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Studies on 1-Alkyl-2(1*H*)-pyridone Derivatives. XIII.[1] Syntheses of 5-*endo*-6-*exo*-Dicyano- and -Dimethoxycarbonyl-2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene

Hiroshi Tomisawa, Reiko Fujita, Katsuyuki Noguchi, and Hiroshi Hongo

Tohoku College of Pharmacy[2]

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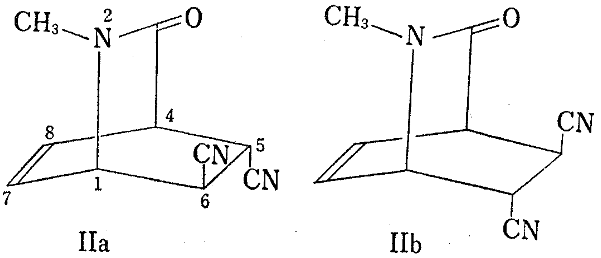
The Diels–Alder reaction of 1-methyl-2(1*H*)-pyridone (I) and fumaronitrile was carried out and the structure of the adduct (II) thereby formed was determined as 5-*endo*-6-*exo*-dicyano-2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene (IIa). IIa was obtained only in a low yield of 3% but the diester compound (Xa) with the same configuration was synthesized in a high yield of 88% by the epimerization of IX, obtained in a quantitative yield from the known VIII.

In a previous work of this series,[3] the Diels–Alder reaction of 1-methyl-2(1*H*)-pyridone (I) was carried out, using maleic anhydride as a dienophile, and an isoquinuclidine derivative having substituents *cis* to each other was obtained. In the present series of work, experiments were carried out in order to obtain isoquinuclidine derivative having substituents *trans* to each other.

First, the Diels–Alder reaction of I and fumaronitrile was attempted. A solution of 2.7 g of I and 2.9 g of fumaronitrile dissolved in 25 ml of toluene was refluxed gently for 111 hr and the reaction mixture was treated to column chromatography over silica gel. A product obtained formed colorless columnar crystals (II) of mp 177—178°, $C_{10}H_9ON_3$, in 0.14 g (3%) yield. The ultraviolet (UV) spectrum of II did not have the absorption for a pyridone ring, while its infrared (IR) spectrum (in Nujol) showed absorption for a cyano group at 2240 cm^{-1} and for a carbonyl in the δ-lactam at 1690 cm^{-1}, so that II is the objective adduct. Consequently, the structure of II must be IIa or IIb, as shown in Chart 1.



IIa IIb

Chart 1

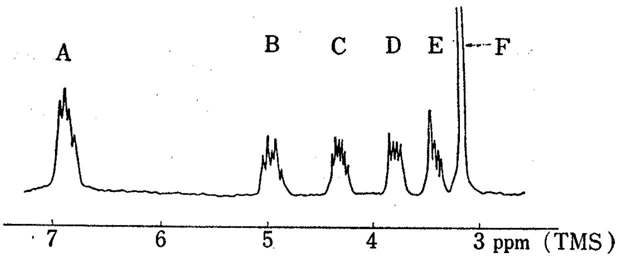


Fig. 1. NMR Spectrum of II in CF_3COOH (100 Mcps)
$J_{BE}=2.0$ cps, $J_{CD}=2.5$ cps, $J_{DE}=4.4$ cps

If the signals in the lower magnetic field in the nuclear magnetic resonance (NMR) spectrum of II (in CF_3COOH) (Fig. 1) are designated arbitrarily as A, B, C, D, E, and F, A(2H) would be assigned to the proton in the double bond between 7- and 8-positions. From their coupling constants of the remaining B, C, D, and E, the protons were found to be lined in the

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1) Part XII: H. Tomisawa, K. Saito, H. Hongo, and R. Fujita, *Chem. Pharm. Bull.* (Tokyo), **18**, 935 (1970).
2) Location: *Nankozawa, Odawara, Sendai.*
3) H. Tomisawa and H. Hongo, *Chem. Pharm. Bull.* (Tokyo), **18**, 923 (1970).

order of B, E, D, and C. In the NMR spectrum (in $CDCl_3$) of 1-methyl-2-pyrrolidone,[4] the proton in the 5-position (3.4 ppm) is assigned to a lower magnetic field than that in the 3-position (2.3 ppm). With consideration of this fact, B must be assigned to the proton in 1-position, or at the base of ring nitrogen. This will give D (3.75 ppm) to the proton in 5-position and E(3.37 ppm) to that in 6-position. The coupling constant between E and D is 4.4 cps and, even from the fact that the starting material is fumaronitrile, the cyano groups at 5- and 6-positions are *trans* to each other. Configuration of the cyano group at 5- and 6-positions was determined in the following way.

