[Chem. Pharm. Bull. 30(1) 67—73 (1982)]

Oxy-functionalization of Adamantane-1-acetic Acid and Adamantane-1-carboxylic Acid by the Ferrous Iron-Molecular Oxygen System in Aqueous Solution[1)]

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(Received May 6, 1981)

Oxygenation reactions of adamantanes with ferrous iron-molecular oxygen in phosphate buffer were investigated and the structures of the products were elucidated. In the reaction of adamantane-1-acetic acid (**1a**), five oxygenated products, the C(2)-oxo, C(4)-oxo, C(2),C(6)-dioxo, C(4)-ol, and C(3)-ol derivatives, were obtained. Similar oxygenation also occurred in the reaction of adamantane-1-carboxylic acid (**2a**) to give three products, the C(4)-oxo, C(4)-ol, and C(3)-ol derivatives. The oxy-functionalization of **1a** and **2a** in 0.5 M phosphate buffer (pH 6.8) was found to occur almost quantitatively on addition of an appropriate amount of ferrous iron.

Keywords——adamantane-1-acetic acid; adamantane-1-carboxylic acid; hydroxyadamantanes; oxoadamantanes; molecular oxygen; ferrous iron-catalyzed oxygenation; oxidation of adamantanes; concentration effects of phosphate buffer; concentration effects of ferrous ions; quantitation of products

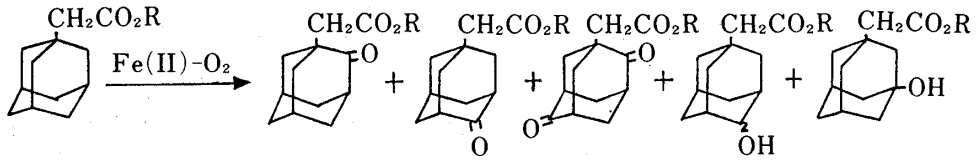
In the previous papers of this series, it was demonstrated that an oxygen function was introduced at the C(15)-positions of deoxycholic acid,[2)] nordeoxycholic acid[3)] and taurodeoxycholic acid[3)] by autoxidation of their aqueous solutions in the presence of ferrous iron. Introduction of an oxygen function of an inert carbon atom by such a simple system prompted us to study it in more detail. Steroidal substrates are not necessarily appropriate in this respect, because of their low solubility in water and the difficulty of products analysis. Adamantanes are known to be reactive substrates and the structures of their oxygenated products can easily be elucidated. In this study, adamantane-1-acetic acid (**1a**) and adamantane-1-carboxylic acid (**2a**) were employed as relatively soluble substrates, and their reactions with the ferrous iron-molecular oxygen system were carried out in phosphate buffer.

Results and Discussion

Products of Adamantane-1-acetic Acid

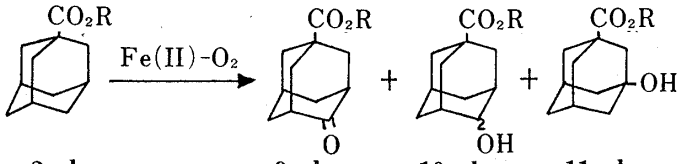
Ferrous sulfate solution was added to a phosphate buffer (pH 6.8) solution of **1a** and the reaction mixture was bubbled through with molecular oxygen at 40°C for 3 h . After work-up as usual, the reaction mixture was methylated with diazomethane and separated by alumina column and Silica gel thin-layer chromatographies to give five compounds, **3b**—**7b**.

The compound **3b** was obtained as a slightly yellow oil. Its mass spectrum showed a peak due to the molecular ion at *m/e* 222, indicating the introduction of one carbonyl oxygen atom into **1b**. The infrared (IR) spectrum also showed the presence of a carbonyl group (1720 cm^{-1}) as well as an ester linkage (1715 cm^{-1}). In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **3b**, the downfield shifts of the signals due to the one methine proton (2.61 ppm) and methylene protons adjacent to the ester linkage ($-CH_2CO_2CH_3$, 2.37 ppm) suggested that the carbonyl oxygen atom was introduced at the C(2)-position of the substrate. Saponification of **3b** with KOH–MeOH gave the acid (**3a**) as colorless crystals, the spectral data and melting point of which were identical with those of **3a**.[4)] Thus, the structure of **3b** was confirmed to be methyl 2-oxoadamantane-1-acetate.



