REACTION OF 1-METHYL-2(1H)-PYRIDONE WITH FUMARIC ACID AND ITS ESTER

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The further studies on the Diels-Alder reaction of 1-methyl-2(1H)-pyridone (I) with fumaric acid and its ester were carried out in various conditions. 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). 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 (VI). Heating of I and fumaric acid at 170° gave VI and 6-methyl-7-oxo-6-azabicyclo[3,2,1]oct-2-ene-2,8-exo-dicarboxylic acid (VII).

In our earlier papers of this series,[1,2] we reported that the Diels-Alder reaction of 1-methyl-2(1H)-pyridone (I) with maleic anhydride produced the adduct (II) in 42% yield, while the adduct (III) was obtained in only 3% yield by the reaction of I with fumaronitrile. It was also reported in that paper that II was transformed into the compound (IV) having the same configura-

tion with III in a good yield as shown in Chart 1.

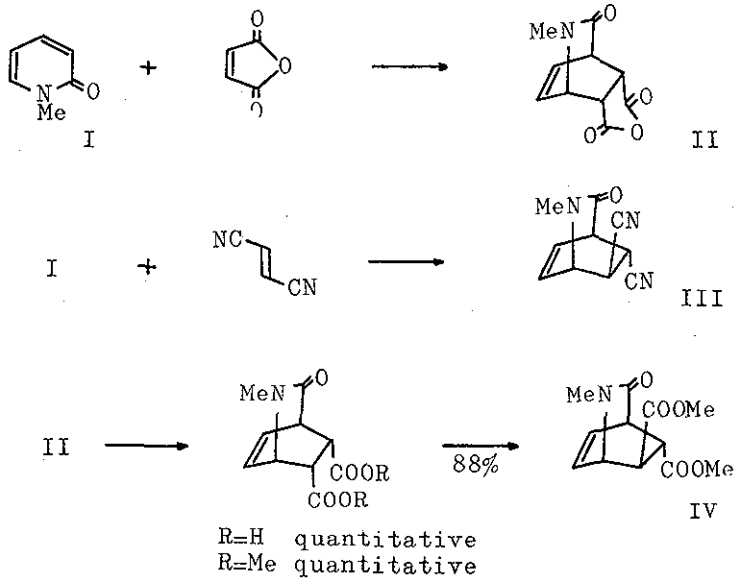


Chart 1

It has been also well known[3] that the structure of the adduct of Diels-Alder reaction depends on the polarity of the solvents used. The continuous efforts were made to disclose clearly the Diels-Alder reaction of I with other dienophiles. This paper deals with the Diels-Alder reaction of I with fumaric acid or its ester. The reaction proceeded in different manner, depending on the solvents used, such as in toluene (nonpolar solvent), water (polar solvent), and neat (no solvent), to result in the formation of the azabicyclo compounds unexpectedly.

A solution of I and dimethyl fumarate 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 IR spectrum with that of the authentic sample[2] and the mixed melting point determination.

Refluxing of a solution of I and fumaric acid in water for 1 week gave a colorless crystalline powder (V) of mp 186-188° in 16.3% yield (the corrected yield 51.7%), which was assigned to be an equimolar complex of I and the adduct (VI) by its NMR spectral analysis, besides the recovery of I in 68.4%. Treatment of V with 10% hydrochloric acid gave a colorless crystalline powder (VI) of mp 268-270° (decomp.) in a quantitative yield. Elemental analysis and molecular-weight determination provided its empirical formula as $C_{10}H_{11}O_5N$. The IR spectrum of VI shows the absorption of the amide carbonyl at 1650 cm^{-1} and two absorptions owing to the carboxylic acid carbonyl at 1720 cm^{-1} and to that conjugated with double bond at 1690 cm^{-1}. The NMR spectrum of VI (in pyridine-d_6) is shown in Table I.

Table I. NMR spectrum of VI in Pyridine-d_6 solution

	Chemical shift (ppm)	Coupling constant (J) Hz
A (1H)	7.2 (multiplet)	
B (1H)	4.52 (doublet)	$J_{BD}=5$
C (1H)	4.05 (multiplet)	
D (1H)	3.7 (triplet)	$J_{BD}=5$
E (1H)	3.0 (double triplet)	$J_{EF}=20$, $J_{AE}=J_{CE}=3$
F (1H)	2.5 (broad doublet)	$J_{EF}=20$
$N-CH_3$	2.9 (singlet)	

Tetramethylsilane was used as an internal standard.