Fraser[5] and Tori, *et al.*[6,7] reported that, in the NMR spectra of compounds possessing a bicyclic ring system, and an interesting shift takes place by the reduction of the double bond on the *endo*- and *exo*-protons of ethylene forming the corresponding side, as shown in Chart 2. In bicyclo[2.2.1]heptane system compounds, reduction of the double bond results in the shift of the *endo*-proton to a lower magnetic field by 0.05 ppm and *exo*-proton to a higher magnetic field by 0.14 ppm, as will be seen in the compounds III, III', IV, and IV'.

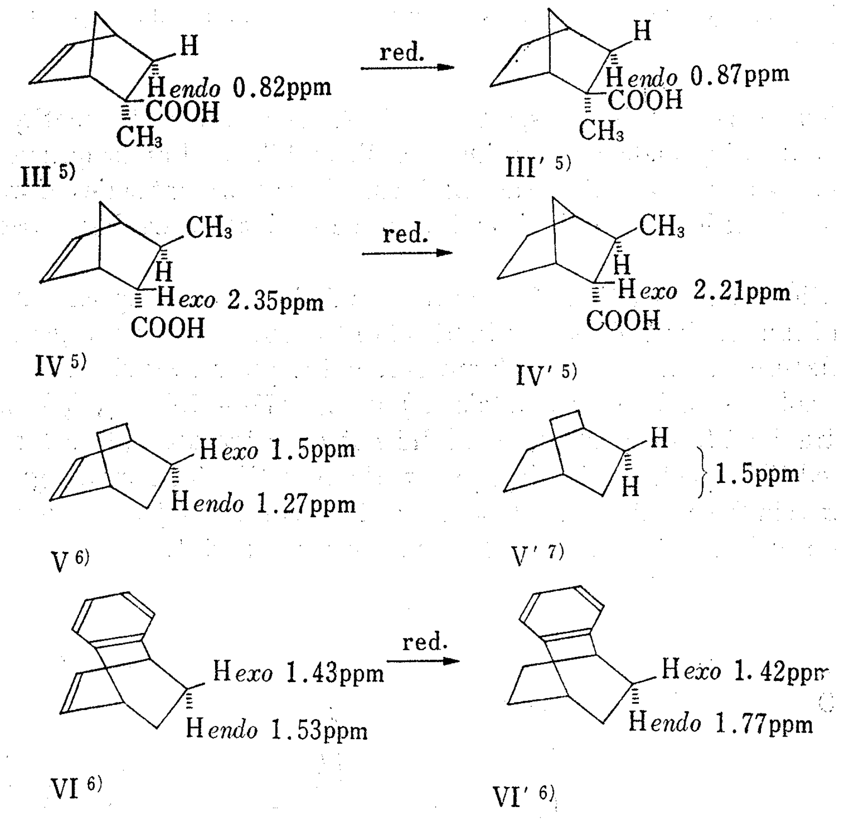

Chart 2

In the bicyclo[2.2.2]octane system, reduction of the double bond results in the shift of the signal for *endo*-proton to a lower magnetic field by 0.23 ppm but that of *exo*-proton remains in approximately the same position, as seen in compound V, V', VI, and VI'. These facts indicate that the *endo*-proton is greatly affected by the diamagnetic anisotropy of the double bond and its signal is shifted to a higher magnetic field in the compounds with a double bond.

