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Studies on 1-Alkyl-2(1*H*)-pyridone Derivatives. XXVI.[1] A Novel Synthesis of 6-Azabicyclo[3.2.1]octane System from 1-Alkyl-2(1*H*)-pyridone

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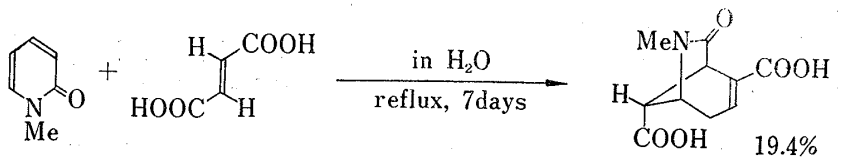
The further studies for synthesis of 6-azabicyclo[3.2.1]octane derivatives from 1-alkyl-2(1*H*)-pyridones (I) are carried out. Reaction of Ia—e with fumaric acid (II) without solvent gave 6-alkyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2,8-*endo*-dicarboxylic acid (IIIa—e) and 6-alkyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2,8-*exo*-dicarboxylic acid (IVa, b, d, e). Reaction of Ia—e with II in water gave IIIa—e. Reaction of Ia with maleic acid in water and without solvent afforded only IIIa.

Keywords——1-alkyl-2(1*H*)-pyridone; 6-azabicyclo[3.2.1]octane; fumaric acid; maleic acid; 6-alkyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2,8-*endo*-dicarboxylic acid; 6-alkyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2,8-*exo*-dicarboxylic acid

There are considerable literatures dealing with the syntheses of 6-azabicyclo[3.2.1]octane derivatives. These compounds are generally prepared by the intramolecular cyclizations of 3-aminohexanecarboxylic acid derivatives,[3] 4-aminomethylcyclohexene derivatives,[4] and cyclohexanecarboxamides.[5] Furthermore, these compounds were synthesized by the rearrangements of tricycloaziridine derivatives,[6] 2-azabicyclo[2.2.2]octane derivatives,[7] and by the intermolecular addition[8] of *p*-menthadiene with methylenebisurethane. In the previous



Ia II IIIa

Chart 1

1) Part XXV: H. Tomisawa, H. Hongo, H. Kato, R. Fujita, and A. Sato, *Chem. Pharm. Bull.* (Tokyo), **26**, 2312 (1978).
2) Location: *4-4-1 Komatsushima, Sendai 983, Japan.*
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paper of this series,[1] we have reported that the reaction of 1-methyl-2(1*H*)-pyridone (Ia) with fumaric acid (II) in water afford 6-methyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2,8-*endo*-dicarboxylic acid (IIIa), as shown in Chart 1. This synthetic method would be more advantageous than the others, because the materials are commercially available and the procedure is simple. Therefore, in order to extend this reaction for synthesis of 6-azabicyclo[3.2.1]octane derivatives, further investigations are carried out and these are reported in the present paper.

Reaction of Ia with II (Without Solvent)

A mixture of Ia and II was heated at 170° for 1 week to give colorless prisms (IVa) of mp 305—306° (dec.) in 13% yield and colorless prisms (IIIa) of mp 268—270° (dec.) in 6.8% yield, besides the recovery of Ia in 33% yield. The structure of IIIa was identified as 6-methyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2,8-*endo*-dicarboxylic acid by the comparison of its infrared (IR) and nuclear magnetic resonance (NMR) spectra with those of an authentic sample.[1]

The structure of IVa was confirmed as 6-methyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2,8-*exo*-dicarboxylic acid by the following way. Elemental analysis and molecular-weight determination of IVa provided its empirical formular as $C_{10}H_{11}NO_5$, which was the same as

