[Chem. Pharm. Bull. 26(8)2312—2315(1978)]

UDC 547.823.04 : 547.462.3.04

Studies on 1-Alkyl-2(1*H*)-pyridone Derivatives. XXV.[1] The Diels-Alder Reaction of 1-Methyl-2(1*H*)-pyridone with Fumaric Acid and Its Ester

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(Received December 21, 1977)

Studies on the Diels-Alder reaction of 1-methyl-2(1*H*)-pyridone (I) with fumaric acid and its ester were carried out. Reaction of I with dimethyl fumarate in toluene gave dimethyl 2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-*endo*-6-*exo*-dicarboxylate (IV) in about 4% yield. Boiling of I and fumaric acid in water afforded 6-methyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2,8-*endo*-dicarboxylic acid (VII) in about 20% yield.

Keywords——2(1*H*)-pyridone; Diels-Alder reaction; 6-azabicyclo[3.2.1]octene; 2-azabicyclo[2.2.2]octene; fumaric acid; dimethyl fumarate

There have been considerable reports published about the Diels–Alder reaction of 1-methyl-2(1*H*)-pyridone (I)[3] with various dienophiles such as benzyne,[3a] maleic anhydride,[3b]

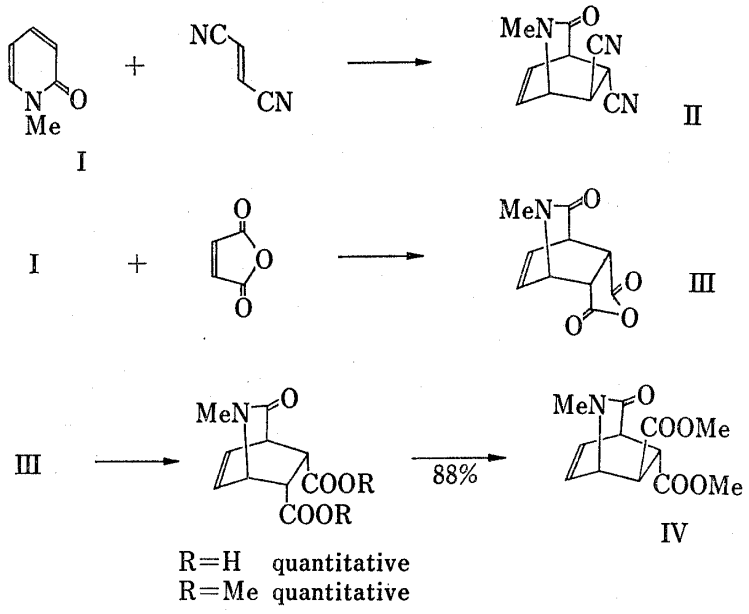

Chart 1

1) Part XXIV: H. Tomisawa, R. Fujita, H. Hongo, and H. Kato, *Chem. Pharm. Bull.* (Tokyo), **23**, 592 (1975).
2) Location: *Komatsushima, Sendai 983, Japan.*
3) *a*) E.B. Sheinin, G.E. Wright, and L. Bauer, *J. Heterocycl. Chem.*, **5**, 859 (1968); *b*) H. Tomisawa and H. Hongo, *Tetrahedron Lett.*, 2465 (1969); *idem*, *Chem. Pharm. Bull.* (Tokyo), **18**, 925 (1970); H. Hongo, *Chem. Pharm. Bull.* (Tokyo), **20**, 226 (1972); *c*) N.P. Shusherina and M.V. Gapeeva, *Zh. Org. Khim.*, **9** (4), 848 (1973) [*C.A.*, **79**, 18611*r* (1973)]; *idem*, *Vestn. Mosk. Univ. Khim.*, **15** (4), 496 (1974) [*C.A.*, **82**, 31286*v* (1975)]; N.P. Shusherina, L.V. Betaneli, G.B. Mndlyan, and A.U. Stepanyants, *Khim. Geterotsikl, Soedin*, **1974** (11), 1512 [*C.A.*, **82**, 57582*p* (1975)]; L.V. Betaneli, N.P. Shusherina, E.A. Tarkhanova, and A.U. Stepanyants, *Zh. Org. Khim.*, **11** (2), 417 (1975) [*C.A.*, **83**, 9848*d* (1975)]; *d*) I. Matsuura, Japan Patent 14698, 25594 (1975) [*C.A.*, **83**, 43295*f*, 131563*x* (1975)]; *e*) U. Heep, *Tetrahedron*, **31**, 77 (1975); *f*) H. Tomisawa, R. Fujita, K. Noguchi, and H. Hongo, *Chem. Pharm. Bull.* (Tokyo), **18**, 941 (1970).