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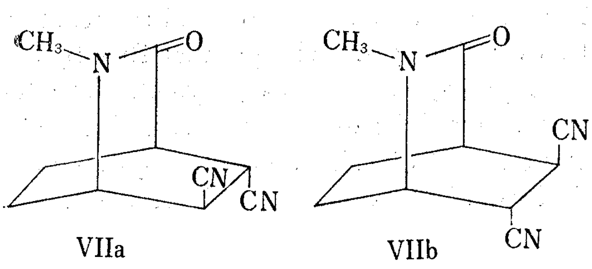
4) R.M. Silverstein and G.C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley & Sons, Inc., New York, 1967, p. 137.
5) R.R. Fraser, *Can. J. Chem.*, **40**, 78 (1962).
6) K. Tori, Y. Hata, R. Muneyuki, Y. Takano, T. Tsuji, and H. Tanida, *Can. J. Chem.*, **42**, 926 (1964).
7) F.A. Bovey, "NMR Data Tables for Organic Compounds," Vol. 1, Interscience Publishers, Inc., New York, 1967, p. 228.

Therefore, reduction of II over palladium-charcoal catalyst was carried out and the reaction was stopped when a calculated amount of hydrogen had been absorbed because, if the reaction were allowed to progress until absorption of hydrogen stops, the cyano group will be reduced to an amino group. The reduction product was obtained quantitatively as colorless needles (VII), mp 140—141°, $C_{10}H_{11}ON_3$. The IR spectrum (in Nujol) of VII exhibited absorptions for a cyano group at 2240 cm^{-1} and for carbonyl in δ-lactam at 1680 cm^{-1}. Consequently, the structure of VII would be either VIIa or VIIb, as shown in Chart 3.



VIIa VIIb

Chart 3

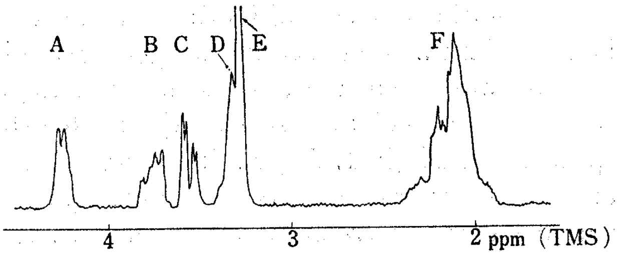


Fig. 2. NMR Spectrum of VII in CF_3COOH (100 Mcps)
$J_{AC}=1.5$ cps, $J_{BC}=5.0$ cps, $J_{BD}=3.0$ cps

If the signals in the lower magnetic field of the NMR spectrum of VII (in CF_3COOH) (Fig. 2) were designated arbitrarily as A, B, C, D, E, and F, and with consideration of decoupling and coupling constants, the protons were found to be lined in the order of A, C, B, and D. A should be assigned to the proton in 1-position, B (3.75 ppm) would therefore be the proton at 5-position, and C (3.54 ppm) the proton at 6-position. The chemical shift of the proton at 5- and 6-positions in II and VII is given in Table I.

Table I. Chemical Shifts[a] and Coupling Constants of II and VII

Compound	Chemical shift (ppm[b])		Coupling constant (J), cps
	C_5–H	C_6–H	J_{5-6}
II	3.75	3.37	4.4
VII	3.75	3.54	5.0

a) solvent: trifluoroacetic acid
b) Tetramethylsilane was used as an internal standard.

According to the values listed in Table I, the proton at 5-position shows the same chemical shift in the two compounds but that at 6-position in the reduced compound is present in a lower magnetic field than that in II by 0.17 ppm. With reference to the NMR data reported by Fraser and by Tori, *et al.*, the above is an evidence that the 5-position is an *exo*-proton and the 6-position is an *endo*-proton. It follows, therefore, that the cyano group in 5-position is in *endo* and that in 6-position is in *exo* configuration, and II would be IIa, or 5-*endo*-6-*exo*-dicyano-2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene.

