[Chem. Pharm. Bull. 33(11)5042—5047(1985)]

Ruthenium Tetroxide Oxidation of 1-Azabicycloalkan-2-ones

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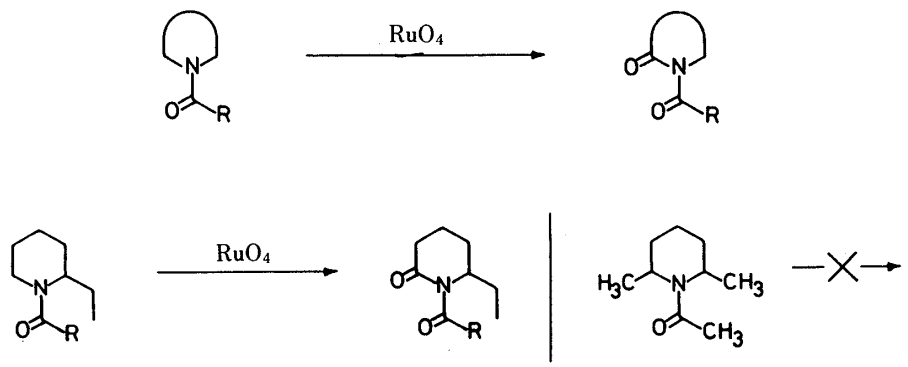
(Received June 3, 1985)

The ruthenium tetroxide (RuO_4) oxidation of 1-azabicycloalkan-2-ones was investigated. The oxidation of quinolizidin-4-one (**4**), indolizidin-3-one (**9**), pyrrolizidin-3-one (**11**) and tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one (**12**) occurred at the bridgehead tertiary carbon atom and afforded the corresponding hydroxy compounds (from **11** and **12**) or the imidobutyric acid derivatives (from **4** and **9**). This regioselectivity is contrary to the general situation in the oxidation of *N*-acyl cyclic amines. However, 1-azabicyclo[4.2.0]octan-8-one (**17**) was oxidized at the secondary carbon atom to give the 2,8-dione (**18**).

Keywords——oxidation; ruthenium tetroxide oxidation; hydroxylation; regioselectivity; 1-azabicycloalkan-2-one; ruthenium tetroxide; two-phase method

Ruthenium tetroxide (RuO_4) is well known as a multi-purpose oxidant which oxidizes various types of organic compounds.[1] Recently it has been used for the oxidation of cyclic amines, generally as their *N*-acyl derivatives, and has given some interesting results.[2] However, the utility of RuO_4 for oxidative transformations of nitrogen-containing heterocyclic compounds has not been widely recognized yet. We wish to report here some of our findings.

As Sheehan found initially,[2a] the reaction of *N*-acylated cyclic amines with RuO_4 produces the corresponding lactams, oxidizing one of the two carbon atoms adjacent to the nitrogen atom. If these carbon atoms are nonequivalent, it would be anticipated that some selective oxidations should occur. In fact, when 1-acetyl- and 1-propionyl-2-ethylpiperidines (**1a**, **b**) were oxidized at room temperature using a catalytic amount of RuO_2 hydrate and excess 10% aqueous sodium metaperiodate in a two-phase system of chloroform–water according to the standard procedure for RuO_4 oxidation,[2a] only the C-6 position methylenes underwent carbonylation to afford 1-acetyl- and 1-propionyl-6-ethylpiperidin-2-ones (**2a**, **b**)



1a : R=CH_3
1b : R=C_2H_5

2a : R=CH_3
2b : R=C_2H_5

3

Chart 1

in 80 and 88% yields, respectively. On the other hand, 1-acetyl-2,6-dimethylpiperidine (**3**) resisted RuO_4 oxidation. These results show that RuO_4 oxidant preferentially oxidizes a secondary carbon atom rather than a tertiary one. Since this selectivity has already been observed with other cyclic amines[2b] and cyclic ethers (to the corresponding lactones),[3] it can be regarded as a common feature of the RuO_4 oxidation. It may be simply explained in terms of which site is more accessible to the RuO_4 oxidant. However, in the oxidation of 1-azabicycloalkan-2-ones noted below, we obtained an opposite result.