maleimide,[3c,d] and dimethyl acetylenedicarboxylate[3e] yielding azabicyclo[2.2.2]octane derivatives. And it has been well known that the Diels-Alder adduct generally has *cis* substituents originating from the dienophiles.

The previous paper[3f] of this series reported that the reaction of I with fumaronitrile exceptionally proceeded in formation of the adduct (II) possessing the *trans* substituents, although the yield was poor (3%). In addition, the *trans* compound (IV),[3f] having the same configuration with II, could be obtained in a good yield by isomerization of the *cis* adduct(III), which was formed in the reaction of I with maleic anhydride, as shown in Chart 1.

Our continuous efforts have been made to get the *trans* isomer of Diels-Alder adduct. This is concerned with the reaction of I with fumaric acid and its dimethyl ester.

A solution of I and dimethyl fumarate (VI) in toluene was refluxed for 1 week to give colorless needles of mp 67—68° in about 4% yield, which was identified as dimethyl 2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-*endo*-6-*exo*-dicarboxylate (IV) by the comparison of its infrared (IR) spectrum with that of the authentic sample and the mixed melting point determination.

Refluxing of a solution of I and fumaric acid in water for 1 week gave cololess prisms (VII), $C_{10}H_{11}NO_5$, mp 268—270° (dec.) in 19.4% yield.

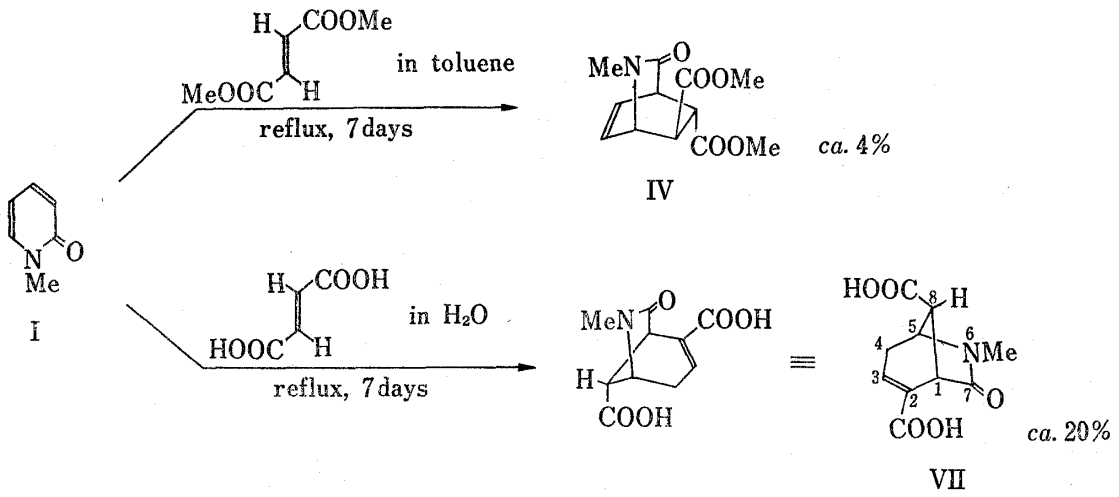

Chart 2

The IR spectrum of VII showed absorption bands of carbonyl groups at 1720 (COOH), 1690 (CH=C–C=O) and 1650 cm^{-1} (N–C=O). The nuclear magnetic resonance (NMR) spectrum of VII (in pyridine-d_5), which is much different from those of the normal Diels-Alder adducts, is shown in Table I.

