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Studies on 1-Alkyl-2(1*H*)-pyridone Derivatives. XXVII.[1] The Diels-Alder Reactions of 1-Methyl-2(1*H*)-pyridone with Methyl Acrylate and Acrylonitrile

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These studies have been made to get the Diels-Alder adducts having one substituent based on dienophiles. Reaction of 1-methyl-2(1*H*)-pyridone (I) with methyl acrylate was carried out. The main product of this reaction followed by hydrolysis was 2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-6-*endo*-carboxylic acid (V). When the reaction of I with acrylonitrile was carried out, the products obtained were 7-*endo*-cyano-2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-5-ene (XI), 7-*exo*-cyano-2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-5-ene (XII), and 8-*exo*-cyano-2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-5-ene (XIII).

Keywords——1-methyl-2(1*H*)-pyridone; Diels-Alder reaction; 2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-6-*endo*-carboxylic acid; 7-*endo*-cyano-2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-5-ene; 7-*exo*-cyano-2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-5-ene; 8-*exo*-cyano-2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-5-ene; methyl acrylate; acrylonitrile

Previous works in this series have shown the Diels-Alder reactions of 1-methyl-2(1*H*)-pyridone (I) with maleic anhydride[3] and fumaronitrile[4] to give 2-azabicyclo[2.2.2]octane derivatives having the two substituents based on the dienophiles. Our continuous efforts have been made to get the Diels-Alder adducts having one substituent, which have not been reported and will be the appropriate intermediates in the syntheses of iboga alkaloids. The reactions of I with methyl acrylate and acrylonitrile were carried out and gave the monosubstituted 2-azabicyclo[2.2.2]octane derivatives, whose substituents were located at the same position as that of iboga alkaloids. These are reported in the present paper.

Reaction of I with Methyl Acrylate

When the reaction of I with methyl acrylate was carried out, the Diels-Alder adducts (II, III and IV) were obtained as a pale yellow oil in about 30% yield, besides the recovery of I in about 50% yield. Attempts to separate the pure adducts from the oil were unsuccessful. The adducts were hydrolyzed with 2% KOH solution to give the carboxylic acid (V), $C_9H_{11}NO_3$, as colorless needles of mp 197—198° in 17.2% overall yield and a mixture of VI and VII as pale yellow solids.

The mixture was submitted to iodolactonization with iodine to give iodolactone (VIII), $C_9H_{10}INO_3$, as colorless needles of mp 149—150° in 2% overall yield and to recover the carboxylic acid (VI), $C_9H_{11}NO_3$, as colorless pillars of mp 158—159° in 2% overall yield. (Chart 1).

The structure of V was confirmed as 2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-6-*endo*-carboxylic acid by the following way. By comparing the nuclear magnetic resonance (NMR) spectrum of V with that of the dicarboxylic acid[3] (IX), the assignment of the signals in the

1) Part XXVI: H. Tomisawa, H. Kato, R. Fujita, and H. Hongo, *Chem. Pharm. Bull.* (Tokyo), **27**, 400 (1979).
2) Location: *Komatsushima, Sendai 983, Japan.*
3) H. Tomisawa and H. Hongo, *Tetrahedron Lett.*, **1969**, 2465; *Idem, Chem. Pharm. Bull.* (Tokyo), **18**, 925 (1970); H. Hongo, *Chem. Pharm. Bull.* (Tokyo), **20**, 226 (1972).
4) H. Tomisawa, R. Fujita, K. Noguchi, and H. Hongo, *Chem. Pharm. Bull.* (Tokyo), **18**, 941 (1970).

