 mL). Refluxing was continued for 2 h, at which point the reaction mixture was cooled to room temperature. The mixture was then washed with water (3 × 50 mL) and dried over anhydrous sodium sulfate. The solvent was removed by atmospheric distillation, and the resulting pale brown liquid residue was eluted with benzene through a silica gel column. Removal of the benzene by atmospheric distillation afforded an off-white residue, which was sublimed to provide **12** (2.4 g, 54% yield) as white prisms. Additional purification by GLC (10 ft. × 0.25 in. DC-550 column, 175 °C) gave **12** as a white solid: mp 193–194.5 °C; ^1H NMR δ ($CDCl_3$) 3.54–3.20 (complex m, 2 H), 3.05–2.60 (complex m, 4 H), 2.02–1.78 (br s, 4 H), 1.71–1.48 (complex m, 2 H); ^{13}C NMR δ ($CDCl_3$) tentative assignments 206.0 (C=O), 71.4 (C-3 and C-5), 45.2 (C-9 and C-10), 45.0 (C-6 and C-8), 43.5 (C-1 or C-2), 43.2 (C-1 or C-2), 33.4 (C-7); IR ν (CCl_4) 2945, 2860, 1765, 1100, 1090, 1050 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.22; H, 8.07.

4-*endo*-Hydroxy-4-*exo*-methyl-2,5-dehydroprotoadamantane (13). A solution of methyllithium (7.8 mL of a 1.84 M solution, ~14.4 mmol) in ether was added at 0 °C to a stirred solution of **12** (500 mg, 3.4 mmol) in anhydrous ether (10 mL). The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 1 h, and then water (40 mL) was added. The resulting mixture was saturated with sodium chloride and extracted with ether (3 × 50 mL). The combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave a white, crystalline solid (573 mg), which by ^1H NMR analysis contained a ~100% yield of alcohol **13** (558 mg). The crude product was sublimed (85 °C, 2.0 mm) to afford **13** (460 mg) as white needles: mp 97–98 °C; ^1H NMR δ ($CDCl_3$) 3.12–2.14 (br m, 7 H), 2.00–1.04 (br m, 9 H, which contains a singlet for $-CH_3$ at δ 1.51); IR ν (CCl_4) 3620, 3450 (br w), 2980, 2930, 2860, 1470, 1445, 1375, 1320, 1165, 1100, 970, 935, 865 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.26; H, 9.57.

1-Methyl-8,9-dehydro-2-adamantanone (16). To a stirred solution of **13** (50 mg, 0.3 mmol) in acetone (5 mL) at 0 °C was added 250 μL of freshly prepared Jones reagent (2.8 g of chromium trioxide, 4.5 mL of sulfuric acid, and 12 mL of water). The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 30 min. At this point water (5 mL) was added and the mixture was stirred for an additional 30 min. The reaction mixture was then neutralized with saturated aqueous sodium bicarbonate, saturated with sodium chloride, and extracted with ether (4 × 15 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and the solvent was evaporated at reduced pressure to provide crude ketone **16** as a colorless liquid (43 mg, 85% yield). The sample was purified by GLC (10 ft × 0.25 in. OV-101 column, 150 °C) to give pure **16** as a white solid: mp 48–49 °C; ^1H NMR δ ($CDCl_3$) 2.98–1.50 (br m, 11 H), 1.10 (s, 3 H, $-CH_3$); IR ν (CCl_4) 3020, 2935, 2860, 1700, 1465, 1445, 1370, 1335, 1110, 1090, 1040, 920, 885, 850 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.70; H, 8.59.

