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Studies on 1-Alkyl-2(1*H*)-pyridone Derivatives. XV.[1] The Confirmation of the Configuration of the Diels-Alder Adduct of 1-Methyl-2(1*H*)-pyridone by NMR Spectroscopy using Deuteration

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In the previous paper, it was reported that the structure of the adduct (II), which was produced from the Diels–Alder reaction of 1-methyl-2-(1*H*)pyridone (I) with maleic anhydride, was estimated to be 2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylic anhydride.[3] It was also mentioned that the structure of the diester compound (IV), which was obtained by the epimerization, was estimated to be dimethyl 2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-*endo*-6-*exo*-dicarboxylate.[4]

In this work, the same reactions were carried out on 3,5-dideutero-1-methyl-2(1*H*)-pyridone(I_D). The structures of II and IV were unambiguously confirmed to the same as those in the previous paper.

In a previous work of this series, the Diels–Alder reaction of 1-methyl-2(1*H*)-pyridone (I) was successfully carried out[3] and an isoquinuclidine derivatives (II) having substituents *cis* to each other was obtained in 42% yield. Its structure was estimated to be 2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylic anhydride. Furthermore, the epimerization of the diester compound (III) derived from II was carried out[4] and an isoquinuclidine derivative (IV) having substituents *trans* to each other was obtained in almost quantitative yield. The structure of IV was estimated to be dimethyl 2-methyl-3-oxo-2-azabicyclo-[2.2.2]oct-7-ene-5-*endo*-6-*exo*-dicarboxylate.

In this work of this series, the same reactions were carried out on 3,5-dideutero-1-methyl-2(1*H*)-pyridone (I_D) and these experiments presented unambiguous evidence supporting the original estimation. Consequently, the configurations of II and IV were confirmed, and these are reported herein.

In the previous paper,[3] the configuration of II was estimated from the examination of the nuclear magnetic resonance (NMR) spectrum (Fig. 1 and Table I) of the bromolactone (V) derived from II.

That was as follows. If the peaks in the lower mangetic field of the NMR spectrum of V were arbitrarily designated as A,F,E,B,D and C, and with considerations to the decoupling and coupling constants, the protons were found to be lined in the order of A,B,C,D,E and F. In addition, with consideration to the reports of VerNooy,[5] Woodward,[6] and Berson, *et al.*,[7] the possible structures of V are shown as Va—Vc (Chart 1). The most reasonable assignment of the peaks in the NMR spectrum for V would be Va′—Vc′ as shown in Chart 2.

If V was considered as taking Va structure, the lowest peak (A, 5.30 ppm in CF_3COOH) in the NMR spectrum of V would be assigned to the proton at the base of oxygen in the lactone

1) Part XIV: H. Tomisawa, H. Hongo, H. Kato, and R. Fujita, *Chem. Pharm. Bull.* (Tokyo). **19**, 2414 (1971).
2) Location: *Nankozawa, Odawara, Sendai.*
3) H. Tomisawa and H. Hongo, *Chem. Pharm. Bull.* (Tokyo), **18**, 925 (1970).
4) H. Tomisawa, R. Fujita, K. Noguchi, and H. Hongo, *Chem. Pharm. Bull.* (Tokyo), **18**, 941 (1970).
5) C.D. VerNooy and C.S. Rondestvedt, Jr., *J. Am. Chem. Soc.*, **77**, 3583 (1955).
6) R.B. Woodward and H. Baer, *J. Am. Chem. Soc.*, **70**, 1161 (1948).
7) J.A. Berson and R. Swidler, *J. Am. Chem. Soc.*, **75**, 1721 (1953).

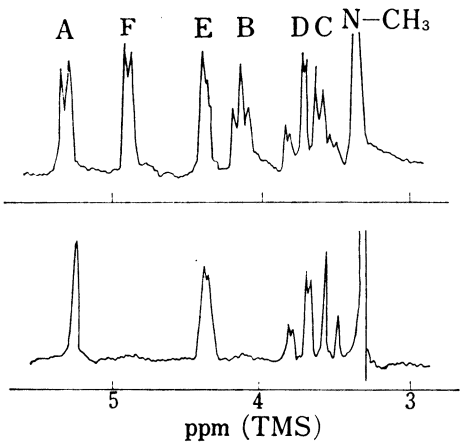

Fig. 1. NMR Spectra of V and V_D in CF_3COOH

Table I.[a] NMR Spectrum[b] of V in CF_3COOH

	Chemical shift (ppm)	Coupling constant (J), cps
A	5.30	$J_{AB}=5$
F	4.87	$J_{FE}=3$
E	4.37	$J_{EF}=3$, $J_{ED}=2.5$
B	4.12	$J_{BA}=5$, $J_{BC}=5$
D	3.73	$J_{DE}=2.5$, $J_{DC}=10$
C	3.57	$J_{CB}=5$, $J_{CD}=10$
N-CH_3	3.34	

a) This was reported in the previous paper.[3]
b) Tetramethylsilane was used as an intrenal standard.