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NMR spectrum of V was accomplished as shown in Table I. In the NMR spectrum of V, decoupling the multiplet at δ 4.7 (C_1–H) caused the multiplet at δ 3.3 (CH–COOH) to collapse to quartet, while the multiplet at δ 1.92—2.3 (–CH_2–) was unchanged. Therefore, the location of carboxyl group of V was at C_6 position. Treatment of V with iodine gave the iodolactone

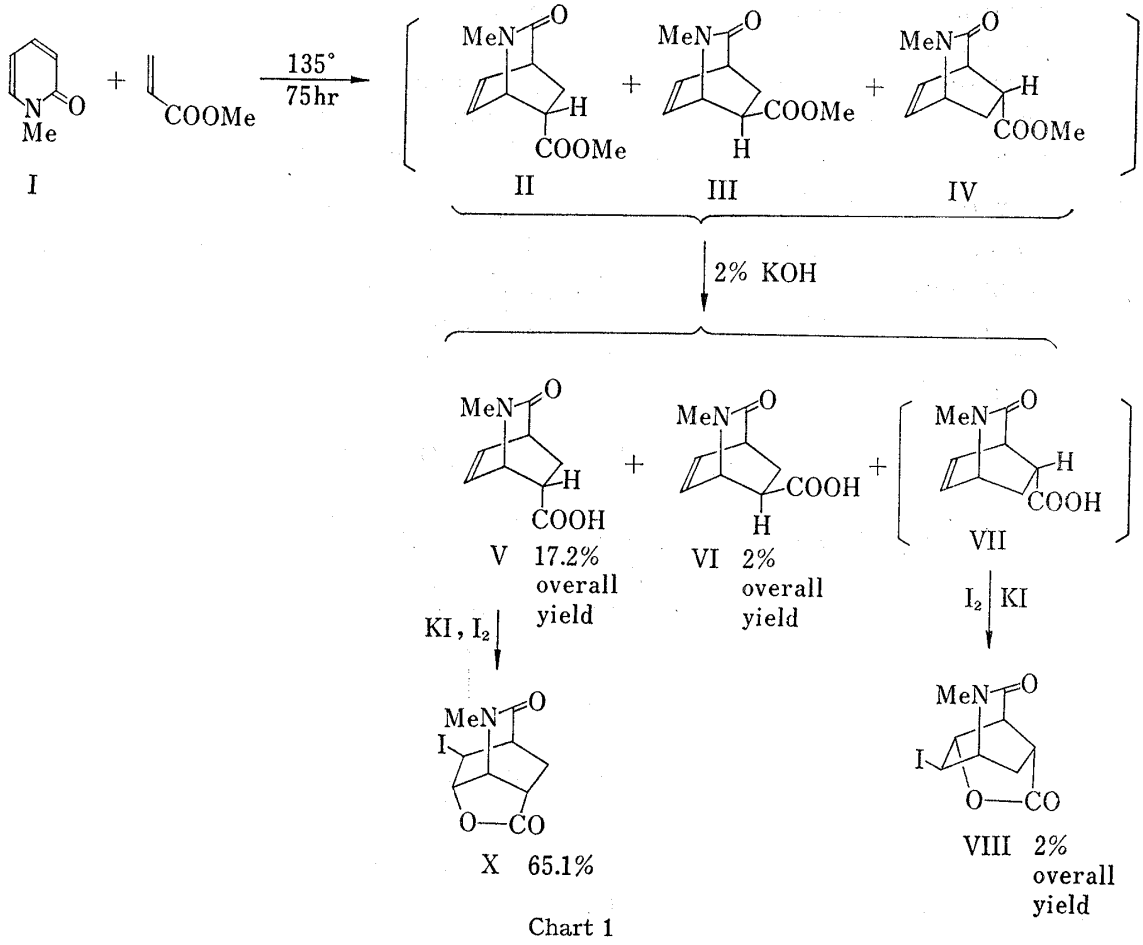
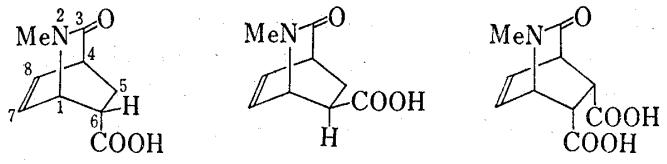