2-*exo*-Hydroxy-4-methylprotoadamantene (17). A solution of alcohol **13** (82 mg, 0.5 mmol) in 2.5 mL of 80% aqueous acetone which was 0.005 M in perchloric acid was stirred at 70 °C for 12 h. The reaction mixture was cooled to room temperature, diluted with water (5 mL), saturated with sodium chloride, and then extracted with ether

(4 × 15 mL). The combined ether extracts were dried over anhydrous magnesium sulfate and concentrated at reduced pressure to give a viscous liquid (88 mg), which by GLC analysis (10 ft × 0.25 in. OV-101 column, 150 °C) showed only a single component with no trace of unreacted **13**. Analysis of the residue by ^{1}H NMR indicated that the product was obtained in ~75% yield. Purification by GLC (above conditions) provided **17** as a white solid: mp 66–68 °C; ^{1}H NMR δ ($CDCl_3$) 5.94 (br d, J_{H_5,H_6} = 8.6 Hz, 1 H, CH_3C=C**H**–), 3.79 [br s, 1 H, C**H**(OH)], 2.77–1.16 (br m, 14 H, containing a doublet, J = 1.5 Hz, for CH_3C=CH– at δ 1.78); IR ν (CCl_4) 3630, 3550–3200 (br), 2920, 1465, 1435, 1375, 1050, 1005 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.58; H, 9.68.

4-Methyl-2-protoadamantenone (18). Chromium trioxide (329 mg, 3.29 mmol) was added in small portions to pyridine (9 mL) at 25 °C.[22] The reaction mixture was stirred for 30 min and then cooled to 0 °C. To this complex was added a solution of **17** (180 mg, 1.09 mmol) in pyridine (4 mL). The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 16 h. The inorganic material was precipitated by the addition of ether (250 mL) and the insolubles were removed by filtration. The filtrate was washed successively with 5% aqueous hydrochloric acid (5 × 25 mL), 5% aqueous sodium bicarbonate (2 × 25 mL), and saturated aqueous sodium chloride (25 mL), and then dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided crude enone **18** as a colorless liquid (130 mg, 75% yield). This material was purified by GLC (10 ft × 0.25 in. OV-101 column, 150 °C) to give **18** as a colorless liquid: ^{1}H NMR δ ($CDCl_3$) 6.18 (br d, J_{H_5,H_6} = 7.6 Hz, 1 H, CH_3C=C**H**–), 3.00–1.24(m, 13H, containing a doublet, J = 1.5 Hz, at δ 1.83 for CH_3C=CH–); IR ν (CCl_4) 3030, 2945, 2870, 2850, 1742, 1732, 1470, 1445, 1440, 1375, 1330, 1305, 1245, 1175, 1135, 1085, 1060, 940, 825 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.16; H, 8.69.

Photorearrangement of 18 to 16. A solution of **18** (100 mg, 0.62 mmol) in spectrograde acetone (5 mL) was irradiated through a Pyrex filter with a Hanovia L 450-W high pressure mercury lamp. Monitoring the photolysis by GLC (10 ft × 0.25 in. OV-101 column, 150 °C) showed a gradual disappearance of **18** (R_t = 10.5 min) and the appearance of a photoproduct of longer retention time (R_t = 12.5 min). After irradiation for 21 h, no starting material remained and only the photoisomer was evident. Evaporation of the solvent at reduced pressure gave a yellow oil (80 mg), which by ^{1}H NMR analysis showed the presence of ~40 mg (40% yield) of **16**. Purification of **16** by GLC (above conditions) afforded a white solid whose infrared spectrum was identical with that of 1-methyl-8,9-dehydro-2-adamantanone prepared by the Jones oxidation of **13**.

3-Methyl-2,4-dihydroxyadamantane (19). A solution of **17** (195 mg, 1.2 mmol) in 5 mL of 80% aqueous acetone which was 0.005 M in perchloric acid was stirred at 70 °C for 8 days. The reaction mixture was cooled to room temperature, diluted with water (25 mL), saturated with sodium chioride, and extracted with ether (4 × 25 mL). The combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided 239 mg of a waxy white solid. Examination of this material by GLC (10 ft × 0.25 in. OV-101 column, 150 °C) showed a minor product (R_t = 14 min) and a major product (R_t = 27 min). The minor product (20 mg, 10% yield by ^{1}H NMR analysis) proved to be unreacted **17**. The major product (153 mg, 70% yield by ^{1}H NMR analysis) was purified by GLC (above conditions) to afford diol **19** as white crystals: mp 240–242 °C; ^{1}H NMR ($CDCl_3$) 3.94 [br s, 0.5 H, C**H**(OH)], 3.64 [br s, 0.5 H, C**H**(OH)], 3.42 [br s, 1 H, C**H**(OH)], 2.44–0.88 (br m, 16 H, containing methyl singlets at δ 1.00 and 0.96); IR ν (CCl_4) 3620, 3460 (br), 3000, 2910, 2860, 1450, 1015, 960, 925 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.53; H, 9.92.

