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Studies on 1-Alkyl-2(1*H*)-pyridone Derivatives. X.[1] The Diels-Alder Reaction of 1-Methyl-2(1*H*)-pyridone with Maleic Anhydride[2]

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The Diels–Alder reaction between 1-methyl-2(1*H*)-pyridone (I) and maleic anhydride was successfully carried out in 42% yield. This constitutes a new synthetic route to isoquinuclidine ring. The structure of the adduct (II) so obtained was proved by the synthesis of various derivatives. It was thereby determined that the structure of II is an *endo*-form IIb, that of dicarboxylic acid (III) is IIIb, that of bromolactone (IV) is IVd, the hydroxy-lactone (V) is Vd, and the dilactone (VI) is VIb.

1-Methyl-2(1*H*)-pyridone (I) is easily prepared from pyridine in two steps.[4] It is an aromatic compound in which electrophilic substitution takes place at 3- and 5-positions. We are attempting the introduction of a carbon side-chain in I and its derivatives by the substitution reaction.[1]

I is easily hydrogenated by catalytic reduction. Since it rapidly decolorizes potassium permanganate solution, it seems to be a compound with high unsaturation. In order to examine the unsaturation of I, its Diels–Alder reaction was attempted. The adduct of I from its Diels–Alder reaction has an isoquinuclidine skeleton specific to iboga alkaloids. Consequently, formation of this adduct offers a new synthetic route to the isoquinuclidine derivatives. Jackman, *et al.*[5] and Thyagarajan, *et al.*[6] carried out the Diels–Alder reaction of I using maleic anhydride but failed to isolate the objective compound. Only Bauer and others[7] succeeded in the production of its adduct by using benzyne as the dienophile but this reaction cannot supply the intermediate for iboga alkaloids.

In the present series, the Diels–Alder reaction of I was carried out with maleic anhydride and synthesis of isoquinuclidine derivatives was also successfully attained. Configuration of the substituents was also confirmed, and these are reported herein.

A solution of 20 g of I and 35 g of maleic anhydride dissolved in 200 ml of toluene was refluxed for 72 hr and allowed to stand over night by which 16 g of a colorless fine crystalline powder (II), mp 178—179°, $C_{10}H_9O_4N$, was obtained in 42% yield as a precipitate (The liquid portion of this product is now being examined).

The ultraviolet (UV) spectrum of II in ethanol lacked the absorption for a pyridone ring, while its infrared (IR) spectrum in Nujol exhibited the absorption of a carbonyl in acid anhydride at 1850 and 1770 cm^{-1}, and that of δ-lactam carbonyl at 1670 cm^{-1}. It is certain from these spectral data that II is the objective adduct.

The following experiments were carried out in order to determine the structure of II. Treatment of II with water at room temperature afforded a dicarboxylic acid (III), mp 173—

1) Part IX: H. Tomisawa, M. Watanabe, R. Fujita, and H. Hongo, *Chem. Pharm. Bull.* (Tokyo), **18**, 917 (1970).
2) A part of this work was preliminarily reported in *Tetrahedron Letters*, **1969**, 2465.
3) Location: *Nankozawa, Odawara, Sendai.*
4) E.A. Prill and S.M. McElvain, *Org. Syn.*, Collected Vol. II, 419 (1943).
5) L.M. Jackman and J.A. Elvidge, *J. Chem. Soc.*, **1961**, 859.
6) B.S. Thyagarajan and K. Rajagopalan, *Tetrahedron*, **19**, 1483 (1963).
7) L. Bauer, C.L. Bell, and G.E. Wright, *J. Heterocyclic Chem.*, **3**, 393 (1966); E.B. Sheinin, G.E. Wright, and L. Bauer, *ibid.*, **5**, 859 (1968).