If the signals in the lower magnetic field were to be arbitrarily designated as A, B, C, D, E, and F, the protons of VI were to be

lined in the order of B, D, C, $\overset{E}{\underset{F}{}}$, and A, as shown in Chart 2, in considerations of the coupling constants and the decoupling method.

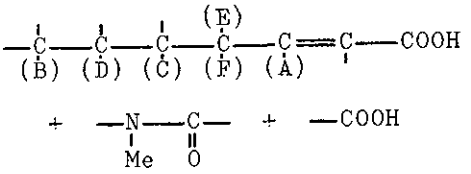


Chart 2

From these data, we can describe 10 possible structures for VI. However, its IR spectrum and chemical stability suggests that the β-lactam ring is unlikely as its partial structure. Treatment of VI with conc. potassium hydroxide gave isophthalic acid in about 50% yield, therefore, the structure of VI must have a six membered ring as a main skeleton. The configuration of carboxylic acid at 8-position was chemically assigned to be an endo form by the formation of bromolactone by treatment of VI with bromine. From these facts, the possible structure of VI was assumed to be VIa or VIb, as shown in Chart 3. Moreover, when the N-methyl peak was irradiated, the integrated intensity of peak C was increased in the NMR spectrum of VI, while that of B was unchanged. This NOE effect indicates that the structure of VI should be VIa, 6-methyl-7-oxo-6-azabicyclo[3,2,1]oct-2-ene-2,8-endo-dicarboxylic acid.

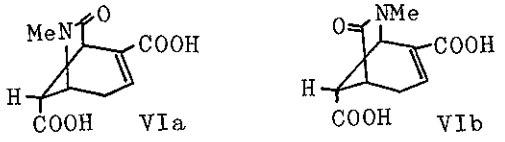


Chart 3

The Diels-Alder reaction of 3,5-dideuterio-1-methyl-2(1H)-pyridone with fumaric acid in D_2O was carried out in the same way to give the dideuterio adduct of VI (VI'). In the NMR spectrum of VI', the peaks A, B, C, and D were exhibited in the same position with those of VI, while those of E and F disappeared. From these data, a most possible path way[4] for the ring formation process of VI is shown in Chart 4, although the mechanism is not clear and speculative at this time.

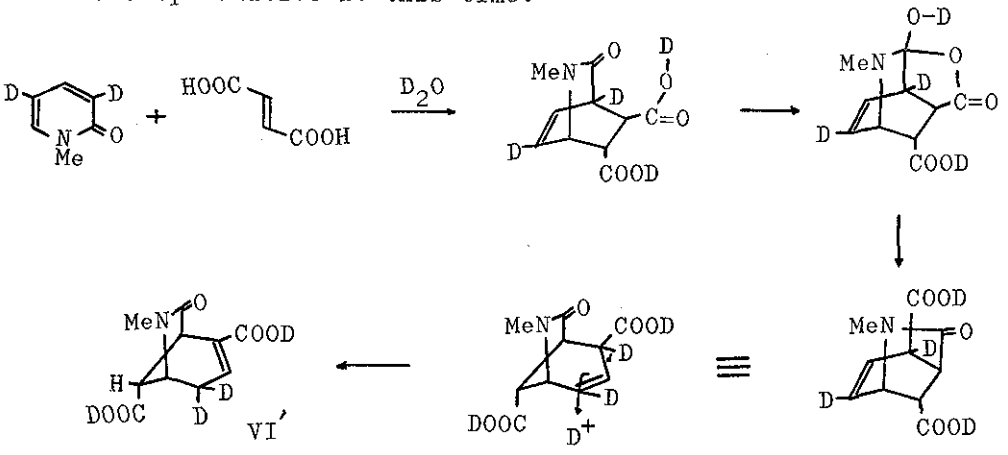
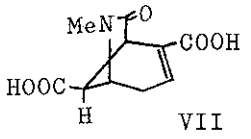


Chart 4

Heating of I and fumaric acid at 170° for 1 week gave VI in 7.7% yield and its stereoisomer VII in 12% yield as colorless prisms of mp 305-306° (decomp.). Esterification of VI and VII gave the corresponding dimethyl ester, VIII as colorless prisms of mp 109-110° and IX as colorless prisms of 116-118°, respectively. Treatment of VIII with lithium diisopropylamide at -78° afforded a mixture of VIII and IX (2:3), and the reaction of VII with bromine did not afford any bromolactone. Accordingly, IX should be an epimer of VIII and the structure of VII was confirmed

as 6-methyl-7-oxo-6-azabicyclo[3,2,1]oct-2-ene-2,8-exo-dicarboxylic acid.



VII

References

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