3-Methyl-2,4-adamantanedione (20). Oxidation of 80 mg (0.5 mmol) of diol **19** with Sarett reagent by the procedure described for **17** → **18** gave 40 mg (45% yield) of **20**. Isolation by GLC (10 ft × 0.25 in. OV-101 column, 150 °C) afforded **20** as a white solid: mp 86–88 °C; ^{1}H NMR δ ($CDCl_3$) 3.10–2.75 [br s, 2 H, –C**H**COC(CH_3)COC**H**–], 2.69–1.76 (m, 9 H), 1.18 (s, 3 H, –CH_3); ^{13}C NMR δ ($CDCl_3$) tentative assignments 209.7 (C-2 and C-4), 67.7 (C-3), 51.7 (C-9), 45.4 (C-1 and C-5), 38.5 (C-6 and C-8), 30.7 (C-10), 28.2 (C-7), 14.6 (CH_3); IR ν (CCl_4) 2930, 2860, 1738, 1708, 1450, 1375, 1340, 1305, 1250, 1070, 1025, 910, 870 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.07; H, 8.27.

2-*endo*-Carboxynoradamantane (26). Powdered **12** (50 mg, 0.34 mmol) was added to a solution of freshly sublimed potassium *tert*-butoxide (632 mg, 5.6 mmol) in dimethyl sulfoxide (2 mL) and water (30 mg, 1.7 mmol). The reaction mixture was stirred at room temperature for 2 h and then poured into water (25 mL). The resulting basic solution was washed with ether (15 mL). The aqueous phase was then acidified with concentrated hydrochloric acid and further extracted with ether (4 × 15 mL). The combined extracts were dried over anhydrous magnesium sulfate. The solvent was evaporated at reduced pressure to provide **26** (58 mg, 98% yield) as off-white crystals. Purification of this material by GLC (10 ft × 0.25 in. OV-101 column, 150 °C) afforded **26** as a white solid: mp 100–101 °C; ^{1}H NMR δ ($CDCl_3$) 11.65 (br s, 1 H, –CO_2H), 3.26–1.29 (br m, 13 H); IR ν (CCl_4) 3450–2300 (br), 2940, 2875, 1698, 1420, 1300, 1290, 1280, 1245, 1210, 1060 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.47; H, 8.25.

2-*endo*-Acetylnoradamantane (27). An ethereal solution of methyllithium (1.84 M, 2.45 mL, ~4.5 mmol) was added dropwise to a vigorously stirred solution of **26** (335 mg, 2.02 mmol) in anhydrous ether (20 mL) at 0 °C at such a rate that the temperature of the reaction mixture did not exceed 5 °C. The reaction mixture was stirred of 0 °C for 30 min and at room temperature for 4 h. At this point the reaction mixture was slowly poured into a saturated solution of ammonium chloride. The aqueous layer was separated and extracted with ether (4 × 15 mL). The combined ether layers were washed with 5% aqueous sodium bicarbonate (4 × 10 mL) and water (2 × 10 mL), and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave crude ketone **27** as a colorless liquid (243 mg, 73% yield). This material was distilled using a molecular distillation apparatus to provide pure **27** (120 mg, 36% yield): ^{1}H NMR δ ($CDCl_3$) 3.0–1.0 (complex m, containing a singlet for –$COCH_3$ at δ 2.16); IR ν (CCl_4) 2940, 2870, 1709, 1460, 1440, 1360, 1310, 1295, 1230, 1180, 1080, 1060 cm^{-1}.

The semicarbazone derivative of **27** was prepared according to the procedure outlined by Fieser[23] and has a melting point of 197–198 °C dec.

Anal. Calcd for $C_{12}H_{19}N_3O$: C, 65.13; H, 8.65. Found: C, 64.86; H, 8.59.

