Reaction of Aromatic *N*-Oxides with Dipolarophiles. XVI.[1] Cycloaddition Behavior of Aromatic *N*-Oxides toward Electron-Deficient Allenes and X-Ray Structure of the 1,4-Dipolar Cycloadduct

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In connection with the pericyclic reaction of pyridine *N*-oxides with dipolarophiles, the cycloaddition behavior of some aromatic *N*-oxides toward electron-deficient allenes was investigated. In the reaction of 2-phenylpyridine *N*-oxide with dimethyl 2,3-pentadienedioate, the 2,3-dihydropyridine type 1 : 1 cycloadducts, which resulted from 1,5-sigmatropic rearrangement of the primary cycloadduct, were isolated. The reaction of 3,5-dihalogenopyridine *N*-oxides with the allene gave the dehydrohalogenated cycloadducts of the 1,5-sigmatropic rearrangement products. The reaction of 3,5-dimethylpyridine *N*-oxide with the allene caused deoxygenation to give 3,5-dimethylpyridine, which in turn reacted with two molecules of the allene to give the 1 : 2 cycloadduct (1,4-dipolar cycloaddition product). The structure of the cycloadduct was determined by single crystal X-ray analysis.

The observed reaction behaviors are discussed in terms of frontier molecular orbital considerations.

Keywords pericyclic reaction; frontier molecular orbital; 1,3-dipolar cycloaddition; 1,4-dipolar cycloaddition; allene; reactivity; X-ray analysis; pyridine *N*-oxide; 1,5-sigmatropy

During the course of an investigation of the 1,3-dipolar cycloaddition reaction of pyridine *N*-oxides with *N*-substituted maleimides, an important question arose concerning the cycloaddition reactivity, *i.e.*, why does only 3,5-dimethylpyridine *N*-oxide show reactivity toward *N*-substituted maleimides?[2a,b] We concluded that the inertness of other types of pyridine *N*-oxides such as unsubstituted pyridine *N*-oxide or 3-methylpyridine *N*-oxide might be attributable to their high degree of aromaticity and stabilization of the ground state by charge-transfer (CT) complex formation[3] between the dipoles and dipolarophiles.

It is well known that cyclic planar addends are prone to form the coplanar π,π-complex at an early point in the reaction coordinate, leading to the formation of the CT complex, which stabilize the ground state energy of the reaction system prior to cycloaddition. In order to avoid such a ground-state stabilization, we tried to use electron-deficient allenes which do not have a cyclic planar π-electron system, but have an orthogonal π-electron system.

This paper describes the results of cycloaddition of pyridine *N*-oxides (I) with dimethyl 2,3-pentadienedioate (II).

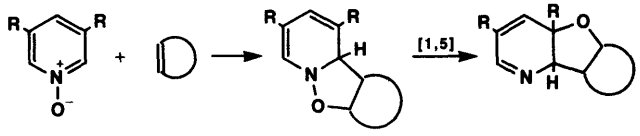
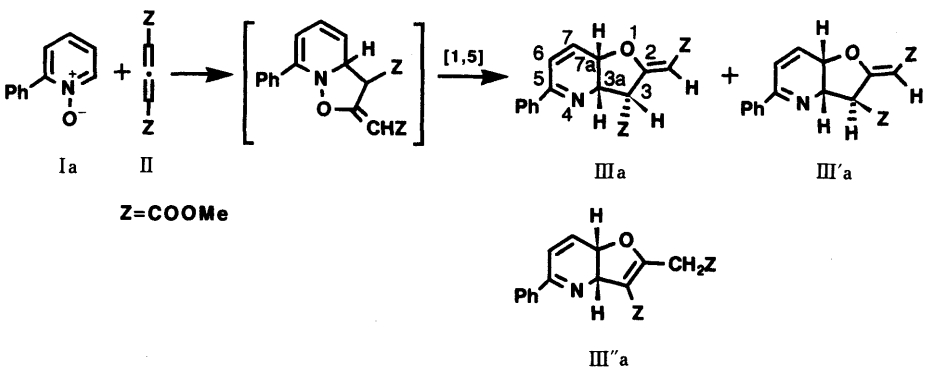


Chart 1

Results

Cycloaddition of 2-Phenylpyridine *N*-Oxide (Ia) with Dimethyl 2,3-Pentadienedioate (II) Pyridine *N*-oxide bearing a phenyl substituent at the 2-position (Ia) readily reacted with II to give a mixture of 1 : 1 cycloadducts assignable to the isomers due to the *exo* and *endo* cycloadditions (IIIa and III'a) (Charts 2 and 3). The pericyclic reaction pathways leading to the 1,5-sigmatropic rearrangement products are depicted in Chart 3. The products were separated by chromatography on silica gel. The infrared (IR) spectra of the isolated crystals (IIIa and III'a) showed conjugated and unconjugated carbonyl absorption bands at *ca.* 1700 and 1740 cm^{-1}, respectively. The carbon nuclear magnetic resonance (^{13}C-NMR) spectra showed three sp^3 carbons, suggesting that the products are not the primary adducts (two sp^3 carbons) but the 1,5-sigmatropically rearranged products, and also showed signals due to an olefinic carbon attached to an oxygen atom (*ca.* 158 ppm, –O–C=) and a carbon ascribable to >C=CH–COOMe (*ca.* 90 ppm).

The stereochemistries of IIIa and III'a were determined by careful inspection of their proton nuclear magnetic resonance (^{1}H-NMR) spectral data. The proton on the exocyclic double bond [–O–C(R)=CH(COOMe)] of IIIa and III'a resonated at 5.36 and 5.31 ppm, respectively. The configuration of the proton is considered to be *trans* with