174° (decomp.), $C_{10}H_{11}O_5N$, in quantitative yield. The IR spectrum of III exhibited absorptions at 1725 and 1705 cm^{-1} for C=O in the carboxyl group, and at 1640 cm^{-1} for a δ-lactam carbonyl. Treatment of III with acetic anhydride at 60° resulted in its reversion to II in a high yield. These facts indicate that II and III have the same configuration and that the two carboxyl groups in III are situated *cis* to each other. Treatment of the aqueous solution of III with bromine gave a bromolactone (IV). mp 234—236°, $C_{10}H_{10}O_5NBr$, in 89% yield. IR spectrum of IV exhibited absorptions at 1780 cm^{-1} for a γ-lactone carbonyl, at 1730 cm^{-1} for C=O in the carboxyl group, and at 1640 cm^{-1} for δ-lactam carbonyl.

In general, configuration of the adduct is determined from the structure of the bromine compound derived from it, as shown in Chart 1.[8] IX is obtained in a high yield from the bromination of the *endo* form (VIII) while the bromination of the *exo* form (X) gives XI and XII, formed by the accompanying rearrangement reaction, in a low yield.

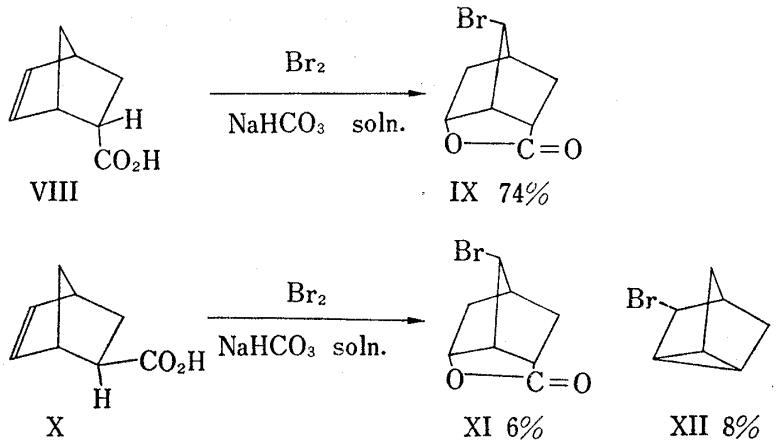

Chart 1

Earlier reports[9] had shown, as indicated in Chart 2, that in the case of heterocyclic compounds, XIII formed by the accompanying rearrangement reaction was obtained in approximately 90% yield from the *exo* form. XIII is indistinguishable from XIV obtained from the *endo* form from elemental analytical values and IR spectrum. In chemical properties, XIV is stable to potassium permanganate and potassium hydroxide solutions while XIII is