1a,b 3a,b 4a,b 5a,b 6a,b 7a,b 8a

a : R=H, b : R=CH_3



2a,b 9a,b 10a,b 11a,b

a : R=H, b : R=CH_3

Chart 1

Compound **4b** was shown to be an isomer of **3b** by its mass spectrum (M^+ *m/e* 222) and IR spectrum (broad band at 1720 cm^{-1} due to carbonyl and ester groups). A downfield shift was observed in the signal due to the two methine protons (2.55 ppm) in the ^{1}H-NMR spectrum rather than in the signal of the methylene protons adjacent to the ester linkage (2.19 ppm). These data indicate that the carbonyl oxygen atom was introduced at the C(4)-position and that **4b** is methyl 4-oxoadamantane-1-acetate. Saponification of **4b** with KOH–MeOH gave 4-oxoadamantane-1-acetic acid (**4a**) as colorless needles, mp 108—109°C.

Compound **5b**, colorless prisms, mp 143.5—146°C, was shown to have two additional carbonyl oxygen atoms by its high resolution mass spectrum (M^+ *m/e* 236.1058, calcd 236.1048). The IR spectrum indicated the presence of carbonyl (1720 cm^{-1}) and ester (1715 cm^{-1}) groups. In the ^{1}H-NMR spectrum, the downfield shifts of the signals due to the three methine protons (2.68—2.78 ppm) as well as the methylene protons adjacent to ester linkage (2.44 ppm) indicated that **5b** was methyl 2,6-dioxoadamantane-1-acetate.

The IR spectrum of **6b** showed the presence of hydroxyl (3600 and 3450 cm^{-1}) and ester (1720 cm^{-1}) groups. The mass spectrum of **6b** showed the molecular ion at *m/e* 224, suggesting the introduction of a hydroxyl group. In the ^{1}H-NMR spectrum, a signal (singlet, 3.85 ppm) due to a proton attached to the carbon atom bearing the hydroxyl group indicated that the hydroxyl group was introduced at the C(2)- or C(4)-position. Upon the Jones oxidation of **6b**, an oxo-compound was obtained which showed the same gaschromatographic behavior as **4b**, not **3b**. Thus, **6b** was assumed to be methyl 4-hydroxyadamantane-1-acetate. Saponification of **6b** with KOH–MeOH afforded 4-hydroxyadamantane-1-acetic acid (**6a**) as colorless prisms, mp 160—163°C. On the other hand, reduction of **4a** with $NaBH_4$ also gave 4-hydroxyadamantane-1-acetic acid (**8a**). The fragmentation pattern in the mass spectrum and the melting point of 8a (136—140°C) were, however, different from those of **6a**. It is assumed from these results that **6a** is the epimer of **8a** and that C(4)-hydroxylation of **1a** in the oxygenation reaction and $NaBH_4$ reduction of **4a** are stereoselective. It is noteworthy that C(4)-hydroxylation occurred stereoselectively in the ferrous iron-molecular oxygen system. The stereochemistry of the C(4)-hydroxyl groups of **6a** and **8a** is under investigation.

The IR spectrum of compound **7b**, $C_{13}H_{20}O_3$, showed the presence of a hydroxyl group (3600 and 3450 cm^{-1}). In the ^{1}H-NMR spectrum, the absence of a signal due to a proton attached to the carbon atom bering the oxygen function indicated that the hydroxyl group is tertiary. In the mass spectrum of **7b**, a characteristic fragment ion at *m/e* 95 ($C_6H_5\overset{+}{O}H_2$) was detectable, which appears with adamantanes containing a tertiary hydroxyl group.[5] Thus, **7b** was assumed to be methyl 3-hydroxyadamantane-1-acetate. The melting points of **7a** and **7b** were in good agreement with the previously reported values.[6]

Products of Adamantane-1-carboxylic Acid(2a)

In order to confirm that another adamantane can also be oxygenated by the ferrous iron-molecular oxygen system, adamantane-1-carboxylic acid (**2a**) was subjected to the same reaction as described above. Subsequent methylation and chromatographic separations of the resulting mixture afforded three oxygenated compounds, **9b**—**11b**.