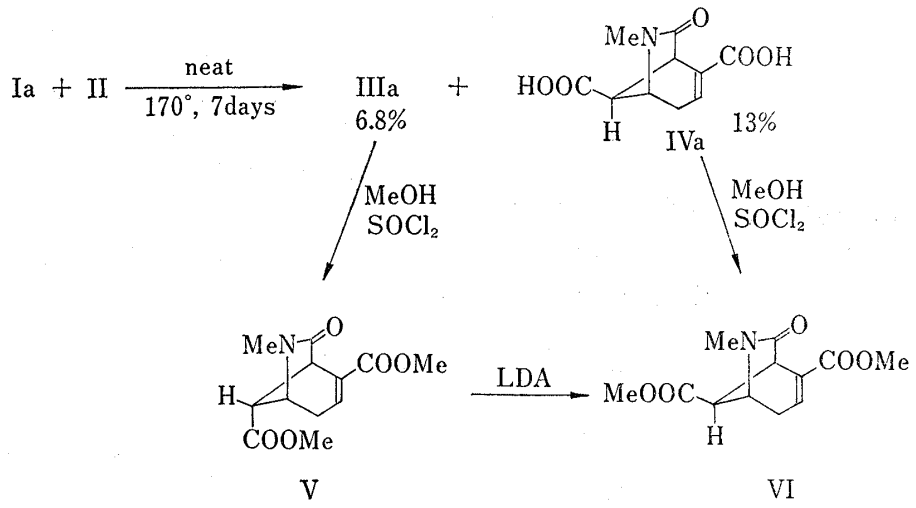


Chart 2

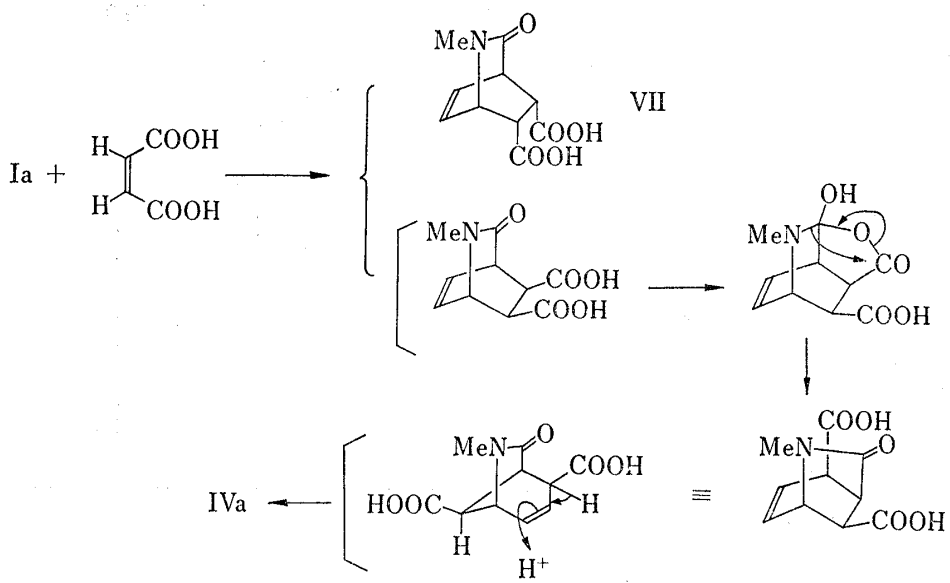


Chart 3

that of IIIa. In order to disclose the relation between IIIa and IVa, following reactions were carried out. Esterification of IIIa and IVa gave the corresponding dimethyl esters, V as colorless prisms of mp 109—110° and VI as colorless prisms of mp 116—118°. Treatment of V with lithium diisopropylamide (LDA) afforded a mixture of V and VI (2:3). V should be an epimer of VI, therefore IVa is an epimer of IIIa. Moreover, the reaction of IVa with bromine did not afford any bromolactone, but that of IIIa with bromine under the same conditions gave the bromolactone.[1] These results supported the carboxyl group of IVa was in *exo* configuration (Chart 2).

Reaction of Ia with Maleic Acid

Considering the path way[1] from Ia with II to IIIa, it would be expected that the reaction of Ia with maleic acid gave IVa and/or adduct[9] (VII) (Chart 3).

Against this expectation, both reactions of Ia with maleic acid in water and without solvent gave only IIIa in 6.6% and 16.9% yield, respectively, besides II and Ia (Chart 4). Boiling of a solution of maleic acid in water gave II and the yield of II was increased by prolonged reaction. The above facts suggested that IIIa was obtained by the reaction of Ia with II derived from maleic acid.