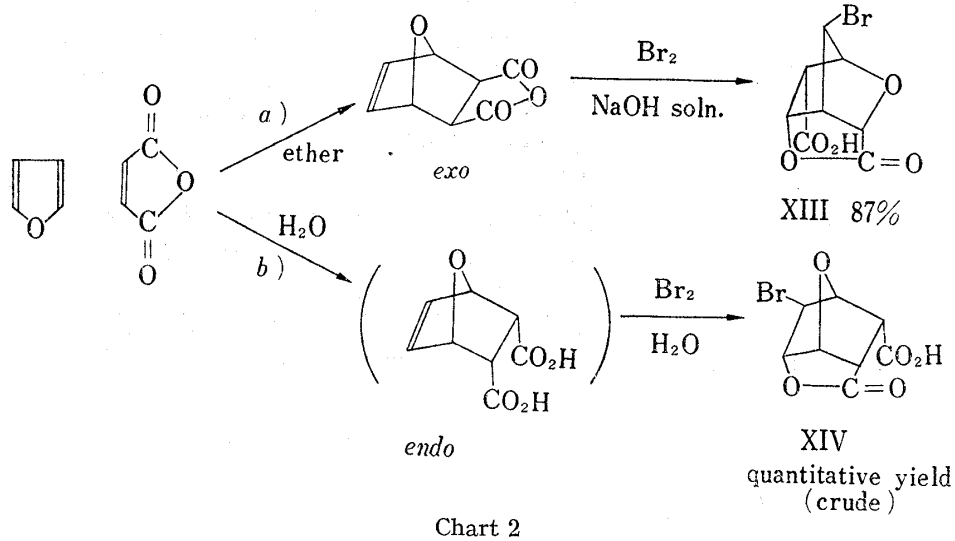

Chart 2

8) C.D. VerNooy and C.S. Rondestvedt, Jr., *J. Am. Chem. Soc.*, **77**, 3583 (1955).
9) *a*) R.B. Woodward and H. Baer, *J. Am. Chem. Soc.*, **70**, 1161 (1948); *b*) J.A. Berson and R. Swidler, *ibid.*, **75**, 1721 (1953).

unstable to them. XIII is obtained only from the bromination of the *exo* form in alkaline reaction.

Therefore, following examinations were made on the structure of IV. As shown in Chart 3, if IV were to be assumed as the rearrangement product from the *exo* form (IIIa), it would be represented as IVa. If the rearrangement reaction from the *endo* form (IIIb), as reported by Huffman, *et al.*,[10] were to be considered, then it would be represented as IVb. In addition, IVc and IVd can also be considered according to the direction of ring formation.