The RuO_4 oxidation of quinolizidin-4-one (**4**) having the same substitution pattern on the piperidine ring as compound **1** was carried out under similar conditions (two-phase system, room temperature, 5 h) and provided 4-glutarimidobutyric acid (**7**) in 76% yield. This product was converted to the methyl ester (**8**) and identified with an authentic sample prepared from glutarimide and methyl 4-bromobutyrate. When ethyl acetate was used in place of chloroform as the organic phase of the above oxidation, the yield of **7** rose to 92%.

In order to examine the production of **7** in detail, the same oxidation was run with careful monitoring of the progress of the reaction by thin layer chromatography (TLC), and halted before the exhaustion of **4**. After chromatographic separation of the reaction mixture on alumina, a small amount of the 9,9a-dehydrocompound (**6**) was obtained. The structure of **6** was confirmed by spectroscopic analyses and further chemical transformation. Thus, on treatment of **6** with RuO_4 in the same manner, it was rapidly oxidized to **7** in 79% yield. These observations can be well explained by the reaction pathway presented in Chart 2, *i.e.*, compound **4** is initially oxidized at the bridgehead carbon atom to produce 9a-hydroxyquinolizidin-4-one (**5**), which is dehydrated to **6**, and then the double bond in **6** is cleaved at the second step of oxidation to afford **7**. Oxidative cleavage of an olefin to a carboxylic acid with RuO_4 is well known.[1] Although TLC analysis suggested that the hydroxy compound **5** existed as an intermediate in the initial reaction solution together with **4**, **6**, and **7**, it could not be isolated. Elimination of the hydroxyl group in **5** to form the enamide **6** might be accelerated under acidic conditions with the aqueous sodium metaperiodate employed in this oxidation. Therefore, compound **4** was again subjected to RuO_4 oxidation under basic conditions using aqueous sodium hypochlorite as a co-oxidant[4] for the generation of RuO_4 from RuO_2. As expected, the reaction stopped at the first oxidation step, and compound **5** was isolated in 83% yield as colorless needles of mp 98—100 °C (dec.). It was characterized on the basis of the spectral data. As reported by Schumann,[5] compound **5** was very unstable, being converted into **6** on standing at room temperature or in dry chloroform.