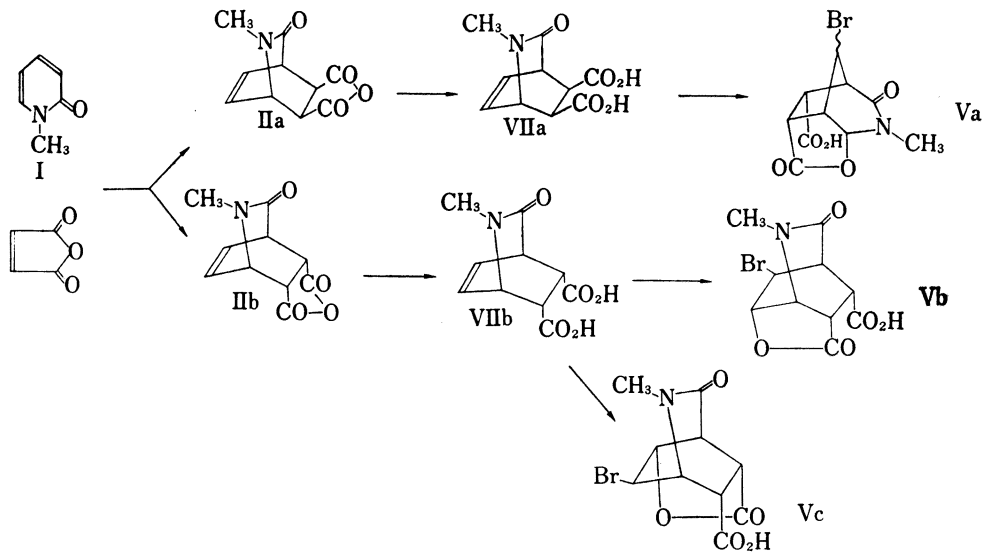

Chart 1

Me
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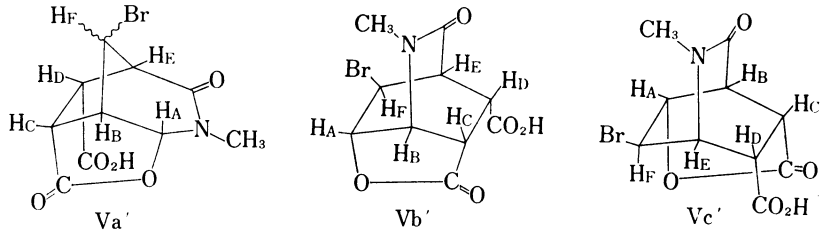
and of nitrogen on the lactam (-COOCHNCO-). With reference to the NMR spectral data[8] of the proton (5.63 ppm in $CDCl_3$) in -COOCH_2NHCO-, it seems that the chemical shift of the peak A is too high to be considered as the proton at the base of oxygen in the lactone in Va. It was the reason that the structure of Va was excluded. But, the compounds having the same or analogous structure to Va were not known yet, so it seems to be impossible to exclude the structure of Va for no other reason than that the peak A was present in too high a magnetic field. Consequently, it would be very difficult but not be impossible to assume the structure of Va as V.

Whether V was Vb or Vc, was estimated by the two considerations for NMR spectrum of V. First, the peak A (5.30 ppm) in the NMR spectrum of V was present in almost the

8) R.N. Silverstein and G.S. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley & Sons, Inc., New York, 1967, p. 143.