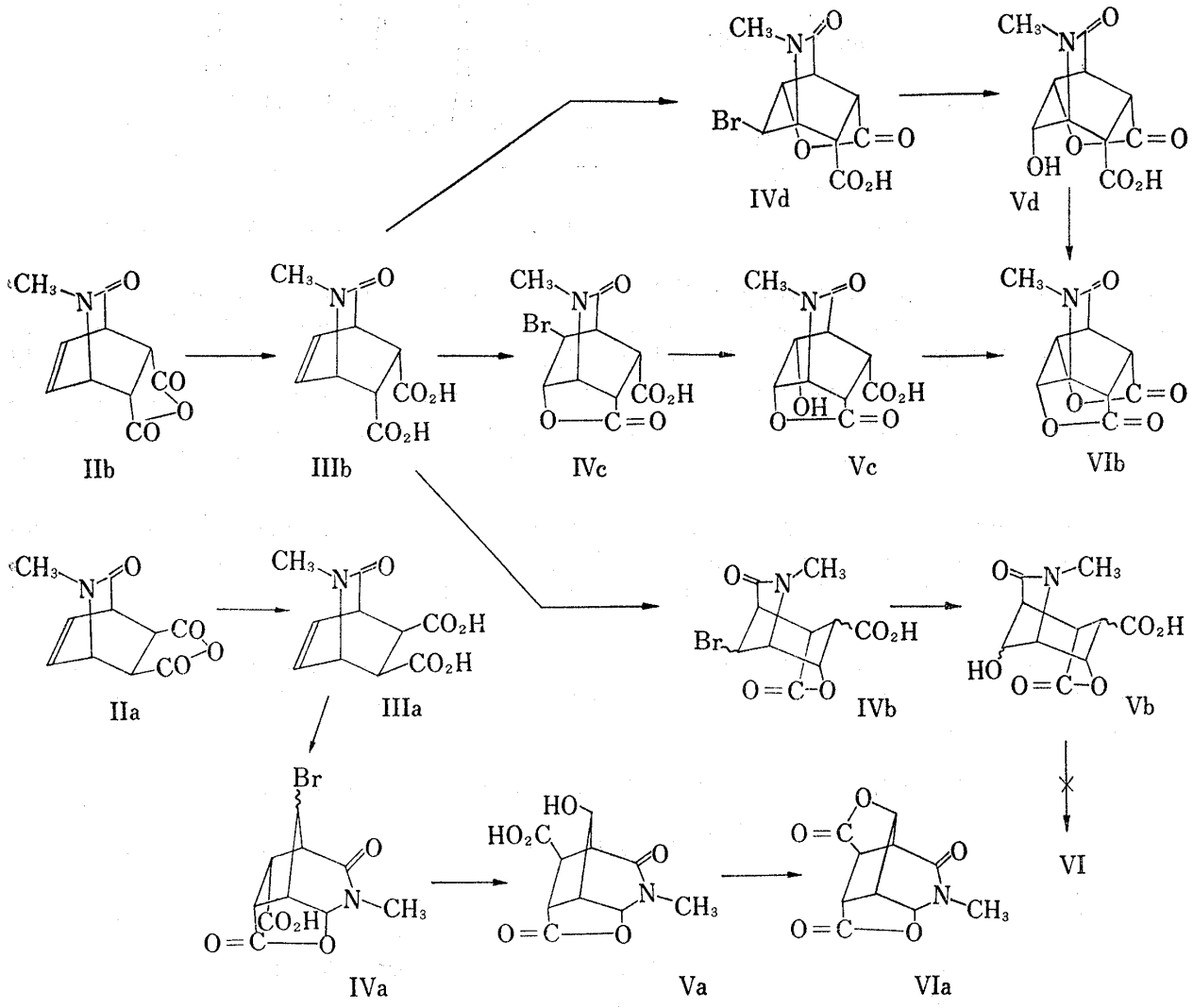

Chart 3

In order to elucidate these points, the following experiments were carried out. Boiling of IV in ethanolic potassium hydroxide for 10 hr afforded a hydroxy-lactone (V), mp 236—237°, $C_{10}H_{11}O_6N$, in 40% yield, whose IR spectrum (in Nujol) exhibited absorptions at 3410 cm^{-1} for a hydroxyl group, at 1780 cm^{-1} for a γ-lactone carbonyl, at 1720 cm^{-1} for a carboxyl group carbonyl, and at 1640 cm^{-1} for a δ-lactam carbonyl. Treatment of V with acetic anhydride at 100° also gave a dilactone (VI), mp 283—286°, $C_{10}H_9O_5N$, in 90% yield. Catalytic reduction of III in methanol over platinum dioxide gave a dihydro compound (VII), mp 186—188° (decomp.), $C_{10}H_{13}O_5N$, by saturation of the double bond. If IV were to be in IVa form derived from the *exo* form (IIIa), then it would not be impossible to assume the structure Va for V and VIa for VI. However, as iterated above, IV is stable enough to give V on being

10) J.W. Huffman and T. Kamiya, *Tetrahedron Letters*, **1966**, 1857.

boiled in ethanolic potassium hydroxide. XIII is unstable to alkalis. There are also reports that XV[11] and XVI,[12] having partial structures similar to IVa, as shown in Chart 4, are unstable to alkalis. Consequently, it would be difficult to consider IV as existing in IVa form from its chemical properties.

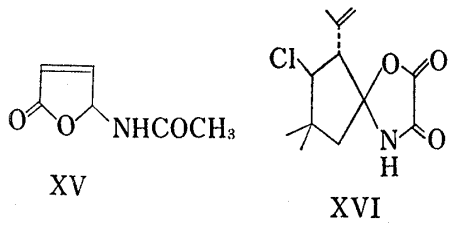

Chart 4

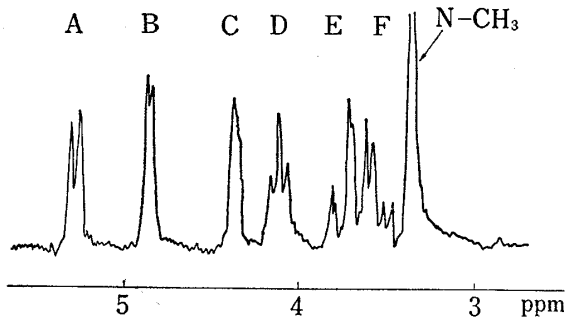

Fig. 1. NMR Spectrum of IV in CF_3COOH

The nuclear magnetic resonance (NMR) spectrum of IVa (in CF_3COOH) would probably show a peak for the proton at the base of oxygen in the lactone group (–COOC<u>H</u>–) in a much lower magnetic field than 5.63 ppm[13] and the proton at the base of bromine (Br–C<u>H</u>–) would show a triplet or quartet peak by coupling with two protons. Consideration of the chemical shift and coupling in the NMR spectrum of IV (Fig. 1) (in CF_3COOH) makes it impossible to explain from the structure of IVa. Consequently, at least IV was not derived from the *exo* form IIIa.