Compound **9b** was obtained as a yellow oil. Its mass spectrum revealed the molecular ion at *m/e* 208, suggesting the introduction of a carbonyl oxygen atom into **2b**. The presence of the carbonyl group was also supported by the IR spectrum (broad peak at 1720 cm^{-1} due to carbonyl and ester groups). In the ^1H-NMR spectrum of **9b**, the downfield shift of the signal due to the methine protons on C(3) and C(5) (2.60 ppm) indicated that **9b** is methyl 4-oxoadamantane-1-carboxylate. Saponification of **9b** with KOH–MeOH yielded 4-oxoadamantane-1-carboxylic acid (**9a**) as colorless prisms, mp 169.5—171°C.

Compound **10b** was shown to have a hydroxyl group by the mass (M^+ *m/e* 210) and IR 3600 and 3450 cm^{-1}) spectra. The ^1H-NMR spectrum of **10b** showed a signal (3.86 ppm) due to a proton on the carbon atom bearing the hydroxyl group, suggesting its introduction at the C(2)- C(4)-position. The oxidation product of **10b** with the Jones reagent showed the same gas chromatographic behavior as that of **9b**, indicating that **10b** was methyl 4-hydroxyadamantane-1-carboxylate. Saponification of **10b** with KOH–MeOH gave 4-hydroxyadamantane-1-carboxylic acid (**10a**) as colorless prisms, which were assumed to be an epimeric mixture, judging from the broad melting point (117—128°C). As previously reported by Tabushi *et al.*,[7] $NaBH_4$ reduction of **9a** also gave 4-hydroxyadamantane-1-carboxylic acid as an oil, whose mass and ^1H-NMR spectral data as well as gas chromatographic behavior were in good agreement with those of **10a**. These results suggested that the C(4)-hydroxylation of **2a** in the oxygenation reaction and $NaBH_4$ reduction of **9a** were not stereoselective in contrast to the cases of **1a** and **4a**.

Compound **11b** was obtained as a yellow oil and its mass (M^+ *m/e* 210) and IR (3600 and 3450 cm^{-1}) spectra indicated the introduction of a hydroxyl group into **2b**. The tertiary character of the hydroxyl group was indicated by the absence of a ^1H-NMR signal due to a proton on the carbon atom bearing the oxygen fuction and also by the presence of the fragment ion at *m/e* 95 ($C_6H_5\overset{+}{O}H_2$) in the mass spectrum. The evidence fully supports the conclusion that **11b** is methyl 3-hydroxyadamantane-1-carboxylate. Saponification of **11b** with KOH–MeOH afforded 3-hydroxyadamantane-1-carboxylic acid (**11a**) as colorless crystals, mp 210—212.5°C.

In the oxygenation reaction of **2a**, no evidence was obtained for the formation of C(2)-oxygenated products, in contrast to the case of **1a**.

These results indicate that rather high yields of oxygenated products are obtainable in the reactions of these adamantanes with the ferrous iron-molecular oxygen system, and these substrates are thus appropriate for use in investigation of the reactions of this system.

Concentration of Phosphate Buffre

The substrate **1a** is insoluble in solutions below pH 5.0. Addition of ferrous ion solution into phosphate buffer immediately gave pale blue precipitates of ferrous phosphate, resulting in a decrease in the buffer capacity and in the pH of the reaction medium. A decrease in pH can also be caused by the oxidation of ferrous to ferric ions during the reaction. In the present oxygenation reactions in 0.1 M phosphate buffer (pH 6.8), the final pH of the reaction medium was found to be 4.8 and the conversion of **1a** to oxygenated products was 74%, as shown in Table I. When 0.2 M buffer was employed in the same reaction, the final pH was 6.4 and the conversion was 93%. In the 0.5 M phosphate buffer, no change in pH was observed during the reaction and **1a** was consumed almost quantitatively (96%). Thus, the 0.5 M phosphate buffer (pH 6.8) was employed as a solvent in the following experiments.

Table I. Effect of Buffer Concentration

Buffer concentration	Final pH	Conversion (%)
0.1 M	4.8	74
0.2	6.4	93
0.5	6.5	96

Reaction conditions: **1a** (1 mM), 2 N NaOH (0.05 ml), $FeSO_4 \cdot 7H_2O$ (4.3 mmol), phosphate buffer (pH 6.8, 100 ml), O_2 bubbling, at 40°C for 3 h.