2-*endo*-Hydroxynoradamantane (29). A solution of trifluoroperoxyacetic acid (prepared by the addition of 80 μL of 97% trifluoroacetic anhydride to a stirred ice-cold suspension of 20 μL of 90% hydrogen peroxide in 20 mL of methylene chloride) was added dropwise to a stirred suspension of disodium hydrogen phosphate (190 mg, 1.3 mmol), ketone **27** (35 mg, 0.2 mmol), and methylene chloride (4 mL) at room temperature. The reaction mixture was stirred at reflux for 30 min and then cooled to room temperature. The insolubles were removed by filtration and washed with methylene chloride (2 × 10 mL). The filtrate and washings were combined and washed with 10% aqueous sodium carbonate (2 × 10 mL), and then dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave a yellow liquid (25 mg). Purification of this material by GLC (10 ft × 0.25 in. OV-101 column, 150 °C) provided 6 mg of **2-*endo*-acetoxynoradamantane (28)** as a colorless liquid: IR ν (CCl_4) 1735, 1245 cm^{-1}.

Lithium aluminum hydride (10 mg) was added to a solution of acetate **28** (6 mg) in anhydrous ether (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for ~12 h. The excess lithium aluminum hydride present was destroyed by the dropwise addition of 10% aqueous ammonium chloride (2 mL). The resulting mixture was saturated with sodium chloride and extracted with ether (2 × 15 mL), and the combined extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave an oily residue (4 mg). Purification of this material by GLC (10 ft × 0.25 in. OV-101 column, 150 °C) afforded 2 mg of 2-*endo*-hydroxynoradamantane (**29**) as a white solid whose infrared spectrum was identical with that of an authentic sample of **29**.[18]

4-Methoxy-3-oxatetracyclo[5.3.1.0^{2,6}.0^{5,9}]undecane (32). A solution of **12** (300 mg, 2 mmol) in spectrograde methanol (15 mL) was irradiated through a quartz filter with a Hanovia L 450-W high-pressure mercury lamp. Monitoring the photolysis by GLC (10 ft × 0.25 in. OV-101 column, 150 °C) showed a gradual disappearance of **12** (R_t = 9.8 min) and the appearance of a photoproduct of longer retention time (R_t = 11.8 min). After irradiation for 13.5 h, no starting material remained and only a single photoproduct was evident by GLC analysis. Evaporation of the solvent at reduced pressure afforded **32** as a yellow liquid (329 mg, 90% yield). Purification by GLC (above conditions) gave **32** as a colorless liquid: ^{1}H NMR δ ($CDCl_3$) 5.06 (s, 1 H, –OC**H**OCH_3), 4.80–4.49 (m, 1 H, –CHO–), 3.41 (s, 3 H, –OCH_3), 3.14–1.18 (m, 11 H); IR ν (CCl_4) 2945, 2865, 1470, 1375, 1350, 1265, 1250, 1230, 1200, 1115, 1090, 1070, 1065, 1040 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.57; H, 9.02.

3-Oxatetracyclo[5.3.1.0^{2,6}.0^{5,9}]undecan-4-one (33). A. To a stirred solution of **32** (100 mg, 0.55 mmol) in acetone (10 mL) at 0 °C was added 1.2 mL of freshly prepared Jones reagent (2.8 g of chromium trioxide, 4.5 mL of sulfuric acid, and 12 mL of water). The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 1 h. At this point water (20 mL) was added and the mixture was stirred for an additional 30 min. The reaction mixture was then saturated with sodium chloride and extracted with ether (4 × 15 mL). The combined ether extracts were washed with 5% aqueous sodium bicarbonate (2 × 15 mL) and water (15 mL), and then dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave crude **33** as a viscous liquid (78 mg, 55% yield). Purification by GLC (10 ft × 0.25 in. OV-101 column, 150 °C) provided lactone **33** as a white solid: mp 207–209 °C; ^{1}H NMR δ ($CDCl_3$) 5.10–4.80 (complex m, 1 H, –CHO–), 3.53–3.10 (complex m, 1 H, –CHCO–), 3.00–1.45 (br m, 10 H); IR ν (CCl_4) 2950, 2875, 1795, 1782, 1756 (w), 1470, 1445, 1355, 1340, 1225, 1165, 1100, 1090, 1050, 1030, 985 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: 73.01; H, 7.09.

