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Reaction of Aromatic *N*-Oxides with Dipolarophiles. VII.[1a] Effect of Aromaticity on 1,3-Dipolar Cycloaddition Reactivity of Substituted Pyridine *N*-Oxides and Preparation of Oxazolo[4,5-*b*]pyridine Derivatives[1b]

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The 1,3-dipolar cycloaddition reactivity of pyridine *N*-oxides to phenyl isocyanate was calculated by the MINDO/3 MO method using the perturbation equation derived by Klopman and Salem.[2] The calculation did not predict the low reactivity of acceptor substituted pyridine *N*-oxides. On the basis of the calculation data, the general 1,3-dipolar cycloaddition reactivity of pyridine *N*-oxides towards various phenyl isocyanates is discussed in terms of the concept of cyclic conjugation. The aromaticity of the pyridine *N*-oxide may play an important role in determination of the reactivity. In connection with the cycloaddition, the 1,5-sigmatropic rearrangement of the primary cycloadducts and the pyrolytic reaction behavior of the 2,3-dihydropyridine derivatives formed by a 1,5-sigmatropic shift from the primary adducts are discussed on the basis of the MINDO/3 calculation data.

Keywords——1,3-dipolar cycloaddition; cyclic conjugation; frontier molecular orbital; pyridine *N*-oxide; phenyl isocyanate; decarboxylation

Many investigators have indicated the importance of the energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) in determining the reactivity in 1,3-dipolar reactions.[3] Further, several workers have found a correlation between $\ln k$ and $[1/(E_{ah}-E_{bl})+1/(E_{bh}-E_{al})]$ for the cycloadditions where E refers to the orbital energies indicated by the subscripts; subscripts a and b refer respectively to the reacting molecules a and b and subscripts h and l refer respectively to the HOMO and the LUMO.[4] However, the values of the coefficients do not have a marked effect on the rates of cycloaddition reactions and this may be explained by Fukui's principle of growing frontier electron density along the reaction path, which states that the coefficients at the reaction sites will be considerably enhanced at the transition state.[5]

Sustmann[6] has classified 1,3-dipolar reactions into three general types depending on the HOMO–LUMO arrangement of the 1,3-dipole and dipolarophile. The three types are the normal electron demand, the inverse electron demand, and the neutral electron demand. The normal electron demand reaction is dominated by the interaction of the HOMO of the 1,3-dipole and the LUMO of the dipolarophile, while the inverse electron demand reaction is dominated by the interaction of the HOMO of the dipolarophile and the LUMO of the 1,3-dipole. In the neutral electron demand reaction, neither frontier orbital interaction is dominant and both significantly affect the reactivity.[6]

In the previous paper,[1a] we showed that the 1,3-dipolar cycloaddition of pyridine *N*-oxides to phenyl isocyanates very probably takes place by a concerted process, like other cycloadditions, on the basis of the stereoselectivity, the lack of solvent dependence, the low activation enthalpy and the strongly negative activation entropy (which is characteristic of a

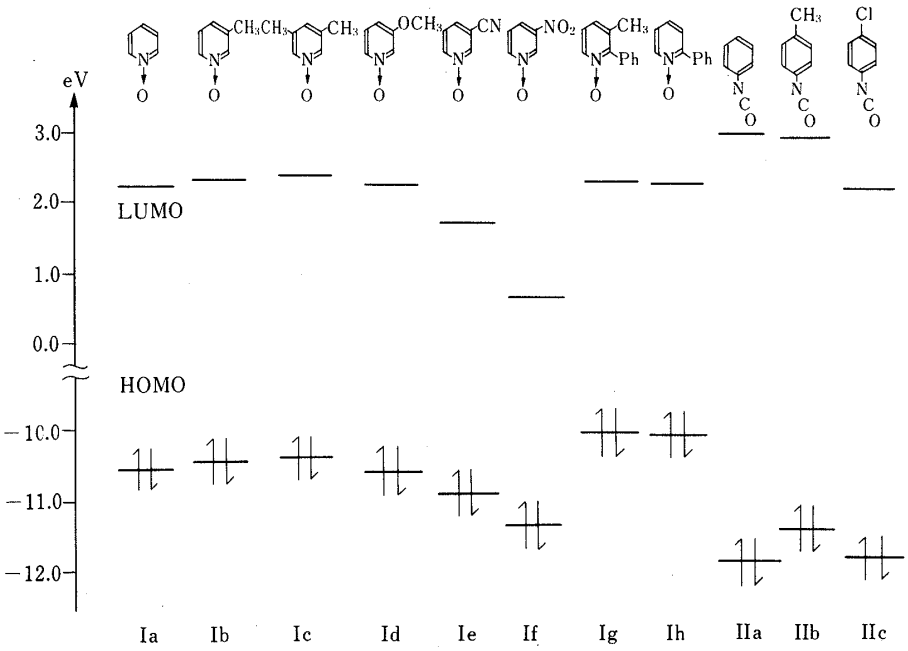


Fig. 1. CNDO/2 FMO Energies of Pyridine *N*-Oxides and Phenyl Isocyanates[a]

a) The calculation for the ... oxides bearing halogeno group could not be performed for technical reason