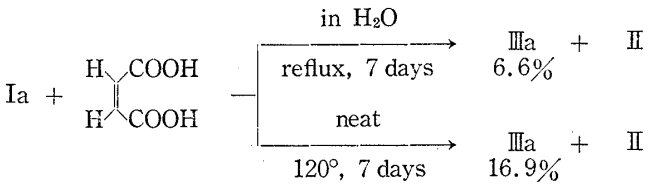
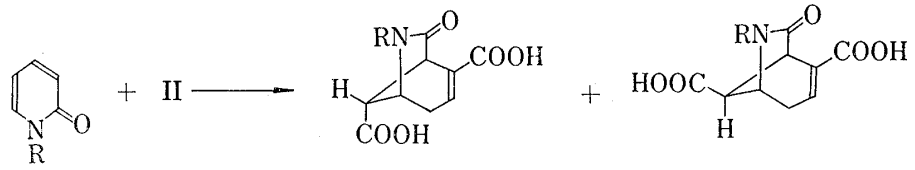


Chart 4

Reaction of 1-Alkyl-2(1*H*)-pyridones with II

Reactions of 1-alkyl-2(1*H*)-pyridones (Ib—e) with II in water (or water–acetic acid) gave IIIb—e, and gave without solvent IIIb—e, IVb, d, e, respectively (Table I). These

Table I. Reaction of I with II



Ia—e IIIa—e IVa,b,d,e

Starting material I	R	Solvent	Temp. (°C)	Time (day)	Product (yield, %) III	IV
a[a)]	Me	H_2O	Reflux	7	19.4	
a	Me	None	170	7	6.8	13
b	Et	H_2O	Reflux	7	8.6	
b	Et	None	170	7	6.2	19.5
c	iso-Pro	H_2O	Reflux	7	15.3	
c[b)]	iso-Pro	None	120	7	17.8	
d	CH_2Ph	H_2O+AcOH	Reflux	7	3.6	
d	CH_2Ph	None	170	7	35.6	18.9
e	$(CH_2)_2Ph$	H_2O+AcOH	Reflux	7	4.8	
e	$(CH_2)_2Ph$	None	170	7	6.3	21.5

a) Reference 1).
b) No product was obtained at 170°.

9) H. Tomisawa and H. Hongo, *Chem. Pharm. Bull.* (Tokyo), **18**, 925 (1970).

structures were confirmed by comparing NMR spectra of the products with those of IIIa and IVa, respectively.

Experimental[10]

Reaction of 1-Methyl-2(1*H*)-pyridone (Ia) with Fumaric Acid (II)——A mixture of Ia (5 g) and II (2.66 g) was heated in an oil bath at 170° for 1 week. $CHCl_3$ (30 ml) and H_2O (30 ml) were added to the reaction mixture, and the mixture was stirred overnight at room temperature. The precipitate formed was collected by filtration, and recrystallized from EtOH to give 6-methyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2,8-*exo*-dicarboxylic acid [IVa (0.67 g)], mp 305—306° (dec.), in 13% yield as colorless prisms. H_2O layer separated from the filtrate was evapolated under a reduced pressure, and the residue was treated with MeOH and 10% HCl. The resulting solid was collected, and recrystallized from EtOH to afford 6-methyl-7-oxo-6-azabicyclo-[3.2.1]oct-2-ene-2,8-*endo*-dicarboxylic acid[1] [IIIa (0.35 g)], mp 268—270° (dec.), in 6.8% yield as colorless prisms. $CHCl_3$ layer from the filtrate was washed with saturated aq. K_2CO_3, and evaporated to recover Ia (1.65 g) in 33% yield. IVa: *Anal.* Calcd. for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.92; N, 6.22. Found: C, 53.41; H, 4.81; N, 6.09. IR ν_{max}^{Nujol} cm^{-1}: 1740, 1690 (COOH), 1630 (NC=O), 1615 (C=C). MS *m/e*: 225 (M^+). NMR (pyridine-d_5) δ: 2.55 (2H, m, C_4–H_2), 2.86 (3H, s, N–Me), 3.05 (1H, s, C_3–H), 4.34 (1H, m, C_5–H), 4.58 (1H, s, C_1–H), 7.10 (1H, m, C_3–H).