Concentration of Ferrous Ions

The oxygenation reaction of **1a** was shown not to occur in the absence of ferrous iron or under bubbling of nitrogen instead of oxygen. No oxygenation occurred on adding ferric ions instead of ferrous ions. These results indicated that the reaction is a ferrous iron-catalyzed oxygenation with molecular oxygen. Since most of the added ferrous ions were precipitated as ferrous phosphate under the present reaction conditions, only a portion of ferrous ions in the solution is assumed to catalyze the oxygenation. Figure 1 shows the effect of the amount of ferrous ion on the conversion of **1a** in the reaction. The oxygenation reaction occurred rapidly and the consumption of **1a** was terminated 5—30 minutes after addition of the ferrous solution. The conversion of **1a** varied with the amount of ferrous ion, and 96% of 1a was converted to oxygenated products by addition of 4.3 mmol of ferrous ion. Upon stepwise addition of ferrous ions, high conversion was also obtained with less of the ions (Fig. 2).

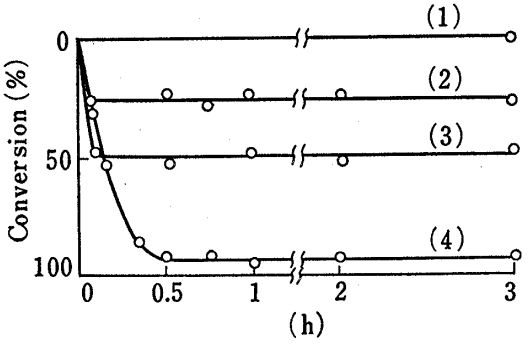


Fig. 1. Effect of Iron Concentration on the Conversion

$[FeSO_4 \cdot 7H_2O]$: (1) 0 mmol, (2) 0.35 mmol, (3) 1.1 mmol, (4) 4.3 mmol.
Reaction conditions: 1a (1 mM), 2 N NaOH (0.05 ml), phosphate buffer (0.5 M, pH 6.8, 100 ml), O_2 bubbling, at 40°C.

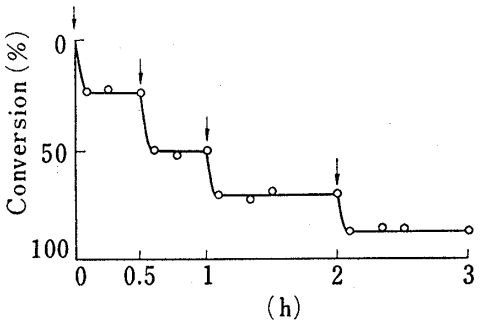


Fig. 2. Effect of Stepwise Addition of Fe(II) on the Conversion

$[FeSO_4 7H_2O]_t = 1.4$ mmol (0.35 mmol × 4).
Reaction conditions: 1a (1 mM), 2 N NaOH (0.05 ml), phosphate buffer (0.5 M, pH 6.8, 100 ml), O_2 bubbling, at 40°C.

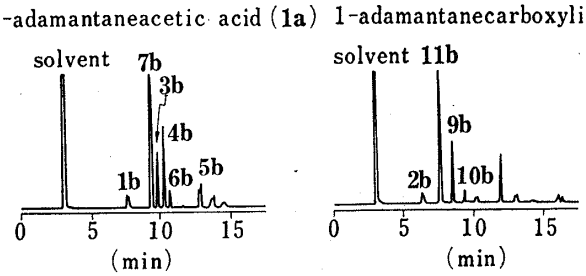


Fig. 3. Gas-Liquid Chromatograms of the Reaction Mixtures

Reaction conditions: 1a or 2a (1 mM), 2 N NaOH (0.05 ml), $FeSO_4 \cdot 7H_2O$ (4.3 mmol), phosphate buffer (0.5 M, pH 6.8, 100 ml), O_2 bubbling, at 40°C for 3 h.

Therefore, in the presence of a ferrous ion regeneration system, the oxygenation reaction may easily occur with a catalytic amount of ferrous species.