If IV were to be considered as taking IVb structure, Vb cannot be derived to VI. Therefore, formation of VI denies the structure of IVb.

Whether IV is IVc or IVd cannot be proved chemically because Vc and Vd are produced from IV and both are derived to VIb. For this reason, NMR spectra of IV were examined in detail. With consideration of the result of decoupling, and by designating the peaks for one proton from the lowest magnetic field in Fig. 1 optionally as A, B, C, D, E, and F, results given in Table I were obtained.

Table I. NMR Spectrum[a] of IV in Trifluoroacetic Acid Solution

	Chemical shift (ppm)	Coupling constant (J), cps
A	5.30	$J_{AD}=5$
B	4.87	$J_{BC}=3$
C	4.37	$J_{CB}=3$, $J_{CE}=2.5$
D	4.12	$J_{DA}=5$, $J_{DF}=5$
E	3.73	$J_{EC}=2.5$, $J_{EF}=10$
F	3.57	$J_{FD}=5$, $J_{FE}=10$
$N-CH_3$	3.34	

a) Tetramethylsilane was used as internal standard.

The NMR spectrum of VI (in CF_3COOH) is shown in Fig. 2. The peak at 5.20 ppm (2H) in the lowest magnetic field in Fig. 2 is the signal for the protons at the base of oxygen in the

11) E.P. White, *J. Chem. Soc.*, **1967**, 346; S.G. Yates, H.L. Tookey, J.J. Ellis, and H.J. Burkhart, *Phytochemistry*, **7**, 139 (1968).
12) T. Sasaki, S. Eguchi, T. Toru, and M. Ohno, "Abstr. of Papers, Symposium on Heterocyclic Chemistry," Osaka, 1968, p. 58.
13) R.M. Silverstein and G.S. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley & Sons, Inc., New York, 1967, p. 143.

two lactones. By the system of numbering of isoquinuclidine skeleton as shown by XVII in Chart 5, this signal may be assigned to the protons in 7- and 8-positions. This agrees with A (5.30 ppm) in Fig. 1 and, consequently, A in Fig. 1 will be assigned to the proton at the base of oxygen in the lactone (–COOCH–). The structures that can satisfy this assignment are IVc′ and IVd′ in Chart 5.