Ia II IIIa III'a

Z=COOMe

III"a

Chart 2

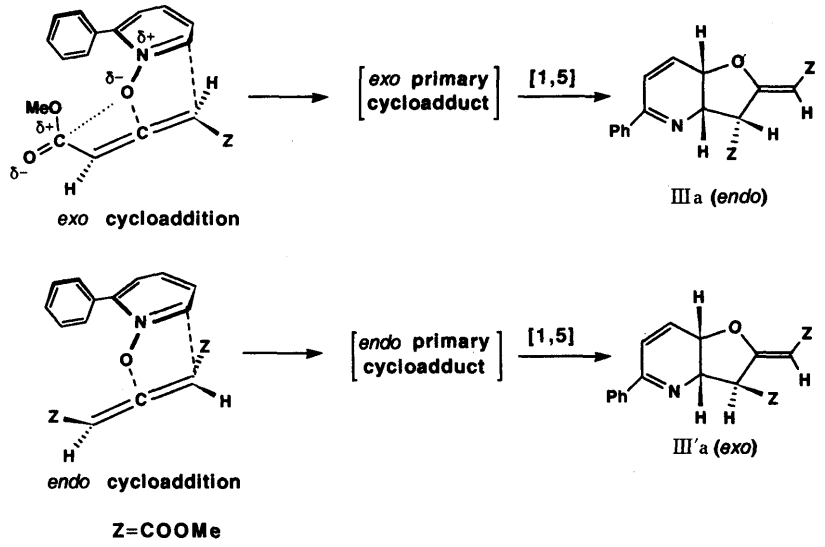


Chart 3

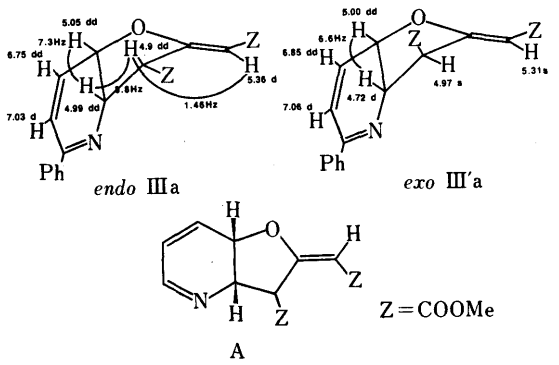


Fig. 1. ^{1}H-NMR Spectral Data of IIIa and III'a Formed by Cycloaddition of 2-Phenylpyridine *N*-Oxide (Ia) with the Allene (II)

respect to the ether group in each case on the basis of the chemical shifts of structurally similar compounds.[4a] This observation rules out the possibility that the ether group and the olefinic proton of the double bond are *cis*-oriented (see structure A in Fig. 1).[4b]

Next, the configuration of the methoxycarbonyl group on C_3, which reflects the stereochemistry of the cycloaddition (*endo–exo* nature of IIIa and III'a) was determined on the basis of the coupling constant between the C_3- and C_{3a}-protons. The ^{1}H-NMR spectral data are shown in Fig. 1. The C_3-proton of IIIa appeared as a weakly split doublet, whereas the proton of III'a appeared as a singlet. Molecular models, which satisfy the above spectral behaviors, suggest that the tetrahydrofuran rings takes a puckered conformation as depicted in Fig. 1.

Inspection of the correlation[4c] between the angle between the plane of the exocyclic double bond and the adjacent σ-bond (C_3-H) and the allylic coupling constant (J_{al}) also supports the assignments. In IIIa, the C_3 proton resonance occurs as a doulbet of doublet ($J_{al}=1.46$ Hz), indicating that the C_3 proton is approximately parallel with the π-orbital of the double bond. However, in III'a, the olefinic resonance appears as a singlet, since allylic coupling to the exocyclic proton is very small ($J_{al}<0.2$ Hz), indicating that the C_3 proton lies nearly in the plane of the double bond.

In the *endo* adduct (IIIa), there appears to be a sizable amount of van der Waals compression between the methoxycarbonyl group and its environment, whereas, in the case of *exo* adduct (III'a), such an interaction must not be serious. This would be consistent with the fact that compound IIIa exhibited the unconjugated ester carbonyl absorption at 1748 cm^{-1}, which is 10 cm^{-1} higher than that of III'a.

It should be noted that the exocyclic double bonds of IIIa and III'a did not isomerize to the endocyclic form (III''a) under the reaction conditions used (see Chart 2).

Cycloaddition of 3,5-Dichloropyridine *N*-Oxide (Ib) and 3,5-Dibromopyridine *N*-Oxide (Ic) with II The 1,3-dipole (Ib) showed high reactivity toward the allene (II), giving the cycloadduct IIIb as a sole product. The mass spectrum (MS) of IIIb showed an M^+ peak suggesting the formation of the furopyridine-type compound through elimination of HCl from the 1,5-sigmatropically rearranged product. The IR spectrum of IIIb exhibited two carbonyl absorption bands at 1740 and 1712 cm^{-1}. The adduct IIIb showed a simple ^{1}H-NMR spectral pattern consisting of a singlet peak due to Ar–CH_2COO– and two aromatic protons having a *meta* coupling. The alternative structure of III'b can be excluded based on the chemical shift of the α-carbon of the furan ring and the other examples of the cycloaddition studied in this work. The presence of triethylamine as a trapping agent for HCl gave a higher yield as compared with the reaction carried out without the base.

In the case of the reaction of 3,5-dibromopyridine *N*-oxide (Ic) with II, a similar result was obtained to give IIIc.

Cycloaddition of Quinoline *N*-Oxide (Id) with II The reaction of Id with II gave pale yellow crystals (IIId). The MS suggested formation of the 1 : 1 adduct. The ^{1}H-NMR spectrum exhibited a broad signal at 17.28 ppm due to a hydrogen-bonded proton. These results indicate that the primary adduct underwent ring cleavage to give the 2-methylene-type compound, which transformed into the 2-vinyl-type compound (see Chart 5). In this reaction, the 1,5-sigmatropic rearrangement could not be observed.

Cycloaddition of 3,5-Dimethylpyridine *N*-Oxide (Ie) with II When II was added to a solution of Ie in $CHCl_3$, the reaction mixture showed a red color. Purification of the product by silica gel chromatography gave unstable orange crystals. When a solution of the crystals in benzene was