Chart 1

TABLE I. NMR Spectra[a] of V, VI, and IX in Pyridine-d_5



V VI IX

Position	V	VI	IX
C_1–H	4.7(m)	4.73(m)	4.65(m)
C_4–H	3.53(m)	3.57(m)	4.14(m)
C_5–H_{exo}	1.92—2.3(m)	2.45(o, J=13, J=4, J=2)	3.79(q, J=10, J=2.5)
C_5–H_{endo}		1.8(o, J=13, J=10, J=3)	—
C_6–H_{exo}	3.3(m)	—	3.92(q, J=10, J=3)
C_6–H_{endo}	—	2.8(o, J=10, J=4, J=2)	—
C_7–H, C_8–H	6.3—6.8(m)	6.2—6.7(m)	6.65—6.97(m)
N–Me	2.9(s)	3.05(s)	2.93(s)

a) Unit: δ (ppm from TMS), J(Hz).

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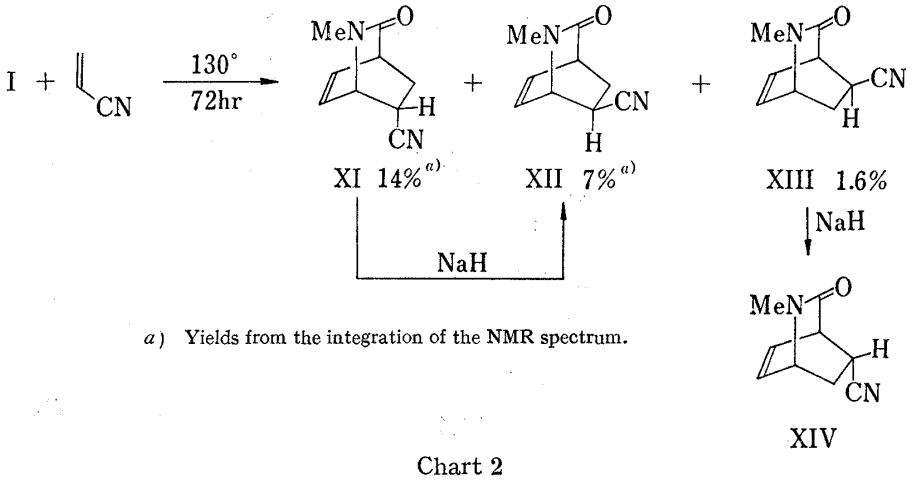
(X), $C_9H_{10}INO_3$, as colorless needles of mp 203—204° in 65.1% yield, and this revealed the configuration of the carboxyl group was in *endo*.

The structure of VI was confirmed as 2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-6-*exo*-carboxylic acid by the following way. The carboxyl group was determined to be at C_6 position by a similar NMR spectral consideration as mentioned above. However, the above-mentioned treatment of VI with iodine did not give any iodolactone. Therefore, the carboxyl group at C_6 is in *exo* configuration.

The iodolactone (VIII) has the same empirical formula as X. The spectral data of VIII suggested that VIII was 8-*endo*-hydroxy-7-*exo*-iodo-2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-5-*endo*-carboxylic acid γ-lactone, which was derived from 5-*endo*-carboxylic acid (VII).

Reaction of I with Acrylonitrile

The reaction of I with acrylonitrile gave a mixture of the adducts as a pale yellow oil in 23.3% yield, besides the recovery of I in 67.3% yield. From this mixture, three kinds of crystals of XI (mp 101—102.5°, colorless prisms), XII (mp 69—69.5°, colorless prisms), and XIII (mp 129—130°, colorless needles) were separated by the silica gel column chromatography (Chart 2).

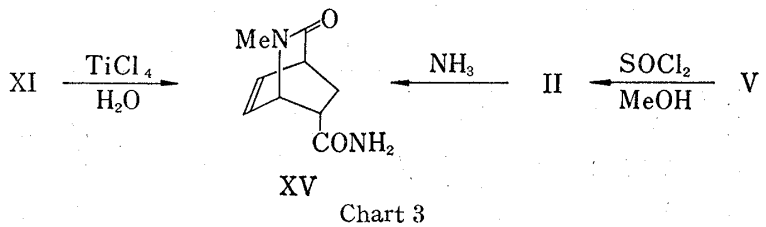


a) Yields from the integration of the NMR spectrum.