TABLE I. FMO Energ... Ia—h and IIa—c Calculated by ... 2 Method

Compound	HOMO[a]	LUMO[a]	NLUMO[a]
Ia[b]	−10.549	2.246	2.977
Ib	−10.484	2.323	2.957
Ic	−10.429	2.396	2.940
Id	−10.597	2.256	3.253
Ie[b]	−10.873	1.723	2.219
If	−11.301	0.671	1.531
Ig	−10.072	2.303	2.753
Ih	−10.099	2.250	2.753
IIa[b]	−11.842	2.946	3.604
IIb	−11.415	2.919	3.639
IIc	−11.801	2.174	2.941

a) In eV.
b) MINDO/2 FMO energies. Ia, −8.88 (HOMO); −0.73 (LUMO); −0.37 (NLUMO). Ie, −9.32 (HOMO); −1.30 (LUMO); −1.05 (NLUMO). IIa, −9.25 (HOMO); −0.03 (LUMO).

rigid, highly ordered transition state). Calculation based on MINDO/3[7] suggested that the reaction falls into the category of a neutral type reaction (HOMO–LUMO controlled) in Sustmann's classification for cycloadditions. The calculation also indicated that the reactivity may result from both the frontier molecular orbital (FMO) interaction[5] and the relatively high degree of coulombic attraction arising from the highly polarized structure of both addends.

During the course of the investigation, an important question arose concerning the 1,3-dipolar cycloadditivity of pyridine *N*-oxides, *i.e.*, why do acceptor-substituted pyridine *N*-oxides such as the 3-cyano- or 3-nitropyridine *N*-oxide show no reactivity towards dipolaro-

TABLE II. Calculated Reactivity of Pyridine *N*-Oxides toward Phenyl Isocyanate Based on the Perturbation Equation Derived by Klopman and Salem[a]

Pyridine *N*-oxides	Energy changes (eV)				Reaction
	I[b]	II[c]	III[d]	ΔE[e]	
Ia[f]	6.663	−1.274	−6.156	−0.767	Obsd.
Ib[f]	6.682	−1.204	−6.169	−0.691	Obsd.
Ic	6.693	−1.193	−6.118	−0.618	Obsd.
Ie[f]	6.655	−1.206	−6.206	−0.758	Not obsd.
If					Not obsd.

a) See ref. 2.
b) The closed shell repulsion term (the 1st term).
c) The coulombic repulsion and attraction term (the 2nd term).
d) The orbital interaction of all the occupied orbitals of the one molecule with all the unoccupied orbitals of the other (the 3rd term).
e) $\Delta E = I + II + III$.
f) Calculated for the addition at atoms O and C_2.

philes in sharp contrast to the FMO predictions based on CNDO/2[8] calculations. In this paper, we present our explanation on the basis of the cyclic conjugation theory[9] and also present general characteristics of the FMO's of the pyridine *N*-oxide family, which can be used to predict modes of cycloaddition in relation to the substitutents on the 1,3-dipole and the dipolarophile.

The CNDO/2 method has been used to predict with reasonable success the cycloaddition behavior of the 1,3-dipolar reaction between various types of 1,3-dipoles and dipolarophiles.[3,10] Therefore, in this study, CNDO/2 was used to estimate the relative dipole reactivity in the 1,3-dipolar cycloaddition reaction between pyridine *N*-oxides and phenyl isocyanates. The molecular orbital calculations were performed with standard bond angles and bond lengths. The important orbital energies for the related compounds studied here are shown in Fig. 1 and Table I. For a more quantitative comparison,[11-13] the MINDO/2 energies of the frontier orbitals of phenyl isocyanate and two representative 1,3-dipoles, pyridine and 3-cyanopyridine *N*-oxides, are given in Table I.

As can be seen in Fig. 1, the frontier molecular orbital energy difference (HOMO–LUMO) of pyridine *N*-oxide is situated among the FMO energy levels of phenyl isocyanate, indicating that pyridine *N*-oxide participates in a neutral-type cycloaddition where both interactions play an important role in determining the reactivity. The MINDO/2 method gave a similar qualitative trend to the MINDO/3 prediction described in our previous paper.[1a]

Inspection of the FMO energies of the reactants based on CNDO/2 indicated that the 1,3-dipole bearing an electron-accepting substituent such as a nitro or cyano group has a very low-lying LUMO energy level as compared with the parent dipole and would show a high cycloaddition reactivity towards phenyl isocyanates with an inverse-type cycloaddition behavior. Contrary to this expectation, nitro- or cyano- substituted pyridine *N*-oxide did not show any reactivity to a series of phenyl isocyanates under various reaction conditions.