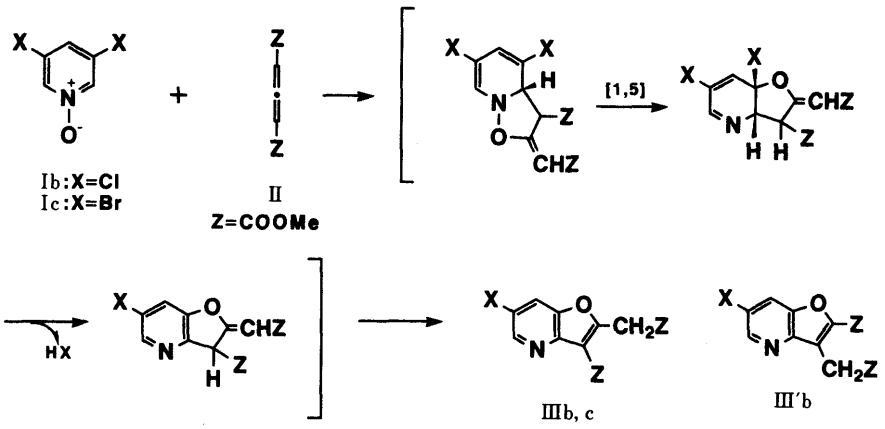


Chart 4

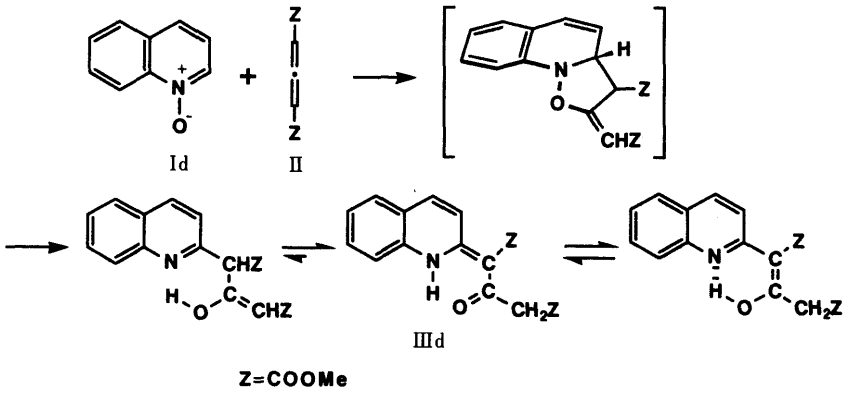


Chart 5

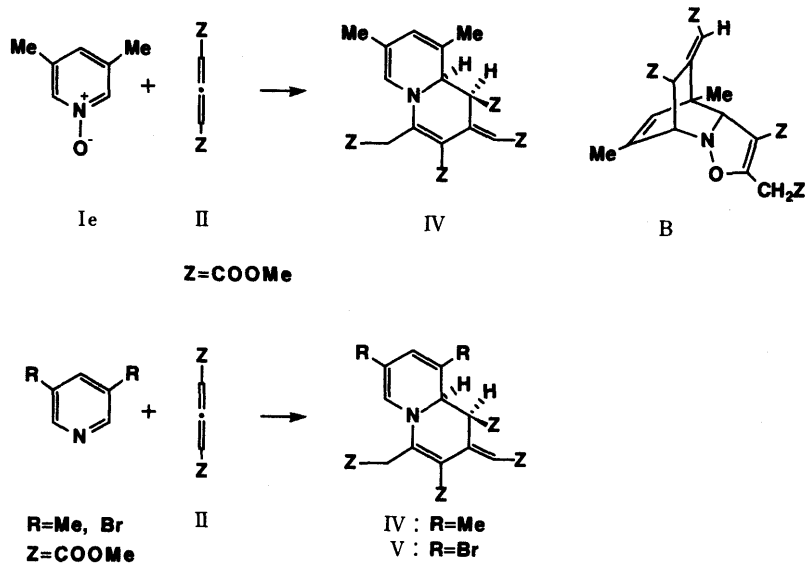


Chart 6

allowed to stand overnight at room temperature, several spots were recognized on a thin layer chromatogram. The MS of the product suggested that the cycloaddition of Ie with II gave a 1:2 cycloadduct (IV). However, the high resolution MS (HRMS) did not give definitive evidence for the 1:2 adduct because the product contained a small amount of impurities. The IR spectrum of IV showed three carbonyl absorption bands at 1760, 1741 and 1708 cm^{-1}. From these observations, we considered the product to be the [4+2]π cycloadduct (B) of the 1,5-sigmatropically rearranged product and II. However, the visible absorption spectrum of IV exhibited an absorption maximum at 480 nm due to a highly conjugated structure and a ^{1}H-NMR study of IV was in apparent disagreement with the structure B. Therefore, we performed a single crystal X-ray analysis.

Fortunately, single crystals of the adduct could be obtained by slow evaporation of a solution in benzene. The structure was solved by the direct method using the

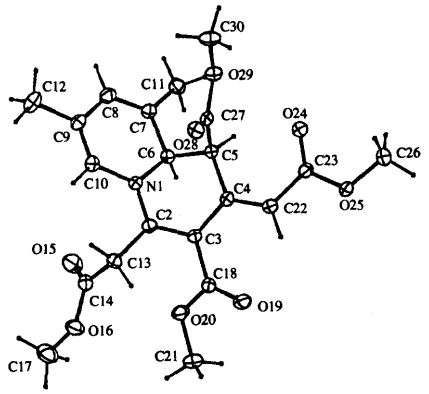


Fig. 2. ORTEP Perspective View of the Cycloadduct (IV), Showing the Atomic Numbering Used in Tables I—III

Table I. Fractional Atomic Coordinates[a] and Isotropic Temperature Factors (B) for Non-hydrogen Atoms with Their Estimated Standard Deviations in Parentheses

Atom	x/a	y/b	z/c	B[b]
N1	2746 (4)	3803 (3)	5538 (3)	3.07 (13)
C2	3238 (5)	2789 (4)	6383 (4)	3.20 (17)
C3	2585 (5)	1486 (4)	6103 (4)	3.23 (17)
C4	1778 (5)	1311 (4)	4713 (4)	3.02 (16)
C5	1218 (5)	2451 (4)	3802 (4)	2.89 (16)
C6	1301 (5)	3335 (4)	4699 (4)	2.97 (16)
C7	698 (5)	4469 (4)	3932 (4)	3.14 (17)
C8	1506 (5)	5760 (4)	3927 (4)	3.95 (19)
C9	2974 (5)	6166 (4)	4655 (4)	3.70 (19)
C10	3537 (5)	5211 (4)	5429 (4)	3.49 (18)
C11	−837 (5)	4013 (5)	3252 (5)	4.21 (20)
C12	3830 (6)	7650 (5)	4568 (6)	5.39 (23)
C13	4509 (5)	3101 (4)	7544 (4)	3.31 (17)
C14	4187 (5)	3226 (4)	8759 (4)	3.93 (19)
O15	3342 (4)	3692 (4)	8687 (3)	5.86 (17)
O16	5019 (4)	2777 (3)	9920 (3)	5.19 (15)
C17	4825 (8)	2825 (7)	11186 (5)	7.34 (31)
C18	2786 (5)	293 (4)	7186 (4)	4.04 (19)
O19	2816 (5)	−726 (4)	7047 (3)	7.48 (19)
O20	2892 (4)	429 (3)	8423 (3)	4.71 (13)
C21	2972 (6)	−736 (5)	9546 (5)	5.77 (24)
C22	1574 (5)	232 (4)	4256 (4)	3.75 (18)
C23	837 (5)	51 (4)	2856 (4)	3.73 (18)
O24	468 (4)	874 (3)	1898 (3)	5.08 (14)
O25	624 (4)	−1214 (3)	2764 (3)	4.84 (14)
C26	−120 (7)	−1530 (5)	1425 (5)	6.13 (25)
C27	1994 (5)	3322 (4)	2690 (4)	3.24 (17)
O28	3206 (3)	3587 (3)	2800 (3)	4.35 (13)
O29	1128 (3)	3831 (3)	1587 (3)	4.02 (12)
C30	1752 (6)	4706 (6)	459 (5)	5.95 (25)

a) Positional parameters are multiplied by 10^4. *b*) Thermal parameters are given by the equivalent temperature factors (Å^2).