Chart 2

These XI, XII, and XIII had the same empirical formula $C_9H_{10}N_2O$ and all their infrared (IR) spectra showed the absorption bands of cyano group at 2240 cm^{-1} and carbonyl group of δ-lactam at 1670 cm^{-1}.

The structure of XI was confirmed as 7-*endo*-cyano-2-methyl-3-oxo-2-azabicyclo[2.2.2]-oct-5-ene as follows. The carboxamide (XV) derived from XI by hydrolysis with titanium tetrachloride was identified by the spectral comparison and the mixed melting point determination with an authentic sample, which was obtained from amidation of the ester (II) derived from V (Chart 3).



XV

Chart 3

The NMR spectrum of XII was similar to that of XI, and this fact suggested that XII would be an epimer of XI. XII was obtained by epimerization of XI with sodium hydride, therefore the structure of XII was confirmed as 7-*exo*-cyano-2-methyl-3-oxo-2-azabicyclo-[2.2.2]oct-5-ene.

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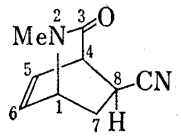
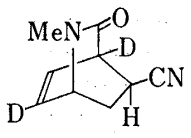
The structure of XIII was confirmed as 8-*exo*-cyano-2-methyl-3-oxo-2-azabicyclo[2.2.2]-oct-5-ene by the following way. The cyano group was determined to be located at C_8 by consideration of the NMR spectra of XIII and XIIId (Table II). XIIId was prepared by the reaction of 3,5-dideuterio-1-methyl-2(1*H*)-pyridone (Id) with acrylonitrile and had two deuteriums at C_4 and C_6. Configuration of the cyano group at C_8 was determined as follows. In the NMR spectrum of XIIId, the coupling constant between the proton at C_8 and the *endo* proton (δ 1.88) at C_7, which was located at higher magnetic field than the *exo* proton (δ 2.10) at C_7 by the anisotropy effect[4,5] of the double bond, was 9.5 Hz, and the coupling constant between the proton at C_8 and the *exo* proton at C_7 was 4.5 Hz. These indicated that the cyano group at C_8 was in *endo* configuration.

TABLE II. NMR Spectra[a] of XIII and XIIId in Pyridine-d_5



XIII



XIIId

Position	XIII	XIIId
C_1–H	4.16(m)	4.16(m)
C_4–H	3.79(m)	—
C_5–H	6.12—6.61(m)	6.26(broad s)
C_6–H		—
C_7–H$_{exo}$	1.75—2.41(m)	2.10(o, J=12.5, J=4.5, J=3.5)
C_7–H$_{endo}$		1.88(o, J=12.5, J=9.5, J=2)
C_8–H$_{endo}$	2.9(m)	2.92(q, J=9.5, J=4.5)
N–Me	2.83(s)	2.85(s)

a) Unit: δ (ppm from TMS), J(Hz).

The compound (XIII) was treated with sodium hydride to give a mixture of XIII and its epimer (XIV, mp 112—113°, colorless columnar crystals) in the ratio 1:2. XIV was separated from this mixture by the preparative thin-layer chromatography. The spectral data supported that the structure of XIV was 8-*endo*-cyano-2-methyl-3-oxo-2-azabicyclo-[2.2.2]oct-5-ene.

There was a possibility that the C_5 epimer of IV and C_8 epimer of XIII would be contained in the crude Diels-Alder adducts of I with methyl acrylate and acrylonitrile, however we could not detect these isomers in the reaction mixture.

The Diels-Alder adducts (V, VI, XI, and XII) obtained by these reactions have the substituents at the same position as the isoquinuclidine skeleton of iboga alkaloids.