Quantitation of the Oxygenated Products

Though the methylated products of **1a** and **2a** were not resolved from each other by general gas chromatographic techniques, good separation was obtained, except in the case of **5b**, by using a capillary column (silicone OV-101, 25 m×0.25 mm), as shown in Fig. 3. The conversions and yields of the products of **1a** and **2a** are summarized in Table II. Tabushi *et al.*[8] studied the oxygenation of adamantane with the system of ferrous complex, molecular oxygen, and thiol compound. The yield of oxygenated products in the reaction was reported to be 100—300%, calculated on the basis of the ferrous complex; the yield based on the substrate was less than 2%. On the other hand, rather high yields were obtained in the reactions of **1a** and **2a** with the ferrous iron-molecular oxygen system in phosphate buffer, as shown in Table II. The reactions of other organic compounds with this system are now under investigation.

Table II. Oxygenation Products formed in the Fe(II)-O_2 System

Substrate	Conversion (%)	Product	Yield (%)
Ad 1-CH_2CO_2H	96	**3a**	12
1a		**4a**	19
		5a	16[a]
		6a	6
		7a	24
Ad 1-CO_2H	95	**9a**	12
2a		**10a**	5
		11a	34

a) Unidentified products were included.
Reaction conditions: 1a or 2a (1 mM), 2 N NaOH (0.05 ml), $FeSO_4 \cdot 7H_2O$ (4.3 mmol), phosphate buffer (0.5 M, pH 6.8, 100 ml), O_2 bubbling, at 40°C for 3 h.

Experimental

General Methods——IR spectra were measured with a JASCO A-102 recording spectrometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-FX 100 machine at 100 MHz using tetramethylsilane as an internal standard. Mass and high resolution mass spectral measurements were run on a JEOL JMS-D3000 spectrometer. Gas chromatography was carried out on Shimadzu GC-4BMPF and GC-4CMPF gas chromatographs equipped with flame ionization detectors. N_2 gas was used as a carrier gas. The columns employed were a glass column (2 m×3 mm i.d.) packed with 1.5% SE-30 on Shimalite W (60—80 mesh) at 130°C (condition 1), and a fused silica capillary column (25 m×0.25 mm i.d.) packed with OV-101 (GASUKURO KOGYO, FSP-015) at 200°C (condition 2). For preparative thin-layer chromatography silica gel (Wakogel B-5F) was used as an adsorbent. Melting points were taken on a micro hot-stage apparatus and are corrected. Abbreviations used are: s=singlet, br=broad.

Materials——$FeSO_4 \cdot 7H_2O$ and $Fe_2(SO_4)_3 \cdot xH_2O$, both guaranteed reagent grade, were purchased from Wako Pure Chem. Ind. Ltd. **1a** and **2a** were obtained commercially and were purified by recrystallization.

Oxygenation of Adamantane-1-acetic Acid (1a)——A suspension of **1a** (100 mg, 0.5 mmol) in 0.05 ml of 2 M NaOH was dissolved in 0.1 M phosphate buffer (pH 6.8, 100 ml), to which was then added a ferrous solution (2.4 g of $FeSO_4 \cdot 7H_2O$ in 5 ml of H_2O). Oxygen was bubbled into the solution for 3 h at 40°C under continuous stirring. In the same procedure, 2.0 g of **1a** (total amount) was treated. The reaction mixtures were collected, acidified with 10% HCl and extracted with AcOEt. The organic layer was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The dark-brown oil (1.80 g) that remained was methylated with diazomethane in Et_2O–MeOH to give a dark-brown residue (1.8 g).

Isolation and Identification of Products from 1a——The methylated residue (1.8 g) was subjected to column chromatography on alumina (60 g). Elution with 800 ml of *n*-hexane–benzene (8: 2) and 500 ml of *n*-hexane–benzene (8: 4) yielded the methyl ester (**1b**, 1100 mg) of the starting material. Elution with 1000 ml of *n*-hexane–benzene (2: 8), 500 ml of benzene and 500 ml of benzene–$CHCl_3$ (9: 1) gave a yellow oily residue (178 mg). The residue was subjected to preparative thin-layer chromatography to yield methyl 2-oxoadamantane-1-acetate (**3b**, 83 mg) and methyl 4-oxoadamantane-1-acetate (**4b**, 49 mg) as light yellow oils.