Unfortunately, the yield of IIa is only 3% and, although this is a reaction for the formation of an isoquinuclidine derivative with *trans* substituents, it would not be possible to use it as a practicable process for its preparation. Therefore, the previously reported 2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylic acid[3] (VIII) was derived to its diester compound (IX) and its epimerization was examined. VIII was esterified with thionyl chloride and methanol by the method of Determann, *et al.*,[8] and IX was obtained quantitatively as colorless plates, mp 112—113°, $C_{12}H_{15}O_5N$. The IR spectrum (in Nujol) of IX exhibited

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8) H. Determann, O. Zipp, and T. Wieland, *Ann.*, **651**, 172 (1962).

absorptions at 1735 cm^{-1} for ester carbonyl and at 1655 cm^{-1} for a carbonyl in the δ-lactam. In the NMR spectrum of IX (in deuteriopyridine) (Fig. 3), if the signals in the lower magnetic field are arbitrarily designated as A, B, C, D, E, and F, A (2H) would be the protons of the double bond at 7, 8 position and B would be assigned to the proton in 1-position. With consideration on the decoupling and coupling constants, the protons would be lined in the order of B, D, E, and C. Therefore, E (3.62 ppm) would be the proton at 5-position and D (3.79 ppm) that at 6-position, and the coupling constant of 10 cps between D and E indicates that they are in maintained in *cis* configuration.

A soultion of 5.06 g of IX dissolved in 40 ml of *tert*-butanol and added with 80 mg of metallic potassium was refluxed in nitrogen stream for 70 min in an oil bath of 110° and the reaction mixture was submitted to column chromatography over silica gel. The product thereby obtained formed colorless scales (X), mp 67—68°, $C_{12}H_{15}O_5N$, in 4.45 g (88%) yield. The IR spectrum of X (in Nuiol) exhibited absorptions at 1730 cm^{-1} for ester carbonyl and at 1657 cm^{-1} for a carbonyl in the δ-lactam, clearly different from that of IX. Consequently, epimerization seems to have occured and the structure of X would be expressed as either Xa or Xb, as shown in Chart 4.

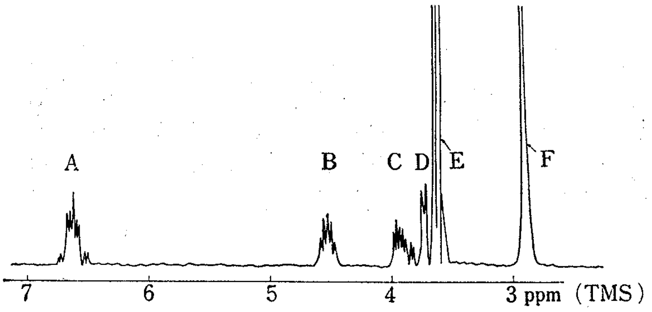


Fig. 3. NMR Spectrum of IX in D-pyridine (100 Mcps)
J_{BD}=2.5 cps, J_{DE}=10.0 cps, J_{CE}=2.3 cps

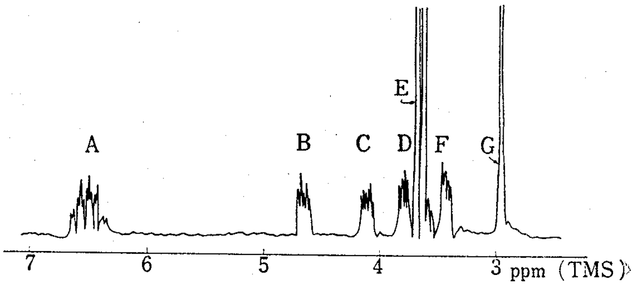
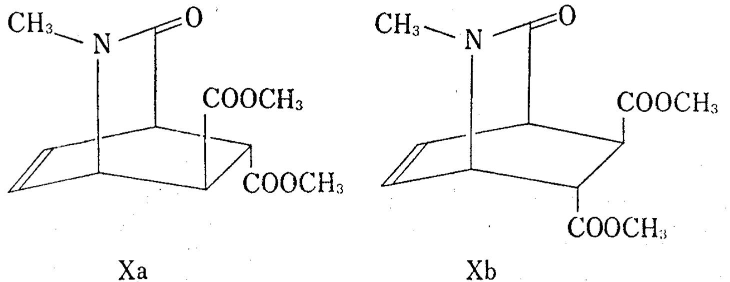
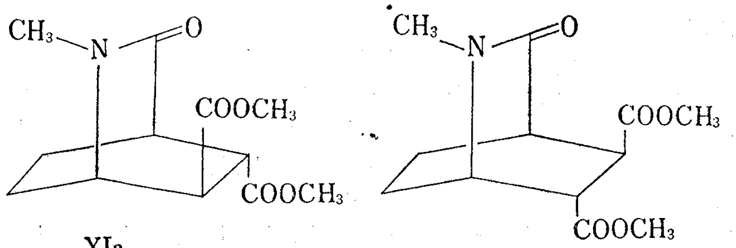