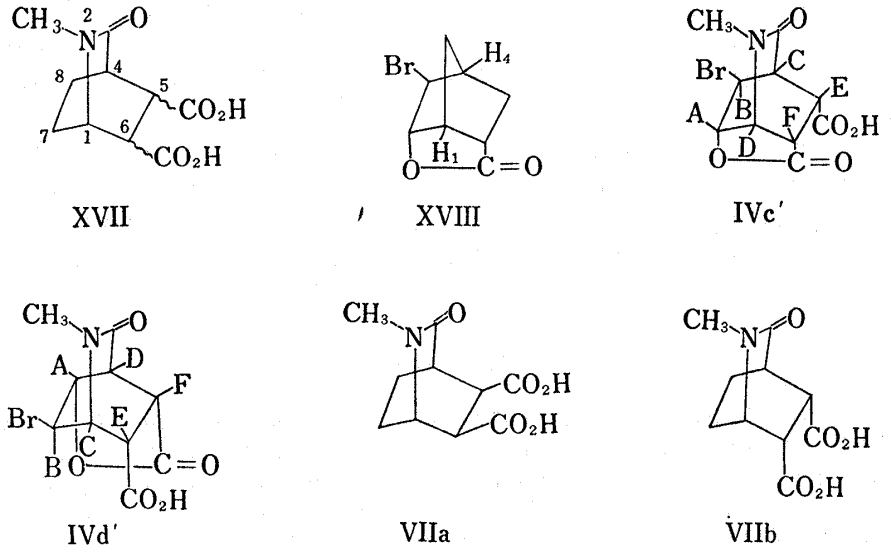

Chart 5

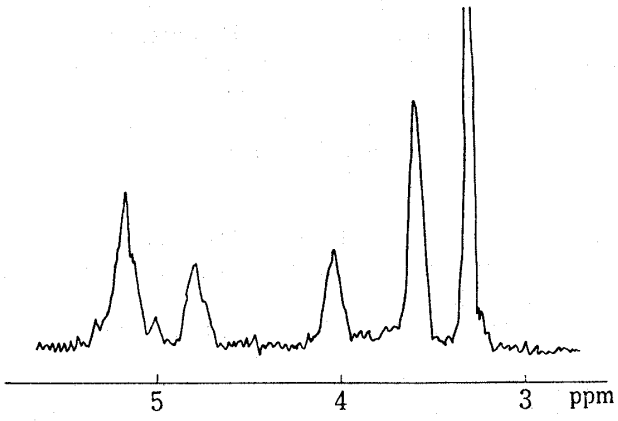

Fig. 2. NMR Spectrum of VI in CF_3COOH

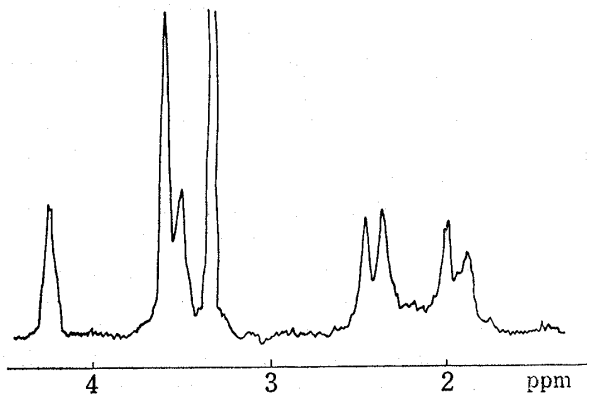

Fig. 3. NMR Spectrum of VII in CF_3COOH

Ramey and others,[14] in the NMR spectrum of XVIII (in $CDCl_3$), had assigned the signal at 3.25 ppm to the proton of C_1-H and that at 2.65 ppm to the proton of C_4-H, and reported that the proton on the γ-lactone side shifts 0.6 ppm to the lower magnetic field due to the anisotorpy of its carbonyl. Their's is a [2.2.1] system but approximately the same effect may be expected for the [2.2.2] system.

In the NMR spectrum of VII (in CF_3COOH) (Fig. 3), the proton in 1-position can be assigned to 4.25 ppm and that at 4-position to 3.49 ppm.

If IV were to be assumed as IVc, the proton in 1-position would be assumed to appear around 4.85 ppm, *ca.* 0.6 ppm lower field than 4.25 ppm of the proton in 1-position of VII. This fact signifies that D in IVc′ is at around 4.12 ppm and this assumption is contrary to the fact.

14) K.C. Ramey, D.C. Lini, R.M. Moriarty, H. Gopal, and H.G. Welsh, *J. Am. Chem. Soc.*, **89**, 2401 (1967).

If IV were to be assumed as IVd, the proton in 4-position (D in IVd') should appear around 4.10 ppm, *ca.* 0.6 ppm in a lower magnetic field than 3.49 ppm of the 4-proton in VII. In fact, D in Fig. 1 is at 4.12 ppm and agrees with the above assumption. The proton in 1-position of IVd' or C is at 4.37 ppm and is close to 4.25 ppm of the 1-proton in VII. Consequently, NMR spectral analysis indicates that IVd' alone satisfies IV and therefore, IV must be IVd.

From the foregoing results, the adduct (II) of 1-methyl-2(1*H*)-pyridone (I) and maleic anhydride is an *endo*-form IIb, the dicarboxylic acid (III) is IIIb, the bromolactone (IV) is IVd, the hydroxy-lactone (V) is Vd, the dilactone (VI) is VIb, and the dihydro compound (VII) is VIIb.