Methyl 2-Oxoadamantane-1-acetate (**3b**): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1715. MS *m/e*: 222 (M^+), 91 (base peak). ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.88—2.03 (12H, C(2)–, C(4—10)–H), 2.37 (2H, s, $-CH_2CO_2-$), 2.61 (1H, s, C(3)–H), 3.66 (3H, s, $-CO_2CH_3$). Saponification of **3b** with KOH–MeOH gave 2-oxoadamantane-1-acetic acid (**3a**) which was crystallized from EtOAc as colorless crystals, mp 146—148.5°C (lit.[4] 146—147°C). IR ν_{max}^{Nujol} cm^{-1}: 1720, 1690. MS *m/e*: 208 (M^+), 91 (base peak). ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.90—2.17 (12H, C(2)–, C(4—10)–H), 2.44 (2H, s, $-CH_2CO_2H$), 2.64 (1H, s, C(3)–H). *Anal.* Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.07; H, 7.63.

Methyl 4-Oxoadamantane-1-acetate (**4b**): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (br). MS *m/e*: 222 (M^+), 91 (base peak). ^{1}H-NMR (10%, $CDCl_3$) δ: 1.88—1.98 (11H, C(2)–, C(4)–, and C(6—10)–H), 2.19 (2H, s, $-CH_2CO_2-$), 2.55 (2H, s, C(3)– and C(5)–H), 3.66 (3H, s, $-CO_2CH_3$). Saponification of **4b** with KOH–MeOH gave 4-oxoadamantane-1-acetic acid (**4a**), which was crystallized from *n*-hexane–ether as colorless needles, mp 108—109°C. IR ν_{max}^{Nujol} cm^{-1}: 1720, 1690. ^{1}H-NMR (10%, $CDCl_3$) δ: 1.90—1.98 (11H, C(2)–, C(4)–, and C(6—10)–H), 2.22 (2H, s, $-CH_2CO_2H$), 2.58 (2H, s, C(3)– and C(5)–H). High resolution MS *m/e* (M^+) Calcd for $C_{12}H_{16}O_3$: 208.1097, Found: 208.1095. MS *m/e*: 208 (M^+), 91 (base peak).

Methyl 2,6-Dioxoadamantane-1-acetate (**5b**): Elution of the column with 500 ml of benzene–chloroform (1: 1) gave a yellow oil (13 mg), which was crystallized as colorless prisms, mp 143.5—146°C, from *n*-hexane. High resolution MS *m/e* (M^+) Calcd for $C_{13}H_{16}O_4$: 236.1048, Found: 236.1058. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (C=O), 1715 (CO_2CH_3). ^{1}H-NMR (10% solution in $CDCl_3$) δ: 2.34—2.36 (8H, C(4)– and C(8–10)–H), 2.44 ($-CH_2-CO_2-$), 2.68—2.78 (3H, C(3)–, C(5)–, and C(7)–H), 3.68 (3H, s, $-CO_2CH_3$). MS *m/e*: 234 (M^+), 107 (base peak).

Methyl 4-Hydroxyadamantane-1-acetate (**6b**): The product **6b** was obtained from the eluate with 1000 ml of benzene–$CHCl_3$ (1: 4) as a light yellow oil (24 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3450, 1720. MS *m/e*: 224 (M^+), 151, 107 (base peak). ^{1}H-NMR (10%, $CDCl_3$) δ: 1.65—1.95 (13H, C(2)–, C(3)–, and C(5—10)–H), 2.10 (2H, s, $-CH_2CO_2-$), 3.66 (3H, s, $-CO_2CH_3$), 3.85 (1H, s, C(4)–H). Oxidation of **6b** with the Jones reagent at 0°C for 1 min in Me_2CO gave a product, the retention time of which was coincident with that of **4b** (11.5 min), not **3b** (10.8 min) in GLC (condition 2).