Table I. NMR Spectrum[a] of VII in Pyridine-d_5 Solution

	Chemical shift (ppm)	Coupling constant (J), Hz
C_3–H	7.2 (multiplet)	
C_1–H	4.52 (doublet)	J (C_1–H: C_8–H) = 5
C_5–H	4.05 (multiplet)	
C_8–H	3.7 (triplet)	J (C_1–H: C_8–H) = 5
C_4–H *exo*	3.0 (double-triplet)	J (C_4–H_{endo}: C_4–H_{exo}) = 20, J (C_3–H: C_4–H_{exo}) = J (C_5–H: C_4–H_{exo}) = 3
C_4–H *endo*	2.5 (broad doublet)	J (C_4–H_{endo}: C_4–H_{exo}) = 20
N–Me	2.9 (singlet)	

a) Tetramethylsilane was used as an internal standard.

These spectral data suggest that the structure of VII is VIIa, VIIb, or their respective stereo isomers (VIIa′ and VIIb′) about configuration of the carboxyl group as shown in Chart 3.

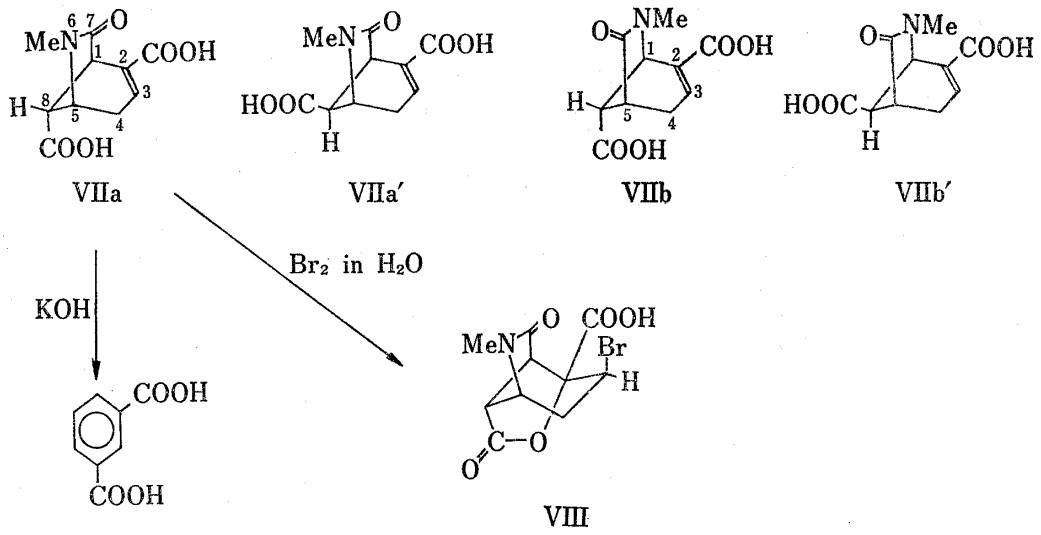

Chart 3

When VII was treated with conc. potassium hydroxide, isophthalic acid was obtained in about 50% yield. In addition, treatment of VII with bromine afforded the bromolactone VIII, $C_{10}H_{10}BrNO_5$, mp 294—297° (dec.), whose IR spectrum showed characteristic absorption band of γ-lactone carbonyl at 1800 cm^{-1}, in about 50% yield.

On the other hand, when the signal due to N-methyl group of VII was irradiated, the integrated intensity of C_5–H signal was increased (7±2%) in the NMR spectrum of VII, while that of C_1–H was unchanged.

From these chemical evidences and results of the nuclear Overhauser effect (NOE), the structure of VII was confirmed as 6-methyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2,8-*endo*-dicarboxylic acid (VIIa).

In the same manner, the dideuterio compound (VIId) was prepared by the treatment of 3,5-dideuterio-1-methyl-2(1*H*)-pyridone (Id) with fumaric acid in D_2O.

In comparison of its NMR spectrum with that of VII, the signals of two protons due to C_4–H (*exo* and *endo*) disappeared and the other signals were observed at the same chemical shifts as those of VII.