Experimental[6]

Reaction of I with Methyl Acrylate——A mixture of I (18.5 g) and methyl acrylate (73 g) was heated in a sealed tube at 135° (an oil bath) for 75 hr. The mixture was evaporated under a reduced pressure, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with 10% HCl (100 ml), dried over $MgSO_4$, and evaporated. The resulting oil (30.4 g) was dissolved in MeOH (200 ml), and the MeOH solution was allowed to stand overnight at room temperature. The precipitate of polymers was filtered off. The filtrate was evaporated, and the residue was dissolved in $CHCl_3$ (50 ml). The $CHCl_3$ solution was washed with 5% HCl (40 ml), dried over $MgSO_4$, and evaporated to give a yellow oil (12.5 g). The washings of 10% and 5% HCl were combined and saturated with K_2CO_3. The basic mixture was extracted with $CHCl_3$. The $CHCl_3$

5) K. Tori, Y. Hata, R. Muneyuki, Y. Takano, T. Tsuji, and H. Tanida, *Can. J. Chem.*, **42**, 926 (1964).
6) All melting points were uncorrected. δ: ppm from tetramethylsilane as an internal standard. Abbreviation used: s=singlet, d=doublet, t=triplet, q=quartet, o=octet, m=multiplet, b=broad.

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extract was washed with saturated aq. NaCl, dried over $MgSO_4$, and evaporated to recover I (9 g) in 48.6% yield. The yellow oil (12.5 g) was passed through a column of silica gel. The fraction eluted with $CHCl_3$–MeOH (25: 1) was evaporated to give a mixture (9.7 g) of the Diels-Alder adducts of I and methyl acrylate in 29.3% yield as a pale yellow oil. A solution of the pale yellow oil (1.9 g) and 10% KOH (8 ml) in MeOH (32 ml) was stirred for 4 hr at room temperature, and the mixture was evaporated under a reduced pressure. The residue was acidified with 10% HCl, and the acidic mixture was continuously extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated, and the residue was extracted with benzene. The residual solid was recrystallized from EtOH to yield 2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-6-*endo*-carboxylic acid [V (1.03 g)], mp 197—198°, in 17.2% overall yield as colorless needles. *Anal.* Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.76; H, 6.13; N, 7.68. MS *m/e*: 181 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1700 (COOH), 1625 (NC=O). NMR (Table I).

The benzene extract was evaporated to give a pale yellow solid (0.45 g). A solution of iodine (1.27 g) and KI (5 g) in H_2O (15 ml) was added to a solution of the solid (0.45 g) in 0.5 N $NaHCO_3$ (18 ml), and the mixture was stirred in the dark at room temperature for 24 hr. The reaction mixture was treated with $NaHSO_3$ and acidified with conc. HCl, then the acidic mixture was continuously extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated, and the residue was chromatographed on a column of silica gel. The fraction eluted with $CHCl_3$ was evaporated, and the resulting solid was recrystallized from benzene–$CHCl_3$ to give 8-*endo*-hydroxy-7-*exo*-iodo-2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-5-*endo*-carboxylic acid γ-lactone [VIII (0.2 g)], mp 149—150°, in 2% overall yield as colorless needles. *Anal.* Calcd. for $C_9H_{10}INO_3$: C, 35.20; H, 3.28; N, 4.56. Found: C, 35.04; H, 3.25; N, 4.58. MS *m/e*: 307 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1780 (γ-lactone C=O), 1670 (NC=O). NMR (pyridine-d_5) δ: 2.15—2.4 (2H, m, C_6–H_{endo}, C_6–H_{exo}), 2.93 (1H, m, C_5–H_{exo}), 3.07 (3H, s, N–Me), 3.37 (1H, t, J=5 Hz, C_4–H), 3.9 (1H, m, C_1–H), 4.57 (1H, d, J=3 Hz, C_7–H_{endo}), 5.33 (1H, d, J=5 Hz, C_8–H_{exo}).

The fraction eluted with $CHCl_3$–EtOH (50: 1) was evaporated, and the resulting solid was recrystallized from benzene-$CHCl_3$ to afford 2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-6-*exo*-carboxylic acid [VI (0.12 g)], mp 158—159°, in 2% overall yield as colorless pillars. *Anal.* Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.48; H, 6.06; N, 7.80. MS *m/e*: 181 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1710 (COOH), 1625 (NC=O). NMR (Table I).