MULTAN78 program[5] and refined by the block-diagonal least-square method. The final *R* value obtained was 0.05. The ORTEP[6] drawing shown in Fig. 2 reveals the product to have a 9*H*-quinolizine-type structure, presumably derived from deoxygenation of 3,5-dimethylpyridine *N*-oxide (Ie) followed by cycloaddition with two molecules of II. The sum of the angles around the N_1 nitrogen atom is about 360, indicating that the N_1 is an sp^2 nitrogen. The atoms of C_7, C_8, C_9, C_{10}, N_1, C_2 and C_3 make a planar structure with which the π-plane defined by the C_4 and C_{22} atoms makes an angle of 25°. The bond lengths indicate that the 14π-electrons form a resonance structure consistent with

Table II. Bond Distances (Å) for Non-hydrogen Atoms with Their Estimated Standard Deviations in Parentheses

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
N1	–C2	1.352 (6)	N1	–C6	1.478 (5)
N1	–C10	1.416 (5)	C2	–C3	1.399 (6)
C2	–C13	1.503 (6)	C3	–C4	1.468 (6)
C3	–C18	1.468 (6)	C4	–C5	1.515 (6)
C4	–C22	1.341 (8)	C5	–C6	1.539 (8)
C5	–C27	1.515 (6)	C6	–C7	1.509 (7)
C7	–C8	1.327 (6)	C7	–C11	1.501 (7)
C8	–C9	1.454 (7)	C9	–C10	1.326 (7)
C9	–C12	1.499 (6)	C13	–C14	1.515 (8)
C14	–O15	1.191 (8)	C14	–O16	1.331 (5)
O16	–C17	1.459 (9)	C18	–O19	1.196 (8)
C18	–O20	1.339 (7)	O20	–C21	1.442 (6)
C22	–C23	1.467 (6)	C23	–O24	1.192 (5)
C23	–O25	1.348 (6)	O25	–C26	1.456 (6)
C27	–O28	1.190 (7)	C27	–O29	1.343 (5)
O29	–C30	1.442 (6)			

Table III. Bond Angles (°) of IV for Non-hydrogen Atoms with Their Estimated Standard Deviations in Parentheses

Atom 2–atom 1–atom 3			Angle	Atom 2–atom 1–atom 3			Angle
C2	–N1	–C6	114.8 (3)	C2	–N1	–C10	123.8 (4)
C6	–N1	–C10	121.5 (4)	N1	–C2	–C3	118.6 (4)
N1	–C2	–C13	119.6 (4)	C3	–C2	–C13	121.8 (4)
C2	–C3	–C4	120.6 (4)	C2	–C3	–C18	119.6 (4)
C4	–C3	–C18	119.7 (4)	C3	–C4	–C5	115.7 (4)
C3	–C4	–C22	122.6 (4)	C5	–C4	–C22	121.6 (4)
C4	–C5	–C6	108.9 (3)	C4	–C5	–C27	112.4 (5)
C6	–C5	–C27	110.7 (3)	N1	–C6	–C5	109.6 (5)
N1	–C6	–C7	113.7 (3)	C5	–C6	–C7	114.7 (3)
C6	–C7	–C8	112.0 (4)	C6	–C7	–C11	115.3 (4)
C8	–C7	–C11	124.7 (5)	C7	–C8	–C9	123.4 (5)
C8	–C9	–C10	119.4 (4)	C8	–C9	–C12	120.3 (5)
C10	–C9	–C12	120.3 (4)	N1	–C10	–C9	121.4 (4)
C2	–C13	–C14	112.9 (5)	C13	–C14	–O15	125.1 (4)
C13	–C14	–O16	110.0 (5)	O15	–C14	–O16	124.8 (5)
C14	–O16	–C17	116.4 (6)	C3	–C18	–O19	127.0 (5)
C3	–C18	–O20	112.0 (5)	O19	–C18	–O20	120.9 (4)
C18	–O20	–C21	116.4 (5)	C4	–C22	–C23	124.4 (4)
C22	–C23	–O24	127.2 (5)	C22	–C23	–O25	110.4 (4)
O24	–C23	–O25	122.4 (4)	C23	–O25	–C26	115.8 (4)
C5	–C27	–O28	125.5 (4)	C5	–C27	–O29	109.5 (4)
O28	–C27	–O29	124.8 (4)	C27	–O29	–C30	115.1 (4)

the visible absorption spectrum observed at 480 nm. The stereochemistry of the two hydrogen atoms on C_5 and C_6 is revealed to be *cis*.

1,4-Dipolar Reactions of 3,5-Dimethylpyridine and 3,5-Dibromopyridine with II In order to clarify the formation mechanism of IV, the reaction of 3,5-dimethylpyridine with II was carried out. When 3,5-dimethylpyridine was mixed with II at room temperature, an exothermic reaction took place to afford IV in 63% yield. In the case of 3,5-dibromopyridine, a similar reaction occurred to afford the 1 : 2 adduct (V).

The structure of V was determined by comparison of the IR and ^{1}H-NMR spectral data with those of IV.

Reactions of Other Pyridine *N*-Oxides with II The allene (II) showed moderate cycloaddition reactivity toward both unsubstituted and electron-deficient pyridine *N*-oxides even at room temperature.

In the reaction of 3-methoxycarbonylpyridine *N*-oxide

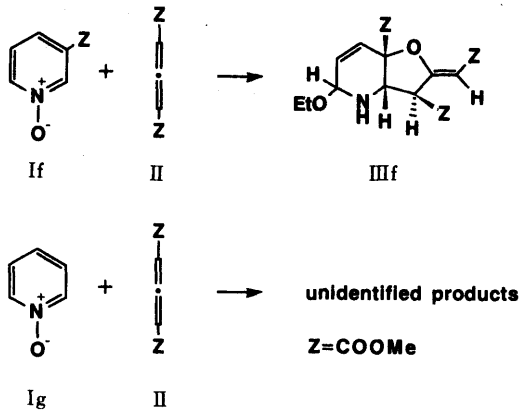


Chart 7

(If) with II, the reaction solution turned red, indicating that the 1,4-dipolar cycloaddition took place. However, the corresponding 1,4-dipolar cycloadduct could not be isolated. The thin-layer chromatogram of the reaction mixture showed the presence of several products. The product isolated was colorless crystals (IIIf), and was determined to be an addition compound of the 1,5-sigmatropic rearrangement product and ethanol. The stereochemistry was confirmed by comparison of the ^{1}H-NMR spectral data with those of IIIa and III'a (Chart 7).