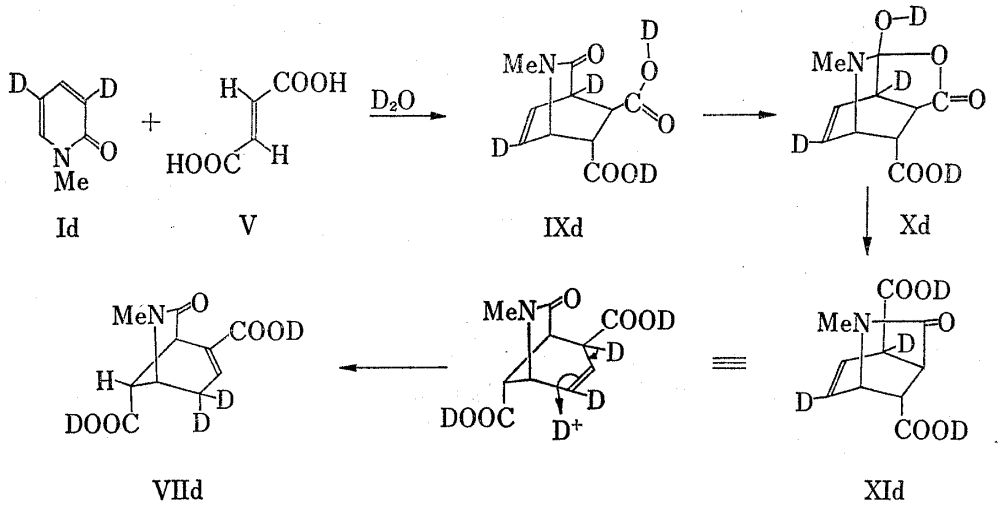

Chart 4

From these facts, this novel synthesis of an azabicyclo[3.2.1]octane system is best rationalized by the following mechanism,[4] as shown in Chart 4, which involves the ring transformation of the normal Diels-Alder adduct (IXd) *via* intramolecular amide acetal (Xd) and subsequent double bond shift of XId.

Experimental[5]

The Diels-Alder Reaction of 1-Methyl-2(1*H*)-pyridone (I) with Dimethyl Fumarate (VI)——A mixture of 9.8 g of I, 13 g of VI, and 100 ml of toluene was refluxed for 1 week, and allowed to stand overnight at room temperature. The precipitate (VI) formed was filtered off. The filtrate was evaporated under a reduced pressure to give 12 g of a brown oil. The oil was chromatographed through a column of silica gel. The fraction eluted with benzene-acetone (20: 1) gave 0.87 g (3.9%) of dimethyl 2-methyl-3-oxo-2-azabicyclo-[2.2.2]oct-7-ene-5-*endo*-6-*exo*-dicarboxylate (IV), mp 67—68° (lit.[3f] mp 67—68°), as colorless needles (ether).

Reaction of 1-Methyl-2(1*H*)-pyridone (I) with Fumaric Acid (V)——A mixture of 5 g of I, 2.66 g of V, and 27 ml of H_2O was refluxed for 1 week and allowed to stand overnight at room temperature. The precipitate (V, 0.65 g) formed was filtered off. The filtrate was evaporated under a reduced pressure to give a brown oil. The oil was washed with hot hexane, and then benzene to give a residue. The washing of hexane and benzene were combined, washed with a saturated aq. K_2CO_3, dried over $MgSO_4$, and evaporated to recover 2.8 g of I. The residue was treated with acetone to give colorless fine crystals, which were treated with 18 ml of MeOH and 6 ml of 10% HCl to give 1 g (19.4%) of 6-methyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2,8-*endo*-dicarboxylic acid (VII), mp 268—270° (dec.), as colorless prisms (EtOH). *Anal.* Calcd. for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.92; N, 6.22. Found: C, 53.13; H, 4.91; N, 6.32. IR ν_{max}^{Nujol} cm^{-1}: 1650 (lactam C=O), 1720, 1690 (carboxylic acid C=O). MS *m/e*: 225 (M^+). NMR (in pyridine-d_5) δ: 7.2 (1H, multiplet, C_3–H), 4.52 (1H, doublet, $J=5$ Hz, C_1–H), 4.05 (1H, multiplet, C_5–H), 3.7 (1H, triplet, $J=5$ Hz, C_8–H), 3.0 (1H, double-triplet, $J=20$ Hz, $J=3$ Hz, C_4–H *exo*), 2.9 (3H, singlet, N–Me), 2.5 (1H, broad doublet, $J=20$ Hz, C_4–H *endo*).