7-*endo*-Hydroxy-8-*exo*-iodo-2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylic Acid γ-Lactone (X)——A solution of iodine (0.27 g) and KI (1.1 g) in H_2O (4 ml) was added to a solution of V (0.1 g) in 0.5 N $NaHCO_3$ (4 ml), and the mixture was stirred in the dark at room temperature for 24 hr. The reaction mixture was treated with $NaHSO_3$ and acidified with conc. HCl, and then the acidic mixture was continuously extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated, and the residue was passed through a column of silica gel. The fraction eluted with $CHCl_3$ was evaporated, and the resulting solid was recrystallized from benzene–$CHCl_3$ to give X (0.11 g), mp 203—204°, in 65.1% yield, as colorless needles. *Anal.* Calcd. for $C_9H_{10}INO_3$: C, 35.20; H, 3.28; N, 4.56. Found: C, 35.41; H, 3.33; N, 4.60. MS *m/e*: 307 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1800 (γ-lactone C=O), 1690 (NC=O). NMR (pyridine-d_5) δ: 2.1—2.4 (2H, m, C_5–H_{endo}, C_5–H_{exo}), 2.8—3.3 (2H, m, C_6–H_{exo}, C_4–H), 3.07 (3H, s, N–Me), 4.55—4.8 (2H, m, C_1–H, C_8–H_{endo}), 5.45 (1H, d, J=5 Hz, C_7–H_{exo}).

Reaction of I with Acrylonitrile——A mixture of I (5.5 g) and acrylonitrile (13.3 g) was heated in a sealed tube at 130° (an oil bath) for 72 hr. The reaction mixture was allowed to stand overnight at room temperature, and the precipitate of polymers was filtered off. The filtrate was distilled under a reduced pressure to recover I (3.7 g) in 67.3% yield. The residue obtained from distillation of the filtrate was dissolved in 10% HCl (30 ml), and the mixtures was extracted with benzene. The benzene extract was dried over $MgSO_4$, and evaporated to give the mixture (1.9 g) of XI, XII, and XIII in 23.3% yield as a pale yellow oil. The mixture was chromatographed on a column of silica gel. The fraction eluted with benzene–acetone (25: 1) was evaporated to give the mixture (1.7 g) of XI and XII in 21% yield as a solid. XI and XII were in the ratio 2(14%): 1(7%) from integration of the NMR spectrum. The solid was recrystallized from ether–benzene (3: 1) to give XI (0.62 g) in 7.6% yield. The mother liquor was concentrated under a reduced pressure to afford a pale yellow oil (1.08 g). The oil (75 mg) was applied to preparative TLC[7] and developed with H_2O. The band (Rf=0.5) was collected and eluted with $CHCl_3$, and then the $CHCl_3$ eluate was evaporated to give XII (20 mg). The fraction eluted with benzene-acetone (20: 1) on the column was evaporated to give XIII (0.13 g) in 1.6% yield.

XI: Colorless prisms, mp 101—102.5°. *Anal.* Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.65; H, 6.13; N, 17.31. MS *m/e*: 162 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240 (C≡N), 1670 (NC=O). NMR ($CDCl_3$) δ: 1.87 (1H, o, J=12.5, J=4.5, J=3 Hz, C_8–H_{endo}), 2.36 (1H, o, J=12.5, J=9.5, J=3 Hz, C_8–H_{exo}), 2.93 (3H, s, N–Me), 3.17 (1H, o, J=9.5, J=4.5, J=3.5 Hz, C_7–H_{exo}), 3.56 (1H, m, C_4–H), 4.48 (1H, m, C_1–H), 6.47—6.97 (2H, m, C_5–H, C_6–H). NMR (pyridine-d_5) δ: 1.66 (1H, o, J=12.5, J=4.5, J=3 Hz, C_8–H_{endo}), 2.22 (1H, o, J=12.5, J=9.5, J=3 Hz, C_8–H_{exo}), 2.83 (3H, s, N–Me), 3.18—3.68 (2H, m, C_7–H_{exo}, C_4–H), 4.55 (1H, m, C_1–H), 6.26—6.74 (2H, m, C_5–H, C_6–H).