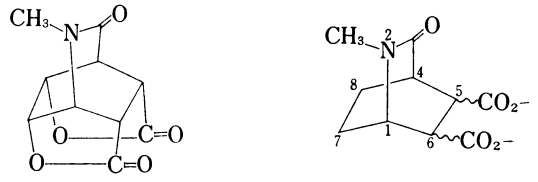


Chart 2

same position of the peak [5.20 ppm (2H) in CF_3COOH], which was assigned to the protons at the base of oxygen in the two lactone in the NMR spectrum of the dilactone (VI) (Chart 2) derived from V. Therefore, the peak A was assigned to the proton at the base of oxygen in the lactone. Second, in the NMR spectrum of a straight-chain amide compound such as R-C(Hn)$_2$-NR-CO-C(Hco)$_2$-R, the peak of Hn was usually assigned to be in a lower magnetic field than that of Hco. Therefore, in the NMR spectrum of V, the peak of the proton in the 1-position was estimated to be in a lower mangetic field than that in the 4-position (the system of numbering of isoquinuclidine derivative skeletion is shown by VIII in Chart 2). According to the NMR spectrum of V, the peak E was present in a lower mangetic field than the peak B. This fact agreed with Vc' in Chart 2. With consideration of those results, the structure of V was estimated as Vc.

However, the structures of Vb and Vc are the characteristic cage form, and the amide group of these structures are rigidly fixed. Consequently, in the NMR spectra of those compounds, the proton in the 4-position would be affected by the deshielding effect of the anisotropy of the carbonyl in the lactam, and would be shifted to a lower mangetic field. From the foregoing consideration, it would be very difficult but not be impossible to assume that the peak of the proton in the 4-position is assigned to be in a lower magnetic field than that in the 1-position. If it was so, the structure of V would be estimated to Vb instead of Vc. For these reasons, it seems to be ambiguous to apply the second cosideration for the cage compounds such as isoquinuclidine derivatives. In the present work, the following experiments were carried out in order to elucidate these points.

I was deuterized with deuterium oxide and deuterium sulfate by the method of Kawazoe, *et al.*,[9] and 3,5-dideutero-1-methyl-2(1*H*)-pyridone (I_D) was obtained. The Diels–Alder reaction of I_D and maleic anhydride was carried out, and the dideutero adduct (II_D) was obtained. II_D was treated with water to afford the dideutero dicarboxylic acid (VII_D). Treatment of the aqueous solution of VII_D with bromine gave the dideutero bromolactone (V_D). The yields and melting points of these dideutero compounds were almost the same as those of their hydrogen derivatives, respectively. However, the protons of these dideutero compounds were two protons less than the relative hydrogen derivatives in the NMR spectra, respectively. The following examination was carried out in order to confirm the structure of V. If V was assumed as Va, Vb and Vc, and by considering the structure of V_D which was

9) Y. Kawazoe and Y. Yoshioka, *Chem. Pharm. Bull.* (Tokyo), **16**, 715 (1968).

derived from I_D, the two deuterons would be assigned to H_B and E_E in Va', H_A and H_E in Vb', and H_B and H_F in Vc', respectively, as shown in Chart 2. The two deuterons should disappear in the NMR spectrum (Fig. 1) of V_D. Comparing the NMR spectrum of V with that of V_D, as shown in Fig. 1, the peaks of B and F disappeared. This result agreed with Vc' in Chart 2.

Therefore, the bromolactone (V) is confirmed as Vc, the same configuration of the previous estimation.[3] Consequently, it was confirmed that the configuration of the all compounds estimated in the previous paper[3] were correct.

In the previous paper,[4] the estimation of the structure of IV derived by the epimerization of III was accomplished by comparing the NMR spectrum of III (Fig. 2 and Table II) with that of IV (Fig. 3 and Table III).

TABLE II.[a] NMR Spectrum[b] of III in D-pyridine

	Chemical shift (ppm), (Position)	Coupling constant (J), cps
A	6.61 (C_7, C_8-H)	
B	4.52 (C_1-H)	$J=2.5$, $J=2.5$, $J=5$
C	3.94 (C_4-H)	$J=2.3$, $J=2.3$, $J=5$
D	3.79 (C_6-H)	$J=2.5$, $J=10$
E	3.62 (C_5-H)	
$CO_2CH_3\times2$	3.62	
N-CH_3	2.9	

a) This was reported in the previous paper.[4]
b) Tetramethylsilane was used as an internal standard.

TABLE III.[a] NMR Spectrum[b] of IV in D-pyridine

	Chemical shift (ppm), (Position)	Coupling constant (J), cps
A	6.5 (C_7, C_8-H)	
B	4.64 (C_1-H)	$J=1.8$, $J=1.8$, $J=5$
C	4.08 (C_4-H)	$J=2.5$ $J=2.5$, $J=5.5$
D	3.76 (C_5-H)	$J=2.5$, $J=4.7$
E	3.39 (C_6-H)	$J=1.8$, $J=4.7$
$CO_2CH_3\times2$	3.65, 3.60	
N-CH_3	2.9	

a) This was reported in the previous paper.[4]
b) Tetramethylsilane was used as an internal standard.