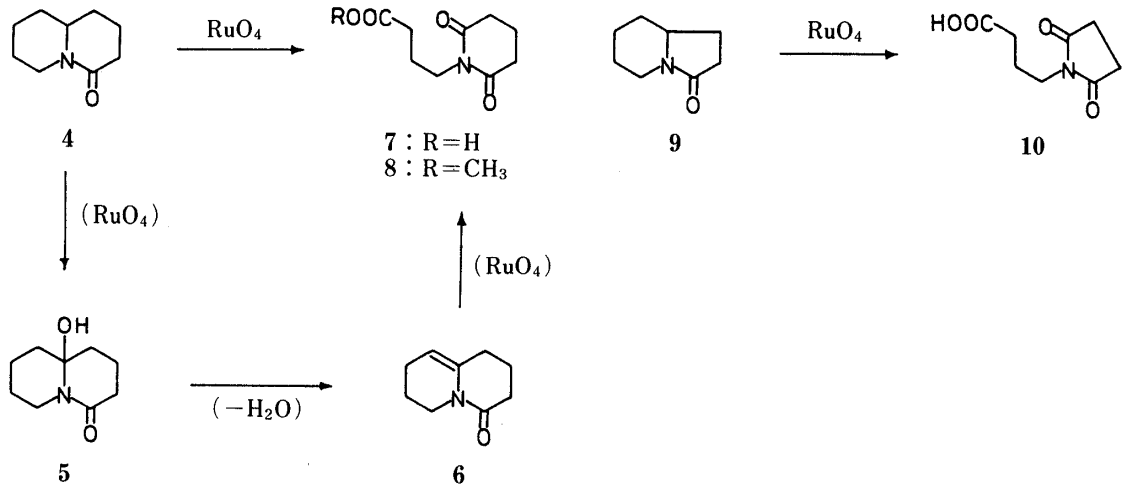


Chart 2

The RuO_4 oxidation of indolizidin-3-one (**9**) under the standard conditions of the two-phase system gave the same result as the above oxidation of **4**, and it afforded 4-succimidobutyric acid (**10**) in 93% yield.

Substantial amounts of the hydroxy compound, the product at the first oxidation step, were obtained in the oxidation of pyrrolizidin-3-one (**11**) and its oxygen-containing analog **12** (Chart 3). The corresponding alcohols **13** and **14** were obtained exclusively in 71 and 81% yields, respectively. The hydroxyl group in these compounds was stable under the conditions used, and elimination or further oxidation did not occur. The structures of **13** and **14** in solution may not be alcohols but may be the ring-opened ketones (**15** and **16**), which might not be susceptible to RuO_4 oxidant. However, this possibility was ruled out by the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra of these compounds in $CDCl_3$; each compound showed one quaternary carbon signal (δ: 97.7 ppm in **13** and 95.4 ppm in **14**) due to a tertiary alcohol.

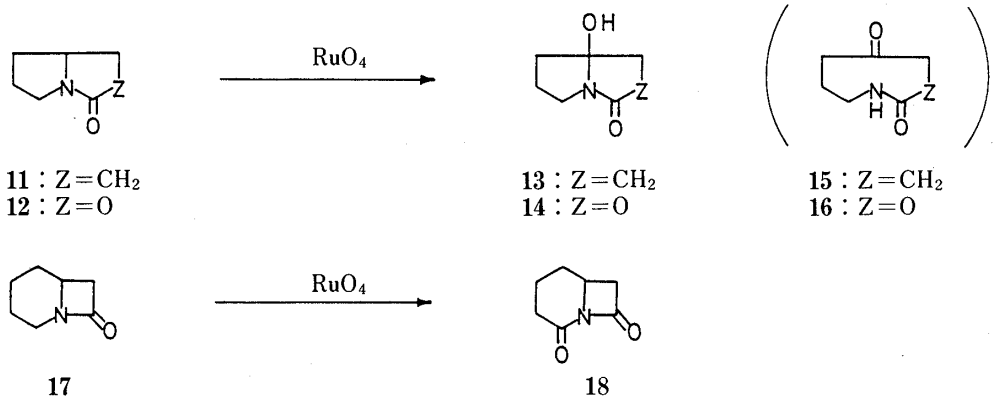


Chart 3

Thus, it was found that the RuO_4 oxidation of these four 1-azabicycloalkan-2-ones occurs predominantly at the tertiary carbon atom even in the presence of a secondary carbon atom. This is contrary to the general situation for *N*-acyl cyclic amines. The bicyclic structure having a rigid carbonyl function may influence the regioselectivity. However, similar treatment of 1-azabicyclo[4.2.0]octan-8-one (**17**) with RuO_4 gave a dioxo compound **18** in 32% yield as a sole product, the structure of which was determined from the signals of two carbonyl carbons (δ: 164.6 and 167.1 ppm) and one tertiary carbon (δ: 51.6 ppm) in the ^{13}C-NMR spectrum. Apparently, this compound resulted from the carbonylation of the methylene carbon atom at the C-2 position.

We can not yet explain the regioselectivity in the RuO_4 oxidations reported here, but we can say that the oxidation of 1-azabicycloalkan-2-ones may belong not to the oxidation category of *N*-acyl cyclic amines but to that of *N*-alkyllactams. This is the first report of such a finding. Further studies are in progress.