7) Preparative thin-layer chromatography (TLC) was carried out on the plate (0.25 or 0.5 mm thickness) of silica gel [Merck silica gel G (type 60)].

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XII: Colorless prisms (ether), mp 69—69.5°. *Anal.* Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.79; H, 6.41; N, 17.34. MS *m/e*: 162 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240 (C≡N), 1670 (NC=O). NMR ($CDCl_3$) δ: 1.68—2.37 (2H, m, C_8–H_{endo}, C_8–H_{exo}), 2.75 (1H, o, J=9.5, J=4.5, J=2 Hz, C_7–H_{endo}), 3.06 (3H, s, N–Me), 3.54 (1H, m, C_4–H), 4.47 (1H, m, C_1–H), 6.37—6.77 (2H, m, C_5–H, C_6–H).

XIII: Colorless needles [ether–benzene (1: 1)], mp 129—130°. *Anal.* Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.83; H, 6.23; N, 17.19. MS *m/e*: 162 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240 (C≡N), 1670 (NC=O). NMR (Table II).

Reaction of Id with Acrylonitrile——A mixture of Id (5.5 g) and acrylonitrile (13.3 g) was heated in a sealed tube at 130° (an oil bath) for 6 days. The mixture was treated in the similar manner described for I to give 4,6-dideuterio-7-*endo*-cyano-2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-5-ene [XId (0.67 g)] in 8.3% yield, and 4,6-dideuterio-8-*exo*-cyano-2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-5-ene [XIIId (0.14 g)] in 1.7% yield.

XId: Colorless prisms [ether–benzene (3: 1)], mp 101—102.5°. *Anal.* Calcd. for $C_9H_8D_2N_2O$: N, 17.06. Found: N, 16.98. MS *m/e*: 164 (M^+). NMR ($CDCl_3$) δ: 1.87 (1H, q, J=12.5, J=4.5 Hz, C_8–H_{endo}), 2.33 (1H, q, J=12.5, J=9.5 Hz, C_8–H_{exo}), 2.91 (3H, s, N–Me), 3.21 (1H, o, J=9.5, J=4.5, J=3.5 Hz, C_7–H_{exo}), 4.50 (1H, m, C_1–H), 6.75 (1H, bs, C_5–H). NMR (pyridine-d_5) δ: 1.67 (1H, q, J=12.5, J=4.5 Hz, C_8–H_{endo}), 2.18 (1H, q, J=12.5, J=9.5 Hz, C_8–H_{exo}), 2.84 (3H, s, N–Me), 3.42 (1H, o, J=9.5, J=4.5, J=3.5 Hz, C_7–H_{exo}), 4.55 (1H, q, J=3.5, J=2 Hz, C_1–H), 6.49 (1H, bs, C_5–H).

XIIId: Colorless columnar crystals [ether–benzene (1: 1)], mp 129.5—130.5°. *Anal.* Calcd. for $C_9H_8D_2N_2O$: N, 17.06. Found: N, 17.11. MS *m/e*: 164 (M^+). NMR (Table II).

7-*exo*-Cyano-2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-5-ene (XII)——A solution of XI (0.96 g) and tetrahydrofuran (THF) (5 ml) was added dropwise to a suspention of NaH (0.45 g) and THF (10 ml), and the mixture was stirred at 50° for 30 min. The reaction mixture was poured into an ice water, and the mixture was extracted with benzene. The benzene extract was dried over $MgSO_4$, and evaporated to give a solid (0.91 g) which was an equimolar mixture of XI and XII from integration of the NMR spectrum. The solid was recrystallized from ether–benzene (3: 1) to recover XI (0.32 g) in 33.3% yield. Concentration of the mother liquor afforded to a pale yellow oil (0.58 g). The oil (0.11 g) was applied to preparative TLC,[7] and developed with H_2O. The band (Rf=0.5) was collected, eluted with $CHCl_3$, and the $CHCl_3$ eluate was evaporated to give XII (46 mg).