The reaction of pyridine *N*-oxide (Ig) with II gave not only the 1,5-sigmatropic rearrangement product but also the 1,4-dipolar cycloaddition product, though their structures have not yet been determined by spectroscopic methods. A coherent interpretation of the spectral data and suitable single crystals for X-ray analysis have not yet been obtained. 3-Methylpyridine *N*-oxide showed similar reaction behavior.

Discussion

As mentioned above, the dimethyl pentadienedioate (II) showed high reactivity toward aromatic *N*-oxides bearing both electron-donating and accepting substituents and the reactions proceeded at room temperature to give the cycloadducts. This is in sharp contrast to the reaction conditions (100—130 °C) required in the 1,3-dipolar cycloaddition reaction with dipolarophiles such as phenyl isocyanate,[7] *N*-substituted maleimides[2a] or epoxynaphthalene.[3b]

As far as we know, there has been no report concerned with the cycloadducts formed by the 1,3-dipolar cycloaddition of aromatic *N*-oxides with allenes.[8] In order to understand the reaction behavior, modified neglect of diatomic overlap (MNDO)[9] calculations were performed. The calculated orbital energy levels and coefficients are listed in Table IV.

As can be seen in Fig. 3, the reaction of pyridine *N*-oxides with II falls into the category of a "normal-type" reaction in Sustmann's classification[10] for cycloadditions, wherein the dominant interaction is the one between the highest occupied molecular orbital (HOMO) of the 1,3-dipole and the lowest unoccupied molecular orbital (LUMO) of the dipolarophile. In the case of 3,5-dichloropyridine *N*-oxide (Ib), the frontier molecular orbital (FMO) energy levels lie between the FMO energy levels of the allene (II), indicating that the "inverse-type" interaction also plays an important

TABLE IV. MNDO Calculation Data for Pyridine *N*-Oxide (Ig), 3,5-Dichloropyridine *N*-Oxide (Ib), 3,5-Dimethylpyridine *N*-Oxide (Ie) and Dimethyl 2,3-Pentadienedioate (II)

Calcd values		Ig[a]	Ib	Ie	II
LUMO (eV),		−0.474	−1.148	−0.473	−0.45
Coefficients (p_z)	O	−0.393	0.393	0.379	
	N	0.529	−0.511	−0.512	
	C	−0.287	0.225	0.254	
					C_1 −0.459
					C_2 0.536
HOMO[a] (eV),		−8.769	−9.351	−8.737	−10.9
Coefficients (p_z)	O	−0.646	0.640	0.649	
	N	0.226	−0.214	−0.227	
	C	0.379	−0.388	−0.376	
					C_1 0.620
					C_2 0.544
Net charges	O	−0.421	−0.394	−0.429	
	N	0.263	0.267	0.261	
	C	−0.080	−0.063	−0.063	
					C_1 −0.026
					C_2 −0.034

a) The large in-plane coefficient (p_y −0.922) was on oxygen in NHOMO (−10.698 eV).

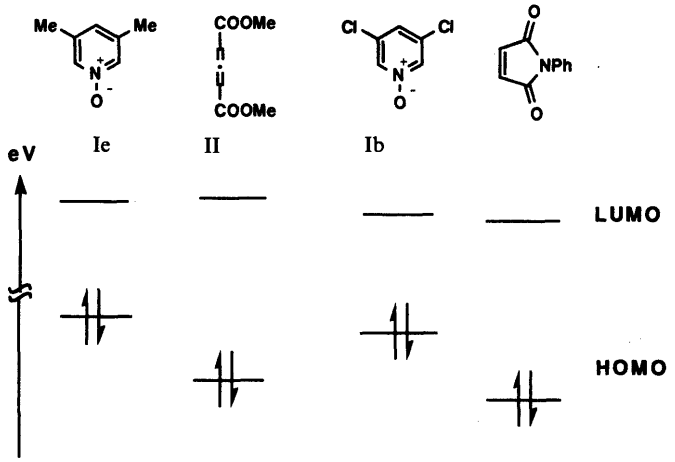


Fig. 3. FMO Interactions of 3,5-Dichloropyridine *N*-Oxide (Ib) and 3,5-Dimethylpyridine *N*-Oxide (Ie) with the Allene (II) and Maleimide

role in determining the cycloaddition reactivity. A similar argument may be applied to the reaction behavior of 2-phenylpyridine *N*-oxide (Ia) because phenyl groups compress the FMO energy levels.[11b]

The LUMO energy level (−1.16 eV) of maleimide is considerably lower than that of II (−0.45 eV) implying that maleimides would show higher cycloaddition reactivity toward I than the allene (II) if only FMO separation was considered. Contrary to expectation, the experimental results are inconsistent with the FMO prediction. This indicates that the primary FMO interaction energy between I and II is perhaps not the sole factor responsible for the high reactivity. Inspection of the MNDO calculation data of pyridine *N*-oxides (I) and II suggests that the huge lobe of the p_y orbital (in the molecular plane) exists on the oxygen atom of I in the next HOMO (NHOMO), which can strongly interact with the p_y orbital of the central carbon atom of II, stabilizing the transition state (Fig. 4). This interaction may contribute to the formation of the $=C=\cdots O\leftarrow N<$ bond, building up the resonance structure

of the enol ether moiety in the primary cycloadduct.[12]

As regards the regiochemistry of the 1,3-dipolar reaction, the observed regiochemistry of the reaction of I with the allene (II) follows the principle of maximum overlap of the FMO theory[11] as exemplified in Fig. 4. Bonding occurs between the central carbon of II and the oxygen atom of I where the largest coefficients of the interacting frontier orbitals are found. The net charges of II are very small, indicating that the coulombic interaction may be unimportant as a controlling factor in the early stage of the reaction.

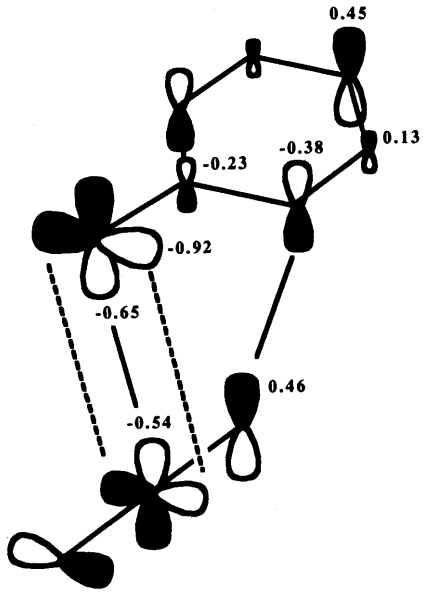


Fig. 4. Secondary Interactions in the Cycloaddition of Pyridine *N*-Oxide (Ig) with Allenes