We adopted the two-phase method of RuO_4 oxidation for this work and, as the organic solvent, we employed ethyl acetate instead of the traditional chlorinated methane (carbon tetrachloride or chloroform). This change improved the reaction time and the yield; details will be presented in a separate paper.[6]

Experimental

All melting points were taken on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (*IR*) spectra were recorded on a JASCO IRA-2 spectrometer. Mass spectra (MS) were measured on a JEOL JMS D-100 or a JEOL JMS D-300 spectrometer. NMR spectra were obtained at 23 °C using tetramethylsilane as an internal

standard with a JEOL JNM-MH-100 or a JEOL JNM-FX-100 spectrometer.

Starting Materials——1-Acetyl-2-ethylpiperidine (**1a**), 1-propionyl-2-ethylpiperidine (**1b**) and 1-acetyl-2,6-dimethylpiperidine (**3**) were prepared by acylation of 2-ethylpiperidine or 2,6-dimethylpiperidine with acetyl chloride and propionyl chloride under Shotten–Baumann conditions (benzene–aqueous Na_2CO_3, 0—5 °C).

All 1-azabicycloalkan-2-ones were prepared according to the literature procedures as indicated below. Octahydro-4*H*-quinolizin-4-one (**4**),[7] octahydroindolizin-3-one (**9**),[8] hexahydro-3*H*-pyrrolizin-3-one (**11**),[8] tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one (**12**),[9] 1-azabicyclo[4.2.0]octan-8-one (**17**).[10]

RuO_4 Oxidation under the Standard Conditions in a Two-Phase System——A solution of a substrate (12 mmol) to be oxidized in an organic solvent ($CHCl_3$ or AcOEt, 40 ml) was added to a mixture of RuO_2·hydrate [Aldrich Chemical Co.] (120 mg) and 10% aqueous $NaIO_4$ solution (120 ml). The mixture was vigorously stirred using a mechanical stirrer with a glass blade at room temperature in a sealed flask. The reaction was monitored by TLC. The work-up procedure and characterization of the products were as described below.

1-Acetyl-6-ethylpiperidin-2-one (2a)——The oxidation of **1a** was carried out under the standard conditions with $CHCl_3$ for 14 h. After the reaction was completed, the layers were separated. The aqueous layer was extracted with $CHCl_3$ (2 × 40 ml) and the combined $CHCl_3$ solution was treated with iso-PrOH (2 ml) for 2 h to destroy the RuO_4. The black RuO_2 that precipitated from the solution was filtered off and the filtrate was washed with H_2O (40 ml), and dried over anhydrous Na_2SO_4. The solution was evaporated *in vacuo* to leave **2a** (80% yield) as a colorless oil, bp 113 °C (9 mmHg). MS *m/e*: 169 (M^+). IR ν_{max}^{film} cm^{-1}: 1690 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.30—2.00 (6H, m, $C\underline{H}_2CH_3$, C_4-H_2 and C_5-H_2), 2.44 (3H, s, $COCH_3$), 2.45—2.62 (2H, m, C_3-H_2), 4.30—4.52 (1H, m, C_6-H).

1-Propionyl-6-ethylpiperidin-2-one (2b)——After the oxidation of **1b** under the standard conditions ($CHCl_3$, 12 h), the reaction mixture was worked up in a manner similar to that described above for **2a**, and **2b** was obtained in 88% yield as a colorless oil, bp 133 °C (15 mmHg). MS *m/e*: 183 (M^+). IR ν_{max}^{film} cm^{-1}: 1693 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7 Hz, CH_2-$C\underline{H}_3$), 1.14 (3H, t, J=7 Hz, $COCH_2C\underline{H}_3$), 1.32—2.12 (6H, m, C_4-H_2, C_5-H_2 and $C\underline{H}_2CH_3$), 2.46—2.64 (2H, m, C_3-H_2), 2.70—3.06 (2H, m, $COC\underline{H}_2CH_3$), 4.38—4.62 (1H, m, C_6-H).