Reaction of 1-Ethyl-2(1*H*)-pyridone (Ib) with II——a) A mixture of Ib (20 g), II (9.43 g) and H_2O (95 ml) was refluxed for 1 week, and the mixture was allowed to stand overnight at room temperature. The precipitate [6.2 g (65.7%) of II] formed was filtered off. The filtrate was evaporated under a reduced pressure, and the residue was extracted with hot hexane. The resulting solid was collected, and recrystallized from EtOH to afford 6-ethyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2,8-*endo*-dicarboxylic acid [IIIb (1.65 g)], mp 254—256° (dec.), in 8.6% yield as colorless prisms. The hexane extract was evaporated to recover Ib (13.4 g) in 67% yield. *Anal.* Calcd. for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.86. Found: C, 55.50; H, 5.46; N, 5.96. IR ν_{max}^{Nujol} cm^{-1}: 1730, 1680 (COOH), 1620 (NC=O). MS *m/e*: 239 (M^+). NMR (pyridine-d_5) δ: 1.13 (3H, t, J=7 Hz, CH_2–Me), 2.45 (1H, broad d, J=20 Hz, C_4–H_{endo}), 2.98 (1H, broad d, J=20 Hz, C_4–H_{exo}), 2.8—4.0 (2H, m, CH_2–Me), 3.6 (1H, t, J=4.5 Hz, C_8–H), 4.15 (1H, m, C_5–H), 4.39 (1H, d, J=4.5 Hz, C_1–H), 7.12 (1H, m, C_3–H).

b) A mixture of Ib (5 g) and II (2.36 g) was heated in an oil bath at 170° for 1 week. $CHCl_3$ (25 ml) and H_2O (25 ml) were added to the reaction mixture, and the mixture was stirred overnight at room temperature. The precipitate formed was collected by filtration, and recrystallized from EtOH to give 6-ethyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2,8-*exo*-dicarboxylic acid [IVb (0.95 g)], mp 288—290° (dec.), in 19.5% yield as colorless prisms. H_2O layer separated from the filtrate was evaporated under a reduced pressure, and the residue was treated with acetone. The resulting solid was collected, and recrystallized from EtOH to afford IIIb (0.3 g) in 6.2% yield. $CHCl_3$ layer from the filtrate was washed with saturated aq. K_2CO_3, and chromatographed on a column of silica gel to recover Ib (2.5 g) in 50% yield. IVb: *Anal.* Calcd. for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.86. Found: C, 55.51; H, 5.61; N, 5.93. IR ν_{max}^{Nujol} cm^{-1}: 1730, 1675 (COOH), 1630 (NC=O), 1610 (C=C). MS *m/e*: 239 (M^+). NMR (pyridine-d_5) δ: 1.1 (3H, t, J=7 Hz, N–CH_2–Me), 2.58 (2H, m, C_4–H_2), 3.02 (1H, s, C_8–H), 2.8—4.0 (2H, m, N–CH_2–Me), 4.43 (1H, m, C_5–H), 4.58 (1H, s, C_1–H), 7.12 (1H, m, C_3–H).

Reaction of 1-Isopropyl-2(1*H*)-pyridone (Ic) with II——a) A mixture of Ic (5 g), II (2.13 g) and H_2O (20 ml) was refluxed for 1 week. $CHCl_3$ was added to the reaction mixture, and the mixture was stirred overnight at room temperature. The precipitate [1.02 g (47.9%) of II] formed was filtered off. H_2O layer separated from the filtrate was evaporated under a reduced pressure, and the residue was treated with 10% HCl. The resulting solid was collected, and recrystallized from EtOH to yield 6-isopropyl-7-oxo-6-azabicyclo-[3.2.1]oct-2-ene-2,8-*endo*-dicarboxylic acid [IIIc (0.71 g)], mp 230—232° (dec.), in 15.3% yield as colorless fine crystals. *Anal.* Calcd. for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.81; H, 6.01; N, 5.62. MS *m/e*: 253 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1725, 1690 (COOH), 1640 (NC=O). NMR (pyridine-d_5) δ: 1.20 (6H, d, J=7 Hz, N–CH Me_2), 2.38 (1H, broad d, J=20 Hz, C_4–H_{endo}), 3.00 (1H, d-t, J=20, J=3 Hz, C_4–H_{exo}), 3.57 (1H, t, J=5 Hz, C_8–H), 4.1—4.55 (3H, m, C_1–H, C_5–H, N–CH Me_2), 7.20 (1H, m, C_3–H).

b) A mixture of Ic (5 g) and II (2.13 g) was heated in an oil bath at 120° for 1 week. $CHCl_3$ (20 ml) and H_2O (20 ml) were added to the reaction mixture. The mixture was treated as the above-mentioned Ic, and gave IIIc (0.82 g) in 17.8% yield, besides recovering II (1.12 g) in 52.6% yield.