4-Hydroxyadamantane-1-acetic Acids (**6a** and **8a**): Saponification of **6b** with KOH–MeOH gave 4-hydroxyadamantane-1-acetic acid (**6a**), which was crystallized as colorless prisms, mp160—163°C, from benzene. IR ν_{max}^{Nujol} cm^{-1}: 3600, 3300 (br), 1700. MS *m/e*: 210 (M^+), 192 (M^+-H_2O), 91 (base peak). ^{1}H-NMR (10%, $CDCl_3$) δ: 1.65—1.95 (13H, C(2)–, C(3)–, and C(5—10)–H), 2 12 (2H, s, $-CH_2CO_2H$), 3.85 (1H, s, C(4)–H). High resolution MS *m/e* (M^+) Calcd for $C_{12}H_{18}O_3$: 210.1254, Found: 210.1237. On the other hand, $NaBH_4$ reduction of **4b** afforded another epimer of 4-hydroxyadamantane-1-acetic acid (**8a**) which was crystallized from benzene as colorless prisms, mp 136—140°C. MS *m/e*: 210 (M^+), 192 (M^+-H_2O, base peak).

Methyl 3-Hydroxyadamantane-1-acetate (**7b**): Further elution of the column with 500 ml of $CHCl_3$ yielded a light yellow oil (395 mg), which could not be crystallized. Saponification of the oil with KOH–MeOH gave 3-hydroxyadamantane-1-acetic acid (**7a**) which was crystallized as colorless prisms, mp 126—128°C (lit.[6a] 127—128°C), from *n*-hexane–Et_2O. IR ν_{max}^{Nujol} cm^{-1}: 3600, 3400 (br), 1700. MS *m/e*: 210 (M^+), 107 (base peak), 95 ($C_6H_5\overset{+}{O}H_2$). ^{1}H-NMR (10%, $CDCl_3$) δ: 1.56—1.68 (12H, C(2—4)–, C(6)–, and C(8—10)–H), 2.20—2.25 (4H, $-CH_2CO_2H$ and C(5)– and C(7)–H). *Anal.* Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.30; H, 8.52. Methylation of **7a** with diazomethane gave methyl 3-hydroxyadamantane-1-acetate (**7b**) which was crystallized as colorless needles, mp 55.5—57°C (lit.[6b] 53—57°C), from *n*-hexane. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3450 (br), 1720. MS *m/e*: 224 (M^+), 107 (base peak), 95 ($C_6H_5\overset{+}{O}H_2$). ^{1}H-NMR (10%, $CDCl_3$) δ: 1.50—1.66 (12H, C(2—4), C(6)–, and C(8—10)–H), 2.16—2.20 (4H, $-CH_2CO_2-$, C(5)–, and C(7)–H). *Anal.* Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.38; H, 8.94.

Isolation and Identification of Products from 2a——The stirred buffer solution of **2a** (100 mg) was treated with the ferrous ion-molecular oxygen system at 40°C for 3 h in the manner described above and 1.0 g of **2a** (total amount) was oxygenated. After work-up and methylation as usual, the reaction mixture gave 1.0 g of a brown oil. The methylated oil was then subjected to column chromatography on alumina (40 g), and elution of the column with 800 ml of *n*-hexane–benzene (1: 1) yielded 400 mg of the methylated starting material (**2b**).

Methyl 4-Oxoadamantane-1-carboxylate (**9b**): Elution with 500 ml of *n*-hexane–benzene (3: 7) gave 61 mg of a brown oil which was subjected to preparative thin-layer chromatography to give **9b** (yellow oil, 49 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (br). MS *m/e*: 208 (M^+, base peak), 180, 149, 79. ^{1}H-NMR (10%, $CDCl_3$) δ: 2.03—2.22 (11H, C(2)– and C(4—10)–H), 2.60 (2H, s, C(3)– and C(5)–H), 3.69 (3H, s, $-CO_2CH_3$). Saponification of **9b** with KOH–MeOH gave 4-oxoadamantane-1-carboxylic acid (**9a**) which was crystallized from Et_2O as colorless prisms, mp 169.5—171°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1715. MS *m/e*: 194 (M^+, base peak), 176, 149, 79. High resolution MS *m/e* (M^+) Calcd for $C_{11}H_{14}O_3$: 194.0942, Found: 194.0907. ^{1}H-NMR (10%, $CDCl_3$) δ: 2.04—2.22 (11H, C(2)– and C(4—10)–H), 2.62 (2H, s, C(3)– and C(5)–H).

Further elution of the column with 500 ml of *n*-hexane–benzene (1: 9), 500 ml of benzene and 500 ml of benzene–$CHCl_3$ (9: 1) gave 319 mg of a brown oil. The oil was subjected to preparative TLC (developed 4 times with *n*-hexane–Et_2O (2: 3)) to give methyl 4-hydroxyadamantane-1-carboxylate (**10b**, 16 mg) and methyl 3-hydroxyadamantane-1-carboxylate (**11b**, 139 mg) as oils.