Oxidation of 1-Acetyl-2,6-dimethylpiperidine (3)——Oxidation of **3** under the standard conditions ($CHCl_3$) did not progress within 72 h and 92% of starting **3** was recovered from the reaction solution.

4-Glutarimidobutyric Acid (7)——1) From Quinolizidin-4-one (**4**): The RuO_4 oxidation of **4** was carried out under the standard conditions with $CHCl_3$ as an organic solvent for 5 h. The layers were separated and the aqueous layer was acidified to pH 1 with 10% hydrochloric acid, then extracted with AcOEt (3 × 40 ml). The extracts were combined with the original $CHCl_3$ solution and treated with iso-PrOH (3 ml) for 8 h. The solution was filtered. The filtrate was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give **7** (76% yield) as a slightly brown oil. MS *m/e*: 199 (M^+). IR ν_{max}^{film} cm^{-1}: 3200 (OH), 1720, 1664 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.76—2.12 (4H, m, C_3-H_2 and $COCH_2C\underline{H}_2$), 2.36 (2H, t, J=7 Hz, C_2-H_2), 2.65 (4H, t, J=7 Hz, two $NCOCH_2$), 3.83 (2H, t, J=7 Hz, C_4-H_2), 7.68 (1H, br s, CO_2H).

A similar oxidation of **4** in AcOEt as the organic solvent was completed within 3 h to give 92% yield of **7**.

2) From **6**: The dehydro compound (**6**) was treated with RuO_4 under the standard conditions (AcOEt, 20 min) to afford **7** (79% yield) which was identical (by comparisons of TLC behavior and IR and NMR spectra) with the sample obtained by method 1.

1,2,3,6,7,8-Hexahydro-4*H*-quinolizin-4-one (6)——1) From **4**: The oxidation of **4** was carried out under the standard conditions ($CHCl_3$), but with half the amount of RuO_2·hydrate (60 mg). The reaction was stopped before the starting **4** ran out. The work-up procedure was similar to that described above for **2a** and the resulting products (containing the starting **4**) were chromatographed on alumina using hexane–AcOEt (4:1, v/v) as the eluent. The dehydro compound **6** (20% yield) was isolated from the first fractions as a colorless oil. It was identical (by comparisons of TLC behavior and IR and NMR spectra) with the sample obtained by method 2.

2) From **5**: A solution of **5** (0.21 g, 1.23 mmol) in $CHCl_3$ was dried over anhydrous Na_2SO_4 for 1 h and evaporated *in vacuo* to leave **6** (0.19 g, 100%) as a colorless oil, bp 70 °C (1 mmHg). MS *m/e*: 151 (M^+). IR ν_{max}^{film} cm^{-1}: 1630 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.55—1.93 (4H, m, C_2-H_2 and C_7-H_2), 1.94—2.18 (2H, m, C_3-H_2), 2.24—2.63 (4H, m, C_1-H_2 and C_8-H_2), 3.61—3.84 (2H, m, C_6-H_2), 4.60—4.78 (1H, m, C_9-H). ^{13}C-NMR ($CDCl_3$) δ: 20.0 (t), 21.6 (t), 22.3 (t), 29.9 (t), 33.2 (t), 40.2 (t), 103.6 (d, C_9), 135.4 (s, C_{9a}), 168.2 (s, C_4).