Reaction of 1-Benzyl-2(1*H*)-pyridone (Id) with II——a) A mixture of Id (20 g), II (6.27 g), H_2O (70 ml) and AcOH (70 ml) was refluxed for 1 week, and the mixture was allowed to stand overnight at room temperature. The precipitate [2.12 g (33.8%) of II] formed was filtered off. The filtrate was evaporated under a

10) All melting points were uncorrected. δ: ppm from tetramethylsilane as an internal standard. Abbreviation used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, d-t=double-triplet, d-q=double-quartet.

reduced pressure, and the residue was chromatographed on a column of silica gel with benzene–acetone (5: 1). Id (13.13 g) was recovered from the former fraction in 65.7% yield, and the solid obtained from the later fraction was treated with 10% HCl to give a crystals, which was recrystallized from EtOH to yield 6-benzyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2,8-*endo*-dicarboxylic acid [IIId (0.58 g)], mp 231—234° (dec.), in 3.6% yield as colorless fine crystals. *Anal.* Calcd. for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.88; H, 5.11; N, 4.71. MS *m/e*: 301 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1720, 1670 (COOH), 1640 (NC=O), 700 (δ CH). NMR (pyridine-d_5) δ: 2.37 (1H, broad d, J=20 Hz, C_4–H_{endo}), 2.93 (1H, d-t, J=20, J=3 Hz, C_4–H_{exo}), 3.70 (1H, t, J=5 Hz, C_8–H), 4.08 (1H, m, C_5–H), 4.35 (1H, d, J=15 Hz, N–CH–Ph), 4.62 (1H, d, J=5 Hz, C_1–H), 4.95 (1H, d, J=15 Hz, N–CH–Ph), 7.1—7.5 (6H, m, C_3–H, aromatic H).

b) A mixture of Id (20 g) and II (6.27 g) was heated in an oil bath at 170° for 1 week. $CHCl_3$ (50 ml) and H_2O (50 ml) were added to the reaction mixture, and the mixture was stirred overnight at room temperature. A precipitate formed was collected by filtration. $CHCl_3$ layer separated from the filtrate was evaporated, and the residue was extracted with hot isopropyl ether. Concentration of the isopropyl ether extract gave a solid, which was recrystallized from EtOH to yield 1.4 g of 6-benzyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2,8-*exo*-dicarboxylic acid (IVd), mp 257—260° (dec.), as colorless fine crystals. The precipitate collected was extracted with a mixed solvent of benzene and acetone, and the resulting solid collected was recrystallized from EtOH to give 1.67 g of IVd. Accordingly, 3.07 g of IVd was obtained in 18.9% yield. The benzene–acetone extract was concentrated, and the residue was treated with hot isopropyl ether. The resulting solid was collected and recrystallized from EtOH to afford IIId (5.8 g) in 35.6% yield. IVd: *Anal.* Calcd. for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.89; H, 5.12; N, 4.80. MS *m/e*: 301 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1730, 1690 (COOH), 1660 (NC=O), 750, 700 (δ CH). NMR (pyridine-d_5) δ: 2.47 (2H, m, C_4–H_2), 3.05 (1H, s, C_8–H), 4.25—4.5 (2H, m, C_5–H, N–CH–Ph), 4.72 (1H, s, C_1–H), 4.95 (1H, d, J=15 Hz, N–CH–Ph), 7.0—7.5 (6H, m, C_3–H, aromatic H).