Reaction of 3,5-Dideuterio-1-methyl-2(1*H*)-pyridone (Id) with V——A mixture of 10 g of Id, 10 g of V, and 100 ml of D_2O was treated under a same condition as for I to give 1.0 g of 4,4-dideuterio-6-methyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2,8-*endo*-dicarboxylic acid (VIId), mp 268—270° (dec.), as colorless prisms (EtOH). *Anal.* Calcd. for $C_{10}H_9D_2NO_5$: N, 6.16. Found: N, 6.26. IR ν_{max}^{Nujol} cm^{-1}: 1640 (lactam C=O), 1720, 1670 (carboxylic acid C=O). NMR (in pyridine-d_5) δ: 7.2 (1H, singlet, C_3–H), 4.52 (1H, doublet, $J=$ 5 Hz, C_1–H), 4.05 (1H, doublet, $J=5$ Hz, C_5–H), 3.7 (1H, triplet, $J=5$ Hz, C_8–H), 2.9 (3H, singlet, N–Me).

Hydrolysis of VII——A solution of 225 mg of VII in 2 g of 40% aq. KOH was heated at 115° (an oil bath) for 24 hr. The cooled mixture was acidified with 6 N HCl, and evaporated to dryness under a reduced pressure. To the residue was added dropwise a cooled mixture of 10 ml of MeOH and 1.1 g of $SOCl_2$. The mixture was stirred for 6 hr and allowed to stand overnight at room temperature. The mixture was poured into ice-water, made alkaline with Na_2CO_3, and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated to give 96 mg (49.5%) of dimethyl isophtharate, mp 61—63° (lit.[6] mp 64°), as colorless needles (hexane).

Reaction of VII with Bromine——A solution of 1 g of VII dissolved in 100 ml of H_2O was maintained at 0—5° and 0.7 g of Br_2 was added dropwise. The mixture was stirred for 2 hr at room temperature. The precipitate formed was collected by filtration to give 0.66 g (48.8%) of 3-*endo*-bromo-2-*endo*-carboxy-2-*exo*-hydroxy-6-methyl-7-oxo-6-azabicyclo[3.2.1]octane-8-*endo*-carboxylic acid γ-lactone (VIII), mp 294—297° (dec.), as colorless fine crystals (H_2O). *Anal.* Calcd. for $C_{10}H_{10}BrNO_5$: C, 39.49; H, 3.31; N, 4.60. Found: C, 39.03; H, 3.44; N, 4.52. IR ν_{max}^{Nujol} cm^{-1}: 1800 (γ-lactone C=O), 1720 (carboxylic acid C=O), 1650 (lactam C=O). MS *m/e*: 303 (M^+), 305 (M^++2). NMR (in CF_3CO_2H) δ: 4.83 (1H, multiplet, C_3–H), 4.38 (1H, broad doublet, $J=6$ Hz, C_5–H), 4.26 (1H, doublet, $J=6$ Hz, C_1–H), 4.04 (1H, triplet, $J=6$ Hz, C_8–H), 3.17 (3H, singlet, N–Me), 2.81 (2H, multiplet, CH_2).

Acknowledgement We wish express our thanks to Dr. T. Hiraoka and Mr. H. Kuwano of Sankyo Co. Ltd., for the works of NMR spectra (NOE).

4) L.A. Paquette, "Modern Heterocyclic Chemistry," W.A. Benjamin Inc., New York, N.Y. 1968, p. 83.
5) All melting points were uncorrected.
6) L. McMaster and F.F. Ahmann, *J. Am. Chem. Soc.*, **50**, 148 (1928).