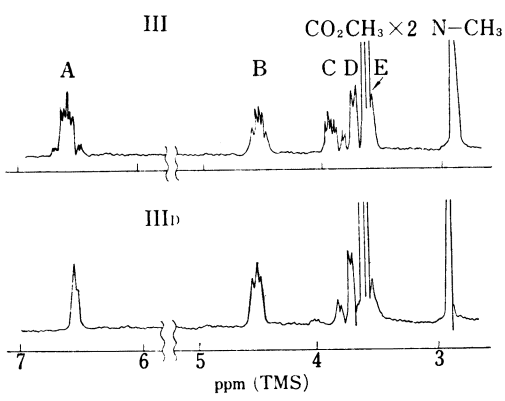


Fig. 2. NMR Spectra of III and III_D in D-Pyridine

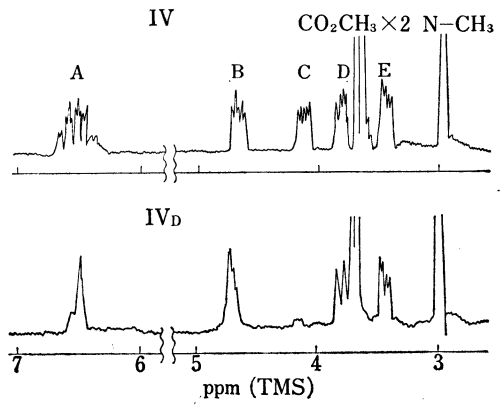


Fig. 3. NMR Spectra of IV and IV_D in D-Pyridine

This comparison was based on the reports of Fraser[10] and Tori, *et al.*,[11] in which they discussed the effect of the anisotropy in the bicyclo[2.2.2] system similar to III and IV. Therefore, that comparison is unambiguous. The NMR assignment of III and IV were carried out as follows. If the peaks in the lower magnetic field of the NMR spectra of III and IV were arbitrarily designed as A, B, C, D and E, both A (2H) should be assigned to the protons in the 7- and 8-positions. With considerations to the decoupling and coupling constants (Table II and III), the protons would be lined in the order of B,D,E and C in the case of III, and in the order of B,E,D and C in the case of IV. Next, it was the problem whether the proton in the 1-position was B or C. That was depended on the second consideration (*vide supra*) in the structral estimation of V. According to this reasoning, the peak B was assigned to the proton in the 1-position, and the peak C to that in the 4-position.

However, the ambiguity of using the second consideration might make it possible to be reversed the assignment of the protons in 5- and 6-positions of III and IV (Chart 3). If it was so, the configuration of IV would be changed to IVb instead of IVa estimated in the previous paper[4] (Chart 3). In the present work, the following examinations were carried out in order to confirm the structures of III and IV.