9a-Hydroxy-octahydro-4*H*-quinolizin-4-one (5)——5% aqueous NaClO solution (12 ml) was added dropwise to a stirred suspension of **4** (0.92 g, 6.0 mmol) in AcOEt (20 ml) and RuO_2·hydrate (30 mg) under cooling in an ice-water bath for a period of 2 h. After the oxidation, iso-PrOH (1 ml) was added to the reaction mixture under stirring and then the organic layer was separated. The aqueous layer was extracted with AcOEt (2 × 40 ml). The extracts were combined with the original AcOEt solution, dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give crude **5** as a colorless solid (0.85 g, 83%), which was recrystallized from ether as colorless prisms, mp 98—100 °C (dec.) [lit[4] mp 124 °C]. MS *m/e*: 169 (M^+), 151 ($M^+ - H_2O$). IR ν_{max}^{KBr} cm^{-1}: 3250 (OH), 1600 (C=O). ^{1}H-NMR (pyridine-d_5) δ: 2.32—2.54 (2H, m, C_3-H_2), 3.18 (1H, t d, J=13 and 3 Hz, C_6-H), 4.67—4.96 (1H, m, C_6-H), 6.75 (1H, br s, OH, disappeared with D_2O), 1.20—2.28 (10H, other protons). ^{1}H-NMR (D_2O) δ: 2.38—2.52 (2H, m, C_3-H_2), 2.74—3.10 (1H, m, C_6-H), 4.16—4.44 (1H, m, C_6-H), 1.20—2.22 (10H, other protons). ^{13}C-NMR (D_2O) δ: 17.9 (t), 21.6 (t), 27.1

(t), 35.0 (t), 39.9 (t), 40.0 (t), 40.4 (t), 80.5 (s, C_{9a}), 176.1 (s, C_4). *Anal.* Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.60; H, 8.97; N, 8.21.

This compound (**5**) is very unstable and decomposes in a short time to the dehydro compound (**6**) on standing at room temperature or in $CHCl_3$ dried over anhydrous Na_2SO_4.

4-Succimidobutyric Acid (10)——The RuO_4 oxidation of indolizidin-3-one (**9**) was carried out under the standard conditions (AcOEt, 4.5 h). After the completion of the reaction, the AcOEt layer was separated. The aqueous layer was washed with CCl_4 (2 × 20 ml) and concentrated under reduced pressure to dryness, leaving a white solid, which was extracted with hot $CHCl_3$ (3 × 50 ml). The combined $CHCl_3$ solution was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to afford **10** (93% yield) as a colorless solid. Recrystallization of the solid from benzene gave colorless needles, mp 104 °C. MS *m/e*: 185 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3050 (OH), 1760, 1730, 1665 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.71—2.10 (2H, m, C_3-H_2), 2.37 (2H, t, J=7 Hz, C_2-H_2), 2.67 (4H, s, $COCH_2CH_2CO$), 3.55 (2H, t, J=7 Hz, C_4-H_2), 10.93 (1H, br s, CO_2H). *Anal.* Calcd for $C_8H_{11}NO_4$: C, 51.89; H, 5.99; N, 7.56. Found: C, 51.79; H, 5.86; N, 7.41.

7a-Hydroxy-hexahydro-3*H*-pyrrolizin-3-one (13)——Pyrrolizidin-3-one (**11**) was oxidized with RuO_4 under the standard conditions (AcOEt, 3 h). The reaction mixture was worked up in a manner similar to that described above for **10**. **13** was obtained in 71% yield as a colorless oil. MS *m/e*: 141 (M^+). IR ν_{max}^{film} cm^{-1}: 3350 (OH), 1664 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 4.77 (1H, br s, OH, disappeared with D_2O), 1.43—3.60 (10H, other protons). ^{13}C-NMR ($CDCl_3$) δ: 25.44 (t, C_6), 33.79 (t, C_1 and C_7), 37.74 (t, C_2), 40.33 (t, C_5), 97.66 (s, C_{7a}), 175.00 (s, C_3).