Reaction of 1-Phenethyl-2(1*H*)-pyridone (Ie) with II——a) A mixture of Ie (20 g), II (5.83 g), H_2O (60 ml) and AcOH (24 ml) was refluxed for 1 week, and the mixture was evaporated under a reduced pressure. $CHCl_3$ (40 ml) was added to the residue. The precipitate [3.75 g (64.3%) of II] formed was filtered off. The filtrate was evaporated under a reduced pressure, and the residue was extracted with hot hexane and then benzene. The resulting solid was collected, and recrystallized from EtOH to afford 7-oxo-6-phenethyl-6-azabicyclo[3.2.1]oct-2-ene-2,8-*endo*-dicarboxylic acid [IIIe (0.76 g)], mp 267—269° (dec.), in 4.8% yield as colorless prisms. The hexane and benzene extracts were combined, and evaporated to recover Ie (15.8 g) in 79% yield. *Anal.* Calcd. for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.91; H, 5.34; N, 4.26. MS *m/e*: 315 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1735, 1690 (COOH), 1650 (NC=O), 760, 690 (δ CH). NMR (pyridine-d_5) δ: 2.4 (1H, broad d, J=20 Hz, C_4–H_{endo}), 2.95 (1H, broad d, J=20 Hz, C_4–H_{exo}), 3.0 (2H, m, N–CH_2–CH_2–Ph), 3.58 (1H, t, J=4.5 Hz, C_8–H), 3.2—4.3 (2H, m, N–CH_2–CH_2–Ph), 4.08 (1H, m, C_5–H), 4.5 (1H, broad d, J=4.5 Hz, C_1–H), 7.15 (1H, m, C_3–H), 7.3 (5H, s, aromatic H).

b) A mixture of Ie (5 g) and II (1.46 g) was heated in an oil bath at 170° for 1 week. $CHCl_3$ (15 ml) and H_2O (15 ml) were added to the reaction mixture, and the mixture was stirred overnight at room temperature. The precipitate formed was collected by filtration, and recrystallized from EtOH to give 7-oxo-6-phenethyl-6-azabicyclo[3.2.1]oct-2-ene-2,8-*exo*-dicarboxylic acid [IVe (0.85 g)], mp 275—277° (dec.), in 21.5% yield as colorless prisms. The mother liquor was concentrated to afford IIIe (0.25 g) in 6.3% yield. $CHCl_3$ layer separated from the filtrate was washed with saturated aq. K_2CO_3, and chromatographed on a column of silica gel to recover Ie (1.75 g) in 35% yield. IVe: *Anal.* Calcd. for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.66; H, 5.24; N, 4.49. IR ν_{max}^{Nujol} cm^{-1}: 1730, 1675 (COOH), 1650 (NC=O), 1615 (C=C), 760, 705 (δ CH). MS *m/e*: 315 (M^+). NMR (pyridine-d_5) δ: 2.52 (2H, m, C_4–H_2), 3.02 (2H, q, J=13.5, J=5.5 Hz, Ph–CH_2–CH_2–N), 3.02 (1H, s, C_8–H), 3.2—4.2 (2H, m, N–CH_2–CH_2–Ph), 4.44 (1H, m, C_5–H), 4.58 (1H, broad s, C_1–H), 7.1 (1H, m, C_3–H), 7.25 (5H, s, aromatic H).

Esterification of IIIa——IIIa (0.5 g) was added to an ice cooled mixture of $SOCl_2$ (0.5 g) and MeOH (5 ml), and the mixture was stirred overnight at room temperature. The reaction mixture poured into ice water was basified with $NaHCO_3$, and the basic mixture was extracted with benzene. The benzene extract was evaporated to give a solid, which was recrystallized from ether to afford dimethyl 6-methyl-7-oxo-6-azabicyclo[3.2.1]-oct-2-ene-2,8-*endo*-dicarboxylate [V (0.42 g)], mp 109—110°, in 75.2% yield as colorless prisms. *Anal.* Calcd. for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.73; H, 6.26; N, 5.33. IR ν_{max}^{Nujol} cm^{-1}: 1735, 1710 (COOMe), 1690 (NC=O). MS *m/e*: 253 (M^+). NMR ($CDCl_3$) δ: 2.4 (1H, broad d, J=20 Hz, C_4–H_{endo}), 2.6 (1H, d-t, J=20, J=3 Hz, C_4–H_{exo}), 2.85 (3H, s, N-Me), 3.38 (1H, t, J=5 Hz, C_8–H), 3.66 (3H, s, COOMe), 3.75—3.85 (4H, COOMe, C_1–H), 3.95 (1H, m, C_5–H), 6.83 (1H, m, C_3–H). NMR (pyridine-d_5) δ: 2.4 (1H, d-q, J=20, J=3.8, J=2 Hz, C_4–H), 2.6 (1H, d-t, J=20, J=3 Hz, C_4–H), 2.83 (3H, s, N-Me), 3.57—3.65 (7H, COOMe×2, C_8–H), 3.91 (1H, m, C_5–H), 4.15 (1H, d, J=5 Hz, C_1–H), 6.88 (1H, m, C_3–H).