Methyl 4-Hydroxyadamantane-1-carboxylate (**10b**): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3450, 1720. MS *m/e*: 210

(M^+), 192 (M^+-H_2O), 151 (M^+-CO_2H, base peak), 133. ^{1}H-NMR (10%, $CDCl_3$) δ: 1.73—2.34 (13H, C(2)–, C(3)–, and C(5—10)–H), 3.65 (3H, s, $-CO_2CH_3$), 3.86 (1H, s, C(4)–H). Oxidation of **10b** with the Jones reagent at 0°C for 1 min in Me_2CO gave a product, the gas chromatographic data (condition 2) for which coincided with that of **9b**. Saponification of **10b** with KOH–MeOH yielded 4-hydroxyadamantane-1-carboxylic acid (**10a**), which was crystallized as colorless prisms, mp 117—128°C, from *n*-hexane–Et_2O. IR ν_{max}^{Nujol} cm^{-1}: 3600, 3450, 1700. MS *m/e*: 196 (M^+), 178 (M^+-H_2O), 151 (M^+-CO_2H, base peak), 133. ^{1}H-NMR (10%, $CDCl_3$) δ: 1.67—2.35 (13H, C(2)–, C(3)–, and C(5—10)–H), 3.85 (1H, s, C(4)–H). High resolution MS *m/e* (M^+) Calcd for $C_{11}H_{16}O_3$: 196.1098, Found: 196.1090.

Methyl 3-Hydroxyadamantane-1-carboxylate (**11b**): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3450, 1720. MS *m/e*: 210 (M^+), 151 ($M^+-CO_2CH_3$, base peak), 95 ($C_6H_5\overset{+}{O}H_2$). ^{1}H-NMR (10%, $CDCl_3$) δ: 1.72—1.85 (12H, C(2—4)–, C(6)–, and C(8—10)–H), 2.26 (2H, C(5)– and C(7)–H), 3.66 (3H, s, $-CO_2CH_3$). Saponification of **11b** with KOH–MeOH gave 3-hydroxyadamantane-1-carboxylic acid (**11a**), which was crystallized as colorless crystals, mp 210—212.5°C, from EtOH. IR ν_{max}^{Nujol} cm^{-1}: 3600, 3450, 1700. MS *m/e*: 196 (M^+), 151 (M^+-CO_2H, base peak), 95 ($C_6H_5\overset{+}{O}H_2$). ^{1}H-NMR (10%, DMSO-d_6) δ: 1.50—1.64 (12H, C(2—4)–, C(6)–, and C(8—10)–H), 2.13 (2H, s, C(5)– and C(7)–H). *Anal.* Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.28; H, 8.37.

Determination of the Conversions of 1a and 2a——The conversions of **1a** and **2a** were determined by the internal standard method of gas chromatography. Reaction conditions are shown in the tables and figures. Aliquots of 5 ml of the reaction mixtures were saturated with NaCl and acidified to pH 2 with conc. HCl to give homogeneous solutions, which were then extracted with EtOAc (2 ml×4). The combined organic layer was washed with saturated NaCl solution (2 ml) and the solvent was evaporated off under a N_2 gas stream. The residue was then dissolved into 2 ml of Et_2O-MeOH (3: 1) containing an internal standard (**2a** for **1a** or 2-adamantanone for **2a**), methylated with diazomethane and subjected to gas chromatography (condition 1). Recoveries of **1a** and **2a** were found to be 103 and 95%, respectively.

Quantitation of the Products——The reaction was carried out under the conditions shown in Table II. After 5 ml of the reaction mixture had been treated in the manner described above except for the addition of the internal standard, the methylated EtOAc extract was subjected to gas chromatography (condition 2). The yields of the products were determined from the gas chromatogram (Fig. 3), without correction for relative sensitivities to the FID detector. Several unidentified products were found in Fig. 3 and their structures are under investigation.

Acknowledgement We are indebted to the staff of the Center for Instrumental Analysis, Hokkaido University, for the elemental analysis and the measurements of NMR and mass spectra. A part of this work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan, for which our thanks are also due.

References and Notes

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