8-*endo*-Cyano-2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-5-ene (XIV)——A solution of XIII (0.18 g) in THF (5 ml) was added dropwise to a suspension of NaH (55 mg) in THF (3 ml), and the mixture was stirred at 60° for 2.5 hr. The reaction mixture was treated as in the case of the above-mentioned preparation of XII to give the mixture (0.15 g) of XIII and XIV as a solid. XIII and XIV were in the ratio 1: 2 from integration of the NMR spectrum. The solid was recrystallized from ether–benzene (1: 1) to recover X (25 mg) in 13.9% yield. The residue (90 mg) obtained by evaporation of the mother liquor was applied to preparative TLC,[7] and developed with H_2O. The band (Rf=0.43) was collected, eluted with $CHCl_3$, and the $CHCl_3$ eluate was evaporated to afford XIV (52 mg) in 28.9% yield.

XIV: Colorless columnar crystals [ether–benzene (1: 1)], mp 112—113°. *Anal.* Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.78; H, 6.21; N, 17.43. MS *m/e*: 162 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240 (C≡N), 1670 (NC=O). NMR ($CDCl_3$) δ: 1.87 (1H, m, C_7–H_{endo}), 2.53 (1H, m, C_7–H_{exo}), 2.92 (3H, s, N–Me), 3.18 (1H, m, C_8–H_{exo}), 3.84 (1H, m, C_4–H), 4.30 (1H, m, C_1–H), 6.53–6.97 (2H, m, C_5–H, C_6–H).

2-Methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-6-*endo*-carboxamide (XV)——a) V (0.8 g) was added to an ice cooled mixture of $SOCl_2$ (0.63 g) and MeOH (7 ml), and the mixture was stirred overnight at room temperature. The reaction mixture was evaporated under a reduced pressure, and the residue was dissolved in benzene. The benzene solution was washed with saturated aq. $NaHCO_3$, dried over $MgSO_4$, and evaporated. The resulting residue was passed through a column of silica gel. The fraction eluted with $CHCl_3$ was evaporated to give methyl 2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-6-*endo*-carboxylate [II (0.8 g)] as a pale yellow oil [IR ν_{max}^{neat} cm^{-1}: 1730 (ester C=O), 1660 (NC=O). NMR ($CDCl_3$) δ: 1.75—2.35 (2H, m, C_5–H_{endo}, C_5–H_{exo}), 2.9 (3H, s, N–Me), 3.15 (1H, m, C_6–H_{exo}), 3.43 (1H, m, C_4–H), 3.67 (3H, s, COOMe), 4.45 (1H, m, C_1–H), 6.25—6.65 (2H, m, C_7–H, C_8–H)]. A solution of II (0.35 g) in MeOH (10 ml) was saturated with NH_3, and the mixture was stirred at 25—30° for 24 hr. The reaction mixture was evaporated, and the residue was recrystallized from EtOH to give XV (0.19 g), mp 239—240°, in 54.6% overall yield as colorless prisms. *Anal.* Calcd. for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.77; H, 6.55; N, 15.36. MS *m/e*: 180 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1670 (NC=O), 1655 (NC=O). NMR (DMSO-d_6) δ: 1.6—1.9 (2H, m, C_5–H_{endo}, C_5–H_{exo}), 2.73 (3H, s, N–Me), 2.95 (1H, m, C_6–H_{exo}), 3.23 (1H, m, C_4–H), 4.45 (1H, m, C_1–H), 6.2—6.5 (2H, m, C_7–H, C_8–H), 6.85, 7.37 (1H, 1H, b, b, $CONH_2$).

b) A mixture of XI (648 mg), $TiCl_4$ (3 g), AcOH (4 ml), and H_2O (1.2 ml) was stirred at room temperature for 24 hr. H_2O (10 ml) was added to the reaction mixture. The mixture was basified with K_2CO_3, and the basic mixture was continuously extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated, and the residue was recrystallized from EtOH to give XV (420 mg), mp 239—240°, in 58.3% yield as colorless prisms.

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