7a-Hydroxy-tetrahydro-1*H*,3*H*-pyrro[1,2-*c*]oxazol-3-one (14)——The oxidation of **12** under the standard conditions (AcOEt, 152 h), followed by work-up in a manner similar to that used for **10**, provided **14** (81% yield) as a colorless solid. Recrystallization from benzene gave colorless needles, mp 92—93 °C. MS *m/e*: 143 (M^+), 125 ($M^+ - H_2O$). IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 1712 (C=O). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3375, 3600 (OH), 1752 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.61—2.56 (4H, m, C_6-H_2 and C_7-H_2), 3.19—3.67 (2H, m, C_5-H_2), 4.32 (2H, s, C_1-H_2), 4.51 (1H, s, OH, disappeared with D_2O). ^{13}C-NMR ($CDCl_3$) δ: 25.4 (t, C_6), 37.0 (t, C_7), 44.4 (t, C_5), 75.3 (t, C_1), 95.4 (s, C_{7a}), 159.6 (s, C_3). *Anal.* Calcd for $C_6H_9NO_3$: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.41; H, 6.35; N, 9.80.

1-Azabicyclo[4.2.0]octan-2,8-dione (18)——The oxidation of **17** was carried out under the standard conditions (AcOEt, 15 h), but using 5 times more RuO_2·hydrate. After the oxidation, the layers were separated and the aqueous layer was extracted with AcOEt (2 × 40 ml). The combined AcOEt solution was treated with iso-PrOH (2 ml) and filtered. The filtrate was dried and evaporated *in vacuo* to leave **18** (32% yield) as a slightly yellow solid, which showed a single spot on a TLC plate. Recrystallization from isopropyl ether gave colorless needles, mp 89—91 °C. MS *m/e*: 139 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1800 (four-membered lactam C=O), 1678 (six-membered lactam C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.20—2.70 (6H, m, C_3-H_2, C_4-H_2 and C_5-H_2), 3.02 (1H, dd, J=16 and 4 Hz, C_7-H), 3.31 (1H, dd, J=16 and 6 Hz, C_7-H), 3.84—4.12 (1H, m, C_6-H). ^{13}C-NMR ($CDCl_3$) δ: 20.3 (t, C_4), 27.6 (t, C_5), 30.7 (t, C_3), 46.2 (t, C_7), 51.6 (d, C_6), 164.6 (s, C_8), 167.1 (s, C_2). *Anal.* Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.53; H, 6.48; N, 10.08.

Methyl 4-Glutarimidobutyrate (8)——1) From **7**: Compound **7** (1.40 g, 7.0 mmol) in MeOH was treated excess diazomethane in ether to furnish the methyl ester **8** (80%), which was identical (by comparisons of TLC behavior and IR and NMR spectra) with the sample prepared by method 2 described below.

2) From Glutarimide: The following procedure was patterned after that developed by Yamazaki, *et al.*[11] for the N-alkylation of lactams. A solution of glutarimide (2.26 g, 0.02 mol) and methyl 4-bromobutyrate (3.98 g, 0.022 mol) in dry THF (50 ml) was added to a suspension of pulverized KOH (2.47 g, 0.044 mol) and tetrabutylammonium bromide (1.29 g, 0.004 mol) in dry THF (20 ml) over 1.5 h at room temperature. After the completion of addition, the reaction mixture was stirred for 1 h. The precipitate was filtered off and the filtrate was evaporated *in vacuo* to leave an oil, to which benzene (50 ml) and H_2O (30 ml) were added. The benzene layer was separated and the aqueous layer was extracted with benzene (2 × 30 ml). The extracts were combined, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure and distillation of the residue gave **8** (2.94 g, 69%) as a colorless oil, bp 128 °C (0.5 mmHg). MS *m/e*: 213 (M^+). IR ν_{max}^{film} cm^{-1}: 1730 (ester C=O), 1670 (imide C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.76—2.08 (4H, m, C_3-H_2 and $NCOCH_2CH_2$), 2.31 (2H, t, J=7 Hz, C_2-H_2), 2.62 (4H, t, J=7 Hz, two $NCOCH_2$), 3.64 (3H, s, CO_2CH_3), 3.79 (2H, t, J=7 Hz, C_4-H_2).

Acknowledgment The authors are greatly indebted to Professor Tozo Fujii of Kanazawa University and Dr. Yoshio Arata for their kind encouragement.

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