Fig. 4. NMR Spectrum of X in D-pyridine (100 Mcps)
J_{BF}=1.8 cps, J_{DF}=4.7 cps, J_{CD}=2.5 cps



Xa Xb

Chart 4



XIa XIb

Chart 5

If the signals in the lower magnetic field of the NMR spectrum of X (in deuteriopyridine) (Fig. 4) were arbitrarily assigned as A, B, C, D, E, F, and G, A (2H) would be assigned to the proton in the double bond at 7—8 position and B to the proton in 1-position. With consideration of decoupling and coupling constants, the protons were found to be lined in the order of B, F, D, and C. Consequently, D (3.76 ppm) would be the proton at 5-position and F (3.39 ppm) that at 6-position. The coupling constant between D and F is 4.7 cps and this value is approximately the same as that (4.4 cps) in II, in which the cyano groups in 5- and 6-positions are in *trans*, so that X underwent epimerization into *trans*. Catalytic reduction of X over platinum dioxide in methanol quantitatively afforded colorless plates (XI), mp 110°, $C_{12}H_{17}O_5N$. The IR spectrum of XI (in Nujol) showed absorptions for ester carbonyl at 1730 and 1720 cm^{-1}, for a carbonyl in the δ-lactam at 1660 cm^{-1}. The structure of XI would therefore be either XIa or XIb, as shown in Chart 5.

If the signals in the lower magnetic field in the NMR spectrum of XI (in deuteriopyridine) (Fig. 5) were to be arbitrarily designated as A, B, C, D, E, and F, the protons were found to be lined in the order of A, C, B, and D, with considerations to the decoupling and coupling constants. As in the case of X, it seems appropriate to assign the signal A in the lowest magnetic field to the proton in 1-position. Consequently, B (3.62 ppm) would be the proton at 5-position and C (3.46 ppm) that at 6-position. The coupling constant between B and C is 5.0 cps and they would be *trans* configuration.

The chemical shift of proton at 5- and 6-positions in IX, X, and XI is listed in Table II.

Table II. Chemical Shifts[a] and Coupling Constants of IX, X, and XI

Compound	Chemical shift (ppm[b]) C_5–H	Chemical shift (ppm[b]) C_6–H	Coupling constant (J),cps J_{5-6}
IX	3.62	3.79	10.0
X	3.76	3.39	4.7
XI	3.62	3.46	5.0

a) solvent: pentadeuteropyridine
b) Tetramethylsilane was used as an internal standard.

IX had been obtained by mild esterification of the structurally identified *endo*:*endo*-dicarboxylic acid (VIII) and the protons in the 5- and 6-positions are maintaining the *cis* configuration so that the configuration in IX would probably be the same as that in VIII. Therefore, the protn in IX would both be *exo*. Comparison of the NMR spectra of IX and X obtained by its epimerization would show that the signal for the proton that has changed to *endo* has shifted to a higher magnetic field and that unchanged proton remains in approximately the same position as IX, as anticipated from Chart 1. From the value listed in Table II, it may be assumed that the proton in 5-position has remained *exo* and that at 6-position has changed to *endo*.