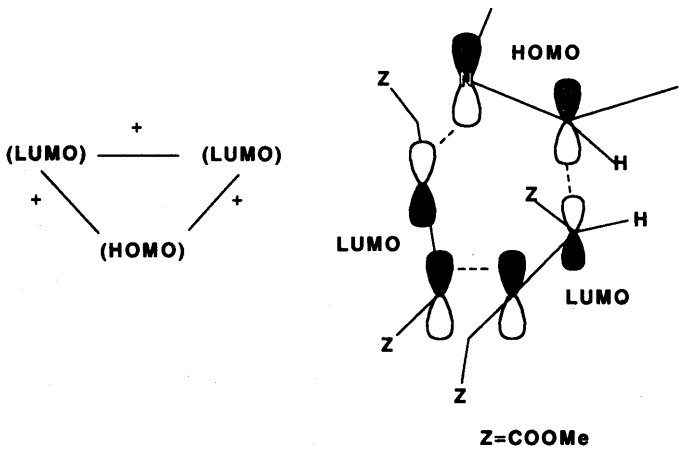


Fig. 5. Three System Interaction for the 1,4-Dipolar Cycloaddition of Pyridines with II

The *endo*-selectivity could not be observed, as exemplified in the 1,3-dipolar reaction of 2-phenylpyridine *N*-oxide (Ia) with II, in which a 1:1 mixture of the *endo* and *exo* cycloadducts was obtained. In the reaction, the secondary orbital overlap[2] between the nitrogen of Ia and the carbonyl carbon of II is considered to be poor.

The configuration of the exocyclic double bonds of IIIa and III'a reflected the stereochemistry of the primary cycloaddition, in which the coulombic attraction of the oxygen atom of Ia and the carbonyl carbon of II may be operative (see Chart 3).

Though the deoxygenation mechanism is still obscure, the formation reaction of 9*H*-quinolizine-type compounds is formally considered to be a so-called "1,4-dipolar cycloaddition"[14] wherein 1,4-dipoles formed from pyridines plus allene react with an additional allene to give $[2\pi+2\pi+2\pi]$ cycloadducts. Taking into consideration that the reactions readily took place in a nonpolar solvent such as benzene, and the central allene carbon (C_β) has a small negative net charge (C_α -0.026, C_β -0.034), the reaction should proceed *via* a nonionic concerted transition state (Fig. 5) rather than *via* an ionic intermediate (see Chart 8). The formation of 9*H*-quinolizine-type compounds can be account for in terms of the three system interaction,[15] in which pyridines act as HOMO[16] and two molecules of allenes act as LUMO's. The structures of the cycloadducts follow the principle that the larger lobe should unite with the larger one (large–large/small–small interaction) according to the perturbation theory.[11b]

An important factor which must be taken into consideration in the interpretation of the cycloaddition behavior of I toward dipolarophiles is the stability of the reactants, *e.g.*, the high degree of aromaticity of I.[7] It is worth mentioning that in the reaction of I with II, the orbital interaction energy overcomes the aromaticity of I.

Experimental

All melting points are uncorrected. ^{1}H-NMR spectra were taken with Hitachi R-600 and JEOL GX-400 spectrometers for *ca.* 10% (w/v) solutions, with tetramethylsilane (TMS) as an internal standard; chemical shifts are expressed in δ values. IR spectra were recorded on a Hitachi 270-30 infrared spectrophotometer. Visible absorption spectra were taken with a Hitachi 150-20 spectrometer. MS were taken with a JEOL JMS-DX303HF double-focussing spectrometer operating at an ionization

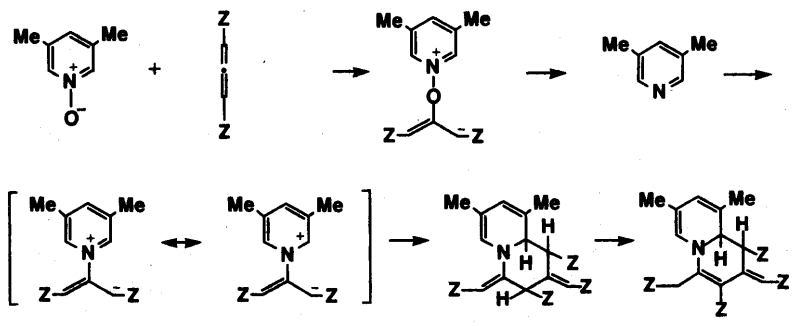


Chart 8

potential of 75 eV. Flash chromatography was carried out with Merck Silica Gel 60.

Molecular orbital (MO) calculations were performed on a FACOM M-360 computer at the Information Processing Center of Kumamoto University. Graphic analysis of the MO calculation and X-ray data were performed on a FACOM G-150 work station and a Fujitsu FMR-60HD personal computer.

Materials Dimethyl 2,3-pentadienedioate (II),[17] 2-phenylpyridine *N*-oxide (Ia),[18] 3,5-dichloropyridine *N*-oxide (Ib),[18] 3,5-dibromopyridine *N*-oxide (Ic),[18] quinoline *N*-oxide (Id),[18] 3,5-dimethylpyridine *N*-oxide (Ie),[18] 3-methoxycarbonylpyridine *N*-oxide (If)[18] and pyridine *N*-oxide (Ig)[18] were prepared according to the established methods.

Cycloaddition of 2-Phenylpyridine *N*-Oxide (Ia) with Dimethyl 2,3-Pentadienedioate (II) Compound II (13 mmol) was added to a solution containing Ia (10 mmol) in CH_2Cl_2. After the addition was complete, the mixture was stirred at room temperature for 12 h. The solvent was evaporated off. The residue was submitted to silica gel chromatography using a benzene : ethyl acetate (4 : 1) mixture as the eluent to give IIIa (yield 8.6%) and III'a (yield 8.3%).

exo Adduct (IIIa): mp 144—146 °C (colorless prisms from benzene). IR (KBr): 1738, 1700 (C=O) cm^{-1}. ^{1}H-NMR (in $CDCl_3$) δ: 3.58 (3H, s, COOMe), 3.78 (3H, s, COOMe), 4.72 (1H, d, J=6.6 Hz, C_{3a}-H), 4.97 (1H, s, C_3-H), 5.00 (1H, dd, J=6.6, 5.8 Hz, C_{7a}-H), 5.31 (1H, s, $C_{2'}$-H), 6.85 (1H, dd, J=5.8, 10.2 Hz, C_7-H), 7.06 (1H, d, J=10.2 Hz, C_6-H), 7.49—7.92 (5H, m, Ar). ^{13}C-NMR (in Acetone-d_6) δ: 51.0 (q, OMe), 52.9 (q, OMe), 58.5 (d, C_3), 63.7 (d, C_{3a}), 73.3 (d, C_{7a}), 90.0 (d, $C_{2'}$), 123.7 (d, C_6), 127.6 (d, Ar), 129.3 (d, Ar), 130.3 (d, C_7), 131.4 (d, Ar), 138.8 (s, Ar), 158.0 (s, C_2), 168.3 (s, C_5), 170.5 (s, C=O), 171.3 (s, C=O). MS m/z: 327 (M^+). HRMS, M^+ for $C_{15}H_{17}NO_5$ m/z: 327.1107. Found: 327.1102.