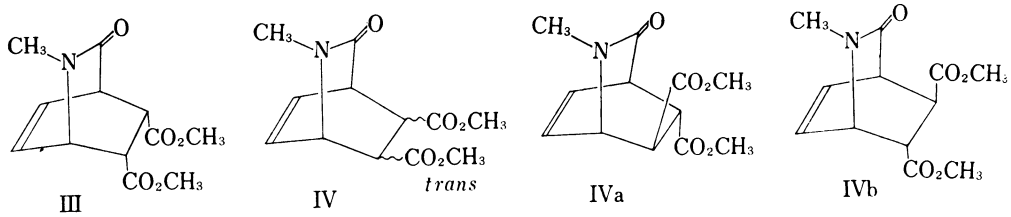


Chart 3

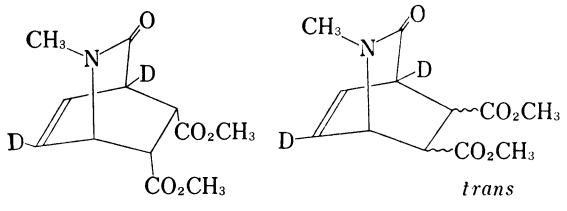


Chart 4

The dideutero dicarboxylic acid (VII_D) was esterified with thionyl chloride and methanol as the previous paper[4] and the dideutero diester compound (III_D) was obtained quantitatively. Its melting point was the same as that of III. The epimerization of III_D was successfully carried out and the epimerized dideutero diester compound (IV_D) was obtained in 67.5% yield. From the fact that the starting material is I_D, the structures of III_D and IV_D are shown in Chart 4. The deuteron must be located in the 4-position of III_D and IV_D. Therefore, if the NMR spectra of III_D and IV_D were compared with those of III and IV, respectively, the peaks, which were assigned to the protons in the 4-position of III and IV should disappear in the NMR spectra of III_D and IV_D. The NMR spectra of III, III_D, IV, and IV_D were given in Fig. 2 and Fig. 3. According to Fig. 2 and Fig. 3, both the peaks C, which were assigned as the protons in the 4-position of III and IV, disappeared in the NMR spectra of III_D and IV_D. Consequently, it follows that the all peaks in the NMR spectra of III and IV would be assigned unambiguously. These results agreed with the assignment of previous paper.[4]

Consequently, it is unambiguously confirmed that III is dimethyl 2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylate, and IV is dimethyl 2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-*endo*-6-*exo*-dicarboxylate (IVa).

10) R.R. Fraser, *Can. J. Chem.*, **40**, 78 (1962).
11) K. Tori, Y. Hata, R. Muneyuki, Y. Takano, T. Tsuji, and H. Tanida, *Can. J. Chem.*, **42**, 926 (1964).

Experimental[12]

4,7-Dideutero-2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylic Anhydride (II_D)——A mixture of 10 g of I_D, 17.5 g of maleic anhydride, and 100 ml of toluene was gently refluxed for 72 hr and allowed to stand overnight at room temperature. The precipitate thereby formed was collected by filtration and recrystallized from Ac_2O to give colorless fine crystalline powder (II_D), mp 180—181°. Yield, 7.9 g (42%). *Anal.* Calcd. for $C_{10}H_7D_2O_4N$: N, 6.70. Found: N, 6.57. IR ν_{max}^{Nujol} cm^{-1}: 1855, 1755 (acid anhydride C=O), 1680 (δ-lactam C=O). NMR (in CF_3COOH) ppm: 3.15 (3H, singlet, N-CH_3), 3.97 (1H, doublet, J=9 cps, C_5-H), 4.14 (1H, quartet, J=9, J=4 cps, C_6-H), 5.00 (1H, multiplet, C_1-H), 6.70 (1H, broad singlet, C_8-H).

4,7-Dideutero-2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylic Acid (VII_D)——A solution of 2.1 g of II_D, dissolved in 16 ml of H_2O was allowed to stand overnight at room temperature. H_2O was then evaporated and the residue was recrystallized from H_2O to give colorless fine crystalline powder (VII_D), mp 175—177° (decomp.). Yield, 2.0 g (87.7%). *Anal.* Calcd. for $C_{10}H_9D_2O_5N$: N, 6.17. Found: N, 6.18. IR ν_{max}^{Nujol} cm^{-1}: 1720 (carboxyl C=O), 1700 (carboxyl C=O), 1625 (δ-lactam C=O). NMR (in CF_3COOH) ppm: 3.21 (3H, singlet, N-CH_3), 3.73 (1H, doublet, J=10.5 cps, C_5-H), 3.88 (1H, quartet, J=10.5, J=2.5 cps, C_6-H), 4.89 (1H, multiplet, C_1-H), 6.70 (1H, broad singlet, C_8-H).

7-*exo*-Bromo-4-deutero-7-*endo*-deutero-6-*endo*-carboxy-8-*endo*-hydroxy-2-methyl-3-oxo-2-azabicyclo-[2.2.2]octane-5-*endo*-carboxylic Acid γ-Lactone (V_D)——A solution of 1.0 g of VII_D, dissolved in 6 ml of H_2O, was maintained at 0—7° and Br_2 was added dropwise until a faint yellow color remained. The precipitate thereby formed was collected by filtration and recrystallization from H_2O to give colorless fine crystalline powder (V_D), mp 230—233° (decomp.). Yield, 1.1 g (82.1%). *Anal.* Calcd. for $C_{10}H_8D_2O_5NBr$: N, 4.58. Found: N, 4.58. IR ν_{max}^{Nujol} cm^{-1}: 1785 (γ-lactone C=O), 1720 (carboxyl C=O), 1645 (δ-lactam C=O). NMR (in CF_3COOH) ppm: 3.31 (3H, singlet, N-CH_3), 3.54 (1H, doublet, J=10 cps, C_5-H), 3.73 (1H, quartet, J=10, J=2.5 cps, C_6-H), 4.37 (1H, multiplet, C_1-H), 5.26 (1H, multiplet, C_8-H).