The *exo*-bromine configuration in IVd can be assumed from the fact that the coupling constant between A and B is almost zero cps in its NMR spectrum (Fig. 1). The *endo*-hydroxyl configuration in Vd is supported by the fact that the coupling constant between 7- and 8-protons is 7 cps in its NMR spectrum (in CF_3COOH), and can be known from the facile conversion of Vd to VIb by treatment with acetic anhydride.

Experimental[15]

2-Methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylic Anhydride (IIb)——A mixture of 20 g of I, 35 g of maleic anhydride, and 200 ml of toluene was gently refluxed for 72 hr and allowed to stand over night at room temperature. The precipitate thereby formed was collected by filtration and recrystallized from Ac_2O to colorless fine crystalline powder (IIb), mp 178—179°. Yield, 16 g (42%). *Anal.* Calcd. for $C_{10}H_9O_4N$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.70; H, 4.59; N, 6.67. IR ν_{max}^{Nujol} cm^{-1}: 1850, 1770 (acid anhydride C=O), 1670 (δ-lactam C=O). NMR (in CF_3COOH) ppm: 3.17 (3H, singlet, N–CH_3), 3.97 (1H, quartet, $J=9$, $J=3.5$ cps, C_5–H), 4.14 (1H, quartet, $J=9$, $J=4$ cps, C_6–H), 4.45 (1H, multiplet, C_4–H), 5.00 (1H, multiplet, C_1–H), 6.65—6.90 (2H, multiplet, C_7–H, C_8–H).

2-Methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylic Acid (IIIb)——A solution of 1.6 g of IIb dissolved in 20 ml of H_2O was allowed to stand over night at room temperature. H_2O was then evaporated and the residue was recrystallized from H_2O to colorless fine crystalline powder (IIIb), mp 173—174° (decomp.). Yield, 1.6 g (92%). *Anal.* Calcd. for $C_{10}H_{11}O_5N$: C, 53.33; H, 4.92; N, 6.22. Found: C, 53.41; H, 5.10; N, 6.10. IR ν_{max}^{Nujol} cm^{-1}: 1725 (carboxyl C=O), 1705 (carboxyl C=O), 1640 (δ-lactam C=O). NMR (in CF_3COOH) ppm: 3.18 (3H, singlet, N–CH_3), 3.68 (1H, quartet, $J=10.5$, $J=2.0$ cps, C_5–H), 3.85 (1H, quartet, $J=10.5$, $J=2.5$ cps, C_6–H), 4.29 (1H, broad doublet, $J=5.5$ cps, C_4–H), 4.85 (1H, multiplet, C_1–H), 6.62—6.91 (2H, multiplet, C_7–H, C_8–H).

Dehydration Reaction of IIIb with Acetic Anhydride——A solution of 360 mg of IIIb dissolved in 4 g of Ac_2O was heated in a water bath at 60° for 45 min. The solvent was evaporated under a reduced pressure and the residue was recrystallized from Ac_2O to 252 mg (76.5%) of IIb.

7-*exo*-Bromo-6-*endo*-carboxy-8-*endo*-hydroxy-2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-5-*endo*-carboxylic Acid γ-Lactone (IVd)——A solution of 17 g of IIIb dissolved in 110 ml of H_2O was maintained at 0—5° 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 colorless fine crystalline powder (IVd), mp 234—236° (decomp.). Yield, 20.4 g (89%). *Anal.* Calcd. for $C_{10}H_{10}O_5NBr$: C, 39.49; H, 3.31; N, 4.60. Found: C, 39.39; H, 3.45; N, 4.57. IR ν_{max}^{Nujol} cm^{-1}: 1780 (γ-lactone C=O), 1730 (carboxyl C=O), 1640 (δ-lactam C=O). NMR (in CF_3COOH) ppm: 3.34 (3H, singlet, N–CH_3), 3.57 (1H, quartet, $J=10$, $J=5$ cps, C_5–H), 3.73 (1H, quartet, $J=10$, $J=2.5$ cps, C_6–H), 4.12 (1H, triplet, $J=5$ cps, C_4–H), 4.37 (1H, broad singlet, C_1–H), 4.87 (1H, doublet, $J=3$ cps, C_7–H), 5.30 (1H, doublet, $J=5$ cps, C_8–H).