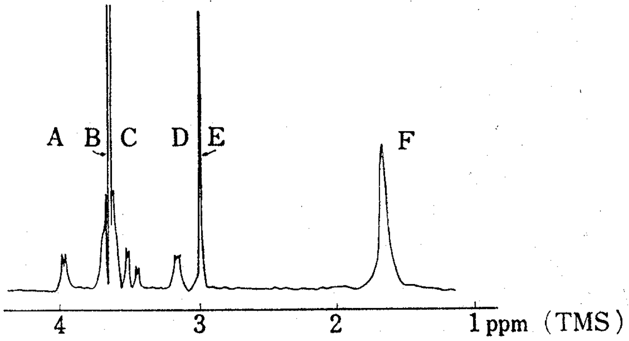


Fig. 5. NMR Spectrum of XI in D-pyridine (100 Mcps)

$J_{AC}=1.8$ cps $J_{CB}=5.0$ cps

With the reduction of X to XI, the *endo*-proton will no longer be under the influence of diamagnetic anisotropy of the double bond and its signal would shift to a lower field. The signal for proton in 5-position has shifted to a higher magnetic field after the reduction while that of the proton in 6-position has inversely shifted to a lower magnetic field. These facts also indicate that the proton in 5-position is *exo* and that in 6-position is *endo* in both X and XI. Therefore, X would be Xa or dimethyl 2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-*endo*-6-*exo*-dicarboxylate and XI would be XIa.

Although the dicyano compound (IIa) was obtained only in 3% yield by the Diels–Alder reaction, the diester compound (Xa) with the same configuration is obtained in a high yield of 88%.

Experimental[9]

5-*endo*-6-*exo*-Dicyano-2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene (IIa)——A solution of 2.7 g of I and 2.9 g of fumaronitrile dissolved in 25 ml of toluene was refluxed gently for 111 hr. The cooled reaction mixture was passed through a chromatographic column of silica gel and the column was eluted with benzene–$CHCl_3$ (3:1). The solvent was evaporated from this fraction and the residue was recrystallized from benzene–$CHCl_3$ (1:3) to IIa as colorless columnar crystals, mp 177—178°. Yield, 0.14 g (3%). *Anal.* Calcd. for $C_{10}H_9ON_3$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.49; H, 4.88; N, 22.20. IR ν_{max}^{Nujol} cm^{-1}: 2240 (C≡N), 1690 (C=O). NMR[10] (5% solution in CF_3COOH) ppm: 6.85 (2H, multiplet, C_7–H, C_8–H), 4.92 (1H, sextet, $J=5.5$, $J=2.0$, $J=2.0$ cps, C_1–H), 4.28 (1H, quintet, $J=5.5$, $J=2.5$, $J=2.5$ cps, C_4–H), 3.75 (1H, quartet, $J=4.4$, $J=2.5$ cps, C_5–H), 3.37 (1H, quartet, $J=4.4$, $J=2.0$ cps, C_6–H), 3.21 (3H, singlet, N–CH_3).

5-*endo*-6-*exo*-Dicyano-2-methyl-3-oxo-2-azabicyclo[2.2.2]octane (VIIa)——A mixture of 0.1 g of IIa and 40 mg of 10% Pd–C in 30 ml of MeOH was allowed to absorb calculated amount of H_2 at room temperature. The catalyst was filtered off and the solvent was evaporated from the filtrate. The residue was recrystallized from benzene–$CHCl_3$ (1:3) to VIIa as colorless needles, mp 140—141°. Yield, quantitative. *Anal.* Calcd. for $C_{10}H_{11}ON_3$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.44; H, 5.96; N, 22.15. IR ν_{max}^{Nujol} cm^{-1}: 2240 (C≡N), 1680 (C=O). NMR[11] (5% solution in CF_3COOH) ppm: 4.25 (1H, doublet, $J=1.5$ cps, C_1–H), 3.75 (1H, octet, $J=5.0$, $J=3.0$, $J=1.3$ cps, C_5–H), 3.54 (1H, quartet, $J=5.0$, $J=1.5$ cps, C_6–H), 3.33 (1H, singlet, C_4–H), 3.29 (3H, singlet, N–CH_3), 1.9—2.5 (4H, multiplet, C_7, C_8–H).