endo Adduct (III'a): mp 119—122 °C (colorless needles from benzene). IR (KBr): 1748, 1704 (C=O) cm^{-1}. ^{1}H-NMR (in $CDCl_3$) δ: 3.57 (3H, s, COOMe), 3.66 (3H, s, COOMe), 4.90 (1H, d, J=8.8 Hz, C_3-H), 4.99 (1H, dd, J=7.3, 8.8 Hz, C_{3a}-H), 5.05 (1H, dd, J=5.1, 10.2 Hz, C_{7a}-H), 5.36 (1H, d, J=1.46 Hz, $C_{2'}$-H), 6.75 (1H, dd, J=5.1, 10.2 Hz, C_7-H), 7.03 (1H, d, J=10.2 Hz, C_6-H), 7.49—7.92 (5H, m, Ar). ^{13}C-NMR (in acetone-d_6) δ: 50.9 (q, OMe), 51.9 (q, OMe), 56.3 (d, C_3), 60.5 (d, C_{3a}), 72.9 (d, C_{7a}), 92.6 (d, $C_{2'}$), 122.9 (d, C_6), 127.5 (d, Ar), 129.1 (d, Ar), 129.3 (d, Ar), 130.5 (d, C_7), 131.2 (d, Ar), 138.5 (s, Ar), 158.5 (s, C_2), 168.3 (s, C_5), 168.5 (s, C=O), 170.2 (s, C=O). MS m/z: 327 (M^+). HRMS, M^+ for $C_{15}H_{17}NO_5$ m/z: 327.1107. Found: 327.1095.

Cycloadditions of 3,5-Dichloropyridine *N*-Oxide (Ib) or 3,5-Dibromopyridine *N*-Oxide (Ic) with II Compound II (6 mmol) was added to a solution containing Ib or Ic (3 mmol) in tetrahydrofuran (THF) (10 ml). After the addition was complete, the mixture was stirred at room temperature for 24 h. The solvent was evaporated off. The residue was submitted to silica gel chromatography using a hexane : ethyl acetate (1 : 1) mixture as the eluent to give IIIb (yield 38%) or IIIc (yield 17%). The reaction of Ib with II in the presence of triethylamine gave IIIb in 69% yield.

Adduct (IIIb): mp 111—112 °C (colorless needles from benzene). IR (KBr): 1740, 1712 (C=O) cm^{-1}. ^{1}H-NMR (in $CDCl_3$) δ: 3.76 (3H, s, COOMe), 4.02 (3H, s, COOMe), 4.32 (2H, s, $-CH_2-$), 7.82 (1H, d, J=2.0 Hz, Ar), 8.86 (1H, J=2.0 Hz, Ar). MS m/z: 283, 285 (M^+, relative intensity 3 : 1). HRMS, M^+ for $C_{12}H_{10}{}^{35}ClNO_5$ m/z: 283.6247. Found: 283.0252. M^+ for $C_{12}H_{10}{}^{37}ClNO_5$ m/z: 285.0222. Found: 285.0243.

Adduct (IIIc): mp 109—111 °C (colorless prisms from benzene). IR (KBr): 1738, 1710 (C=O) cm^{-1}. ^{1}H-NMR (in $CDCl_3$) δ: 3.73 (3H, s, COOMe), 4.02 (3H, s, COOMe), 4.31 (2H, s, $-CH_2-$), 7.96 (1H, d, J=2.0 Hz, Ar), 8.76 (1H, J=2.0 Hz, Ar). MS m/z: 327, 330 (M^+, relative intensity 1 : 0.88). HRMS, M^+ for $C_{12}H_{10}{}^{79}BrNO_5$ m/z: 326.9742. Found: 326.9720. M^+ for $C_{12}H_{10}{}^{81}BrNO_5$ m/z: 328.9724. Found: 328.9723.

Reaction of Quinoline *N*-Oxide (Id) with II A solution of II (10 mmol) in absolute benzene (5 ml) was added to a solution containing Id (10 mmol) in absolute benzene was added. After the addition was complete, the mixture was stirred at room temperature for 2 h. The solvent was evaporated off. The solid was recrystallized from benzene–MeOH to give IIId in 37% yield. mp 116—118 °C (pale yellow prisms from benzene–MeOH). IR (KBr): 1738, 1680, 1634 (C=O) cm^{-1}. ^{1}H-NMR (in $CDCl_3$) δ: 3.77 (3H, s, COOMe), 3.82 (3H, s, COOMe), 3.86 (2H, s, $-CH_2-$), 7.39—8.13 (5H, m, Ar), 17.28 (1H, br, NH). MS m/z: 301 (M^+). HRMS, M^+ for $C_{16}H_{15}NO_5$ m/z: 301.0950. Found: 301.0937.

Cycloaddition of 3,5-Dimethylpyridine *N*-Oxide (Ie) with II Compound II (4 mmol) was added to a solution containing Ie (4 mmol) in $CHCl_3$. After the addition was complete, the mixture was stirred at room temperature for 0.5 h. The solvent was evaporated off. The residue was submitted to silica gel chromatography using a hexane : ethyl acetate (1 : 1) mixture as the eluent to give IV. The crude product was dissolved in ether (20 ml). The ether solution was chilled in a refrigerator for 6 h to give red needles in 17% yield. mp 142—144 °C (red needles from ether). IR (KBr): 1760, 1741, 1708 (C=O) cm^{-1}. UV $\lambda_{max}^{cyclohexane}$ nm (ε): 288 (20000), 480 (16000). ^{1}H-NMR (in $CDCl_3$) δ: 1.67 (3H, s, C_1-Me), 1.91 (3H, C_3-Me), 3.53 (1H, d, J=17.5 Hz, $-CH_2-$), 3.57 (1H, d, J=17.5 Hz, $-CH_2-$), 3.63 (3H, s, COOMe), 3.67 (3H, s, COOMe), 3.75 (3H, s, –COOMe), 3.80 (3H, s, COOMe), 4.55 (1H, d, J=3 Hz, C_{9a}-H), 5.09 (1H, d, J=3 Hz, C_9-H), 5.67 (1H, s, C_2-H), 5.94 (1H, s, =CHCOO–), 6.06 (1H, s, C_4-H). ^{13}C-NMR (in $CDCl_3$) δ: 18.3 (q, OMe), 19.9 (q, C_3-Me), 36.6 (t, $-CH_2-$), 44.0 (d, C_9), 51.1, 51.8, 52.0, 52.5 (q, OMe), 106.9 (d, $C_{8'}$), 109.6 (s, C_1), 118.2 (d, C_4), 122.3 (d, C_2), 128.2 (s, C_3), 144.0 (s, C_7), 145.5 (s, C_6), 167.5, 168.2, 168.7, 169.0 (s, C=O). MS m/z: 419 (M^+). HRMS, M^+ for $C_{21}H_{25}NO_5$ m/z: 419.1580. Found: 419.1551.