Esterification of IVa——IVa (1 g) was added to an ice cooled mixture of $SOCl_2$ (1.1 g) and MeOH (10 ml), and the mixture was stirred overnight at room temperature. The reaction mixture was treated as the above-mentioned esterification of IIIa to give a solid, which was recrystallized from ether to yield dimethyl 6-methyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2,8-*exo*-dicarboxylate [VI (0.88 g)], mp 116—118°, in 78% yield as colorless prisms. *Anal.* Calcd. for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.98; H, 5.81; N, 5.43. IR ν_{max}^{Nujol} cm^{-1}: 1727, 1700 (COOMe), 1685 (NC=O). NMR ($CDCl_3$) δ: 2.58 (2H, broad t, J=3 Hz,

C_4–H_2), 2.76 (1H, s, C_8–H), 2.80 (3H, s, N–Me), 3.73 (3H, s, COOMe), 3.78 (3H, s, COOMe), 3.85 (1H, s, C_1–H), 4.10 (1H, m, C_5–H), 6.89 (1H, m, C_3–H).

Epimerization of V——Butyl lithium solution [2.56 ml (10% (w/v) in hexane)] was added dropwise to a cooled solution (−30°) of diisopropylamine (0.56 ml) and tetrahydrofuran (THF) (2 ml). The mixture was stirred for 30 min at 0°, cooled to −78°, and a solution of V (506 mg) in THF (3 ml) was added dropwise. The mixture was stirred for 30 min at −78°, and treated with saturated aq. NH_4Cl (1 ml). The cooled mixture was warmed with stirring to room temperature, and extracted with benzene. The benzene extract was washed with 10% HCl, saturated aq. NaCl, dried over $MgSO_4$, and evaporated to give a mixture (291 mg) of V and VI as a colorless oil. V and VI were in the ratio 2: 3 from integration of the NMR spectrum.

Reaction of Ia with Maleic Acid——a) A mixture of Ia (5 g), maleic acid (2.66 g) and H_2O (27 ml) was refluxed for 1 week, and the mixture was allowed to stand overnight at room temperature. The precipitate [0.9 g (33.8%) of II] formed was filtered off. The filtrate was evaporated under a reduced pressure, and the residue was extracted with hot hexane and then benzene.

The resulting solid (0.6 g) was collected, and treated with MeOH (11 ml) and 10% HCl (4 ml) to afford IIIa (0.34 g) in 6.6% yield. The extracts of hexane and benzene were combined, washed with saturated aq. K_2CO_3, dried over $MgSO_4$, and evaporated to recover Ia (2.6 g) in 52% yield.

b) A mixture of Ia (5 g) and maleic acid (2.66 g) was heated in an oil bath at 120° for 1 week. $CHCl_3$ (27 ml) and H_2O (27 ml) were added to the reaction mixture. The mixture was stirred overnight at room temperature, and the precipitate [0.7 g (26.3%) of II] formed was filtered off. H_2O layer separated from the filtrate was evaporated under a reduced pressure, and the residue was extracted with hot hexane. The resulting solid (1.05 g) was collected, and treated with MeOH (10 ml) and 10% HCl (3 ml) to yield IIIa (0.87 g) in 16.9% yield. $CHCl_3$ layer from the filtrate and the hexane extract were combined, washed with saturated aq. K_2CO_3, dried over $MgSO_4$, and evaporated to recover Ia (1.89 g) in 37.8% yield.

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