The reactivity difference may arise from the neglect of other orbital interactions or of electrostatic interactions. Therefore, complete calculations of the perturbation equation[2] derived by Klopman and Salem were performed for the reactions of phenyl isocyanate and typical pyridine *N*-oxides Ia—c and Ie using MINDO/3, with the assumptions that the reaction is conducted in toluene ($\varepsilon = 2.38$) and that the distance between the interacting atoms is 1.75 Å.[14]

As can be seen in Table II, relatively large coulombic attractions (the second term energy)

were found in comparison with most pericyclic reactions. This can be attributed to the highly polarized structures (1,3-dipole and cumulene) of both reactants, indicating that the regiochemistry might be, at least in part, determined by the coulombic interaction in addition to the FMO interaction. The calculations indicate that these reactions have very similar stabilization energies (ΔE) and that their orbital interaction energies (the third term energy) are also very similar to each other. Thus, the striking difference in reactivity among electron-rich pyridine *N*-oxides and electron-deficient ones cannot be accounted for by the FMO theory or by more comprehensive treatments of the perturbation theory in which all orbital interactions or all energy terms were considered.

Many controlling factors other than primary orbital interaction have been proposed to explain the cycloaddition behavior of 1,3-dipolar reactions, *i.e.*, secondary orbital interaction or steric interaction.[15] Among them, the more important factor is believed to be secondary orbital interaction. However, in this case, the secondary interactions are considered to be of little importance because of the small difference in the magnitude of the coefficients of the atoms participating in the secondary orbital interaction. Another factor may be the steric interaction between the substituent of the 1,3-dipole and the phenyl ring of the dipolarophile in the transition state. This effect, however, may be insignificant compared to the other factors because 3,5-dimethylpyridine *N*-oxide, which would suffer more steric congestion than the 3-cyano derivative in the transition state, shows high reactivity toward the dipolarophiles.

Though few experimental results helpful in resolving the discrepancy are available, the degree of aromaticity may be a factor in the abnormally high stability of the acceptor substituted pyridine *N*-oxides. Recently, Inagaki reported that the degree of cyclic electron delocalization depends upon the mode of donor-acceptor arrangement of the component systems as well as orbital phase continuity requirements.[9] The concept of continuity–discontinuity of cyclic conjugation has been employed in predicting electron properties of unknown molecules and designing synthons.[16]

The cyclic conjugation theory utilizes a dissection of the molecule in question into π fragments and a consideration of the effect of substituents on the interaction of the frontier orbitals of fragments, in which the orbital phase continuity requirements are as follows; the HOMO's of the neighboring systems should be out of phase; the LUMO's of the neighboring systems should be in phase; the HOMO and the LUMO of the neighboring systems should be in phase.

In pyridine *N*-oxide, the relative donor–acceptor relationship can be estimated from the frontier orbital energies of simple nitrone and ethylene systems: the electron–donating cumulene system and electron–accepting C=C bonds are the donor (D) and acceptor (A's), respectively.[1] The cyclic conjugation is continuous and the orbital phase continuity requirements are satisfied for an aromatic electron system (mode 1 in Fig. 2). The aromatic character of the parent pyridine *N*-oxide reflects its reactivity. The MO calculations show that the frontier orbitals of pyridine *N*-oxides have approximately the same energies as those of simple nitrones which belong to the neutral type reaction category and show high reactivity towards various dipolarophiles, *i.e.*, electron-rich alkenes such as vinyl ether or electron-deficient alkenes such as acrylonitrile. Therefore, qualitative similarities in reactivity between the two types of compounds are expected, but the experimental results are not in accordance with this

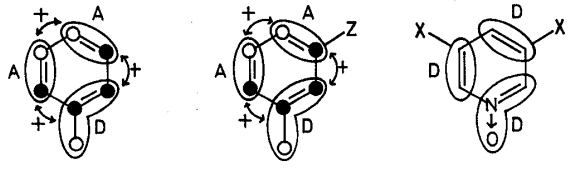
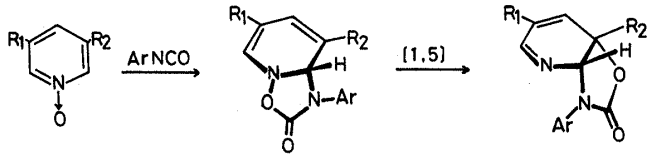


Fig. 2. Cyclic Conjugation in Pyridine *N*-Oxides