6-*endo*-Carboxy-7,8-*endo*-dihydroxy-2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-5-*endo*-carboxylic Acid γ-Lactone (Vd)——A mixture of 6 g of IVd, 3.3 g of KOH, and 80 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, and extracted continuously with acetone. The solvent was evaporated from the extract and the residue was recrystallized from H_2O to colorless fine crystalline powder (Vd), mp 236—237°. Yield, 1.9 g (39.8%). *Anal.* Calcd. for $C_{10}H_{11}O_6N$: C, 49.79; H, 4.60; N, 5.81. Found: C, 49.51; H, 4.52; N, 5.67. IR ν_{max}^{Nujol} cm^{-1}: 3410 (hydroxyl O–H), 1780 (γ-lactone C=O), 1720 (carboxyl C=O), 1640 (δ-lactam C=O). NMR (in CF_3COOH) ppm: 3.27 (3H, singlet, N–CH_3), 3.66 (2H, broad singlet, C_5–H, C_6–H), 4.10 (1H, multiplet, C_4–H), 4.39 (1H, broad singlet, C_1–H), 4.47 (1H, broad doublet, $J=7$ cps, C_7–H), 5.21 (1H, broad triplet, $J=7$ cps, C_8–H).

15) All melting points are uncorrected; NMR spectra were obtained on Japan Electron Optics Lab. Model 4H-A at 100 Mc. Tetramethylsilane was used as an internal standard.

7,8-*endo*-Dihydroxy-2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-5,6-*endo*-dicarboxylic Acid γ-Dilactone (VIb)——A solution of 300 mg of Vd dissolved in 5 g of Ac_2O was heated in an oil bath at 100° for 4 hr. The solvent was evaporated under a reduced pressure and the residue was recrystallized from H_2O to colorless fine crystalline powder (VIb), mp 283—286°. Yield, 250 mg (90%). *Anal.* Calcd. for $C_{10}H_9O_5N$: C, 53.81; H, 4.06; N, 6.28. Found: C, 53.42; H, 4.15; N, 6.06. IR ν_{max}^{Nujol} cm^{-1}: 1810, 1780 (γ-lactone C=O), 1670 (δ-lactam C=O). NMR (in CF_3COOH) ppm: 3.30 (3H, singlet, N–CH_3), 3.59 (2H, broad singlet, C_5–H, C_6–H), 4.03 (1H, multiplet, C_4–H), 4.78 (1H, multiplet, C_1–H), 5.20 (2H, multiplet, C_7–H, C_8–H).

2-Methyl-3-oxo-2-azabicyclo[2.2.2]octane-5,6-*endo*-dicarboxylic Acid (VIIb)——A mixture of 400 mg of IIIb, 100 mg of PtO_2, and 100 ml of MeOH was allowed to absorb H_2. The catalyst was filtered off, the solvent was evaporated, and the residue was recrystallized from H_2O to colorless fine crystalline powder (VIIb), mp 186—188° (decomp.). Yield, 350 mg (81.7%). *Anal.* Calcd. for $C_{10}H_{13}O_5N$: C, 52.86; H, 5.77; N, 6.17. Found: C, 52.66; H, 5.82; N, 6.15. IR ν_{max}^{Nujol} cm^{-1}: 1730, 1710 (carboxyl C=O), 1630 (δ-lactam C=O). NMR (in CF_3COOH) ppm: 1.70—2.45 (4H, multiplet, C_7–H, C_8–H), 3.30 (3H, singlet, N–CH_3), 3.49 (1H, broad singlet, C_4–H), 3.58 (2H, broad singlet, C_5–H, C_6–H), 4.25 (1H, broad singlet, C_1–H).

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