4-Deutero-7-*exo*-deutero-7,8-*endo*-dihydroxy-2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-5,6-*endo*-dicarboxylic Acid γ-Dilactone (VI_D)——A mixture of 2g of V_D, 1.1 g of KOH, and 27 ml of EtOH was refluxed for 10 hr. The reaction mixture was rendered acid to Congo Red with conc. HCl. The precipitate that formed was collected by filtration. A solution of 2.4 g of the precipitate dissolved in 30 g of Ac_2O was heated in an oil bath at 110° for 4 hr. The solvent was evaporated under a reduced pressure and the residue was recrystallized from H_2O to give colorless fine crystalline powder (VI_D), mp 280—284°. Yield, 0.45 g (30.5%). *Anal.* Calcd. for $C_{10}H_7D_2O_5N$: N, 6.22. Found: N, 6.51. IR ν_{max}^{Nujol} cm^{-1}: 1805, 1780 (γ-lactone C=O), 1685 (δ-lactam C=O). NMR (in CF_3COOH) ppm: 3.34 (3H, singlet, N-CH_3), 3.66 (2H, borad singlet, C_5-H, C_6-H), 4.87 (1H, multiplet, C_1-H), 5.30 (1H, broad singlet, C_8-H).

Dimethyl 4,7-Dideutero-2-methyl-3-oxo-2-azabicyclo[2.2.2]-oct-7-ene-5,6-*endo*-dicarboxylate (III_D)——Into 50 ml of ice cooled MeOH, 5.5 g of $SOCl_2$ was added dropwise, followed by 4.9 g of VII_D, and the mixture was allowed to stand overnight at room temperature. The reaction mixture was poured into ice water and basified with $NaHCO_3$. This was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and the solvent was evaporated from the extract. The residue was recrystallized from benzene to give colorless needles (III_D). mp 114—115°. Yield, 5.5 g (85.1 %). *Anal.* Calcd. for $C_{12}H_{13}D_2O_5N$: N, 5.49. Found: N, 5.60. IR ν_{max}^{Nujol} cm^{-1}: 1740 (methoxycarbonyl C=O), 1665 (δ-lactam C=O). NMR (in deuteropyridine) ppm : 2.88 (3H, singlet, N-CH_3), 3.53—3.64 (7H, C_5-H, $COOCH_3 \times 2$), 3.76 (1H, quartet, J=10, J=2.5 cps, C_6-H), 4.52 (1H, multiplet, C_1-H), 6.57 (1H, broad singlet, C_8-H).

Dimethyl 4,7-Dideutero-2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-*endo*-6-*exo*-dicarboxylate (IV_D)——A solution of 2 g of III_D, which dissolved in 16 ml of *tert*-BuOH and added with 35 mg of metallic K, was refluxed under N_2 for 60 min. The cooled reaction mixture was poured into ice water and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$. The evaporation of $CHCl_3$ from the extract left 1.8 g of oil. The oily residue was submitted to column chromatography over silica gel and the column was eluted with MeOH-$CHCl_3$ (1:49). The evaporation of the solvent and the recrystallization of the residue from ether gave IV_D as colorless needles, mp 64—65°. Yield, 1.35 g (67.5%). *Anal.* Calcd. for $C_{12}H_{13}D_2O_5N$: N, 5.49. Found: N, 5.67. IR ν_{max}^{Nujol} cm^{-1}: 1730 (methoxycarbonyl C=O), 1650 (δ-lactam C=O). NMR (in deuteropyridine) ppm: 2.95 (3H, singlet, N-CH_3), 3.43 (1H, quartet, J=5, J=2 cps, C_6-H), 3.64 (3H, singlet, $COOCH_3$), 3.71 (3H, singlet, $COOCH_3$), 3.78 (1H, doublet, J=5 cps, C_5-H), 4.70 (1H, multiplet, C_1-H), 6.49 (1H, broad singlet, C_8-H).

Acknowledgement The author is greatly indebted to Prof. H. Tomisawa of this College for the kind advice and encouragements. He also wishes to thank the members of his laboratory for some discussions. He certainly wants to express the thank to Mr. F. Sakakibara of this College for the microanalysis, the Analysis Center of the Institute of Pharmacy, Tohoku University School of Medicine and Japan Electron Optics Lab. for the measurement of NMR spectra.

12) All melting points are uncorrected.