Cycloaddition of 3,5-Dimethylpyridine with II 3,5-Dimethylpyridine (2.56 mmol) was added to a solution containing II (5.12 mmol) in $CHCl_3$ (10 ml) under ice-cooling. After the addition was complete, the mixture was stirred at room temperature for 0.5 h. The solvent was evaporated off. The residue was submitted to silica gel chromatography using a hexane : ethyl acetate (1 : 1) mixture as the eluent to give a red solid. The crude product was dissolved in ether (20 ml). The ether solution was chilled in a refrigerator for 6 h to give IV as orange needles in 63% yield. This compound was identical with the material obtained from the reaction of Ie and II.

Cycloaddition of 3,5-Dibromopyridine with II A solution containing 3,5-dibromopyridine (2 mmol) and II (6 mmol) in benzene (5 ml) was refluxed for 8 h. After cooling, the mixture was stirred at room temperature for 12 h. The solvent was evaporated off. The residue was submitted to silica gel chromatography using a hexane : ethyl acetate (1 : 4) mixture as the eluent to give red solid, which was dissolved in ether (20 ml). The ether solution was chilled in a refrigerator to give crude V (mp 116—121 °C) in 60% yield. The crude product was again purified by chromatography on silica gel to give a pure sample, mp 120—123 °C, in 36% yield. IR (KBr): 1746, 1728, 1704 (C=O) cm^{-1}. ^{1}H-NMR (in $CDCl_3$) δ: 3.46 (1H, d, J=17.6 Hz, $-CH_2-$), 3.65 (1H, d, J=17.6 Hz, $-CH_2-$), 3.70, 3.72, 3.77, 3.83 (3H, s, COOMe), 4.82 (1H, d, J=2.9 Hz, C_{9a}-H), 5.36 (1H, d, J=2.9 Hz, C_9-H), 5.88 (1H, s, $C_{8'}$-H), 6.43 (1H, split s, C_2-H), 6.62 (1H, split s, C_4-H). MS m/z: 547, 549, 551 (M^+, relative intensity 1 : 3 : 1).

Cycloaddition of 3-Methoxycarbonylpyridine *N*-Oxide (If) with Dimethyl 2,3-Pentadienedioate (II) Compound II (6.6 mmol) was added to a solution containing If (3.3 mmol) in $CHCl_3$. After the addition was complete, the mixture was stirred at 0 °C to room temperature for 48 h. The solvent was evaporated off. The residue was submitted to silica gel chromatography using a benzene : ethyl acetate (1 : 1) mixture as the eluent to give IIIf (yield 21%). mp 168—172 °C (colorless needles from benzene). IR (KBr): 1740, 1712 (C=O) cm^{-1}. ^{1}H-NMR (in DMSO-d_6) δ: 1.07 (3H, t, J=7.0 Hz, Me of ethyl), 3.54 (2H, q, J=7.0 Hz, methylene of ethyl), 3.57 (6H, s, two COOMe), 3.70 (3H, s, COOMe), 4.09 (1H, d, J=3.3 Hz, C_{3a}-H), 4.41 (d, J=3.3 Hz, N-H), 4.58 (1H, br s, C_3-H), 4.62 (1H, br s, C_5-H), 5.44 (1H, br s, >C=CZ–H), 7.43 (1H, br dd, J=6.8 Hz, C_6-H), 7.50 (1H, d, J=6.8 Hz, C_7-H). MS m/z: 355 (M^+ + EtOH), 324 (M^+ − OMe), 310 (M^+ − OEt), 138 (methyl nicotinate + H^+). HRMS, M^+ for $C_{16}H_{21}NO_6$ m/z: 355.1267. Found: 355.1250.

X-Ray Crystallography Crystal Data. $C_{21}H_{25}NO_5$ (IV) M=419.2: triclinic, a=10.818 (11) Å, b=11.026 (11) Å, c=10.677 (10) Å, α=70.36 (8)°, β=110.31 (8)°, γ=114.43 (8)°, V=1059 (2) Å^3, D_m=1.307 g cm^{-3} (aq. KI), D_c=1.315 g cm^{-3}, Z=2, MoK_α radiation (40 kV-20 mA), λ=0.7107 Å.

The cell constants were determined by a least-squares procedure using the value of the Bragg angles of 17 reflections measured on a Rigaku AFC-6 four-circle autodiffractometer equipped with a graphite monochromated MoK_α source. The apparatus was interfaced to a PANAFACOM U-1200 minicomputer.

The space group $P\bar{1}$ (No. 2) was selected from the number of molecules per unit cell (Z=2) and was later confirmed in the course of the structure refinement. Intensity data were collected in the range of $2\theta < 55°$ using the θ—2θ scan technique. A variable scan rate was adopted. Two reflections were monitored after measurement of every 100 reflections. Of the 2372 independent reflections, 1627 were treated as observed ($F_o > 3\sigma$ F). The intensities were corrected for Lorentz and polarization effects, but no correction was applied for absorption.

Structure Solution and Refinement An overall temperature factor obtained from a Wilson plot did not give the correct solution. Therefore, the value of 5.0 Å^2 was used to calculate the normalized structure factor. The structure was solved by the direct method using the MULTAN78

series of programs.[5] An E map calculated with 390 signed E's ($E>1.2$), which gave a combined figure of merit of 2.255, revealed the positions of all the expected nonhydrogen atoms. Refinements were carried out by the block-diagonal least-squares method. Six cycles of isotropic refinement and 6 cycles of anisotropic refinement led to an R index of 0.094. All the hydrogens were located at calculated positions. After adding the hydrogens but keeping their thermal parameters fixed ($B(H)=B(C)+1.0$), we obtained a final R of 0.0501. Thermal parameters of the hydrogens attached to the methyl and methoxy groups were fixed for their anisotropic vibration. In final refinements, the following weights were used for the observed reflections: $w=1.0$ for $F_o<20.0$, $w=400/F_o^2$ for $F_o>20.0$.

All structure-solving programs were from the Information Processing Center of Kumamoto University with the Universal Crystallographic Computation Program System (UNICS III).[19]

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