B. Oxidation of 65 mg (0.44 mmol) of **12** with trifluoroperoxyacetic acid by the procedure described for **27** → **28** gave 70 mg (95% yield) of **33** as a white solid whose infrared spectrum was identical with that of **33** obtained by procedure A.

3-Oxatetracyclo[5.3.1.0^{2,6}.0^{5,9}]undecane (34). A solution of **33** (91 mg, 0.55 mmol) in anhydrous ether (5 mL) was added over 15 min to a stirred refluxing slurry of lithium aluminum hydride (200 mg, 5.2 mmol) in anhydrous ether (15 mL). The reaction mixture was stirred at reflux for an additional 30 min and then cooled to 5 °C. The excess lithium aluminum hydride present was destroyed by the successive dropwise addition of water (0.2 mL), 15% aqueous sodium hydroxide (0.2 mL), and water (0.6 mL). The resulting white slurry was filtered and the filtrate was dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave a white solid (95 mg, 100% yield), which by GLC analysis (10 ft × 0.25 in. OV-101 column, 180 °C) showed only a single component. Purification by GLC (above conditions) provided **34** as a white solid: mp 181–182 °C; ^{1}H NMR δ (acetone-d_6) 4.6–3.9 (complex m, 3 H, –CH_2OCH–), 3.0–1.2 (complex m, 11 H); IR ν (CCl_4) 2935, 2865, 1710, 1460, 1355, 1085, 1050, 1025 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 80.22; H, 9.33.

Jones oxidation of **34** by the procedure described for **32** → **33** gave **33**.

4-*endo*-Hydroxy-2,5-dehydroprotoadamantane (37). A solution of ketone **12** (500 mg, 3.4 mmol) in methanol (5 mL) was added dropwise to a stirred solution of sodium borohydride (400 mg, 10.5 mmol) in methanol (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 1 h, and then diluted with water (10 mL). The resulting solution was saturated with sodium chloride and extracted with ether (3 × 50 mL). The combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure gave a white solid (553 mg), which by ^{1}H NMR analysis contained a ~80% yield (400 mg) of **37**. The crude product was sublimed to afford **37** as white platelets: mp 206–207 °C; ^{1}H NMR δ ($CDCl_3$) 4.28 [t, J = 5.3 Hz, 1 H, C**H**(OH)], 3.3–0.96 (br m, 13 H); IR ν (CCl_4) 3630 (m), 3400 (br w), 2940, 2860, 1235, 1110, 1090, 1015 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.71; H, 9.28.

2-*exo*-Hydroxyprotoadamantene (38). A solution of **37** (62 mg, 0.41 mmol) in 2.5 mL of 80% aqueous acetone which was 0.005 M in perchloric acid was stirred at ~70 °C for 48 h. The solution was diluted with water (5 mL) and extracted with ether (4 × 15 mL). The combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure afforded a white solid (59 mg), which by GLC analysis (10 ft × 0.25 in. OV-101 column, 150 °C) contained two components. The major component (R_t = 9 min) was identified as **38** and the minor component (R_t = 10 min) proved to be unreacted **37**. Analysis of the crude reaction mixture by ^{1}H NMR indicated that the reaction had gone to ~70% completion, providing 19 mg of **37** and 37 mg of **38** (86% yield). Purification of alcohol **38** by GLC (above conditions) provided material whose infrared spectrum was identical with that of an authentic sample of 2-*exo*-hydroxyprotoadamantene.[3]

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Registry No.—**9**, 29603-52-9; **9** Na, 63609-73-4; **10**, 63609-74-5; **12**, 63609-75-6; **13**, 63609-76-7; **16**, 63609-77-8; **17**, 63609-78-9; **18**, 56933-51-8; **19**, 63609-79-0; **20**, 63609-80-3; **26**, 59042-78-3; **27**, 63699-56-9; **27** semicarbazone, 63609-81-4; **32**, 63609-82-5; **33**, 63609-83-6; **34**, 63609-84-7; **37**, 63609-85-8; oxalyl chloride, 79-37-8.

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(12) Analogous treatment of 4-*endo*-hydroxy-2,5-dehydroprotoadamantane gives 2-*exo*-hydroxyprotoadamantene (see Experimental Section).
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