Dimethyl 2-Methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylate (IX)——Into 10 ml of ice-cooled MeOH, 1.05 g of $SOCl_2$ was added dropwise, followed by 1 g of VIII, and the mixture was allowed to stand over night at room temperature. The reaction mixture was poured into ice water covered with benzene and basified with $NaHCO_3$. This was extracted with benzene and the solvent was evaporated from the extract. The residue was recrystallized from benzene to 0.68 g of colorless columnar crystals (IX), mp 112—113°. The aqueous layer was further extracted with $CHCl_3$ and 0.42 g of IX was obtained. Total yield, 1.10 g (98%). *Anal.* Calcd. for $C_{12}H_{15}O_5N$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.84; H, 5.98; N, 5.64. IR ν_{max}^{Nujol} cm^{-1}: 1735 (C=O), 1655 (C=O), 1165 (C–O). NMR[10] (in deuteriopyridine) ppm: 6.61 (2H, multiplet, C_7,C_8–H), 4.52 (1H, quintet, $J=2.5$, $J=2.5$, $J=5.0$ cps, C_1–H), 3.94 (1H, sextet, $J=2.3$, $J=2.3$, $J=5.0$ cps, C_4–H), 3.79 (1H, quartet, $J=2.5$, $J=10$ cps, C_6–H), 3.62 (7H, C_5–H, $COOCH_3 \times 2$), 2.9 (3H, singlet, N–CH_3).

Dimethyl 2-Methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-*endo*-6-*exo*-dicarboxylate (Xa)——A solution of 5.06 g of IX dissolved in 40 ml of *tert*-BuOH added with 80 mg of metallic K was refluxed in N_2 stream at 110° for 70 min. The cooled reaction mixture was poured into ice water and extracted with $CHCl_3$. Evaporation of $CHCl_3$ from the extract left 4.46 g of an oil. The aqueous layer was salted out with NaCl and extracted with $CHCl_3$, from which 0.156 g of oil was obtained. The combined oily residue as a $CHCl_3$ solution was submitted to column chromatography over siilca gel and the column was eluted with *tert*-BuOH–AcOEt (3:1). Evaporation of the solvent and recrystallization of the residue from ether gave Xa as colorless needles, mp 67—68°. 4.45 g (87.9%). *Anal.* Calcd. for $C_{12}H_{15}O_5N$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.86; H, 6.12; N, 5.69. IR ν_{max}^{Nujol} cm^{-1}: 1730 (C=O), 1657 (C=O), 1190 (C–O). NMR[10] (in deuteriopyridine) ppm: 6.5 (2H, multiplet, C_7,C_8–H), 4.64 (1H, sextet, $J=1.8$, $J=1.8$, $J=5.0$ cps, C_1–H), 4.08 (1H, sextet, $J=2.5$, $J=2.5$, $J=5.5$ cps, C_4–H), 3.76 (1H, quartet, $J=2.5$, $J=4.7$ cps, C_5–H), 3.60 (3H, singlet, $COOCH_3$), 3.65 (3H, singlet, $COOCH_3$), 3.39 (1H, quartet, $J=1.8$, $J=4.7$ cps, C_6–H), 2.9 (3H, singlet, N–CH_3).

Dimethyl 2-Methyl-3-oxo-2-azabicyclo[2.2.2]octane-5-*endo*-6-*exo*-dicarboxylate (XIa)——A solution of 0.5 g of Xa dissolved in MeOH and added with 50 mg of PtO_2 was submitted to reduction for 1 day. The catalyst was filtered off and the solvent was evaporated from the filtrate. The residue was recrystallized from ether to XIa as colorless plates, mp 110°. Yield, 0.5 g (99%). *Anal.* Calcd. for $C_{12}H_{17}O_5N$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.59; H, 6.74; N, 5.69. IR ν_{max}^{Nujol} cm^{-1}: 1730 (C=O), 1720 (C=O), 1660 (C=O), 1160 (C–O). NMR[10] (in deuteriopyridine) ppm: 3.96 (1H, singlet, C_1–H), 3.62 (7H, C_5–H, $COOCH_3 \times 2$), 3.46 (1H, quartet, $J=1.8$, $J=5.0$ cps, C_6–H), 3.15 (1H, singlet, C_4–H), 2.96 (3H, singlet, N–CH_3), 1.65 (4H, singlet, C_7, C_8–H).

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[9] All melting points are uncorrected.

[10] NMR spectrum was obtained on Japan Electron Optics Lab., Model 4H-A spectrograph at 100 Mc.

[11] NMR spectrum was obtained on Varian Model S-100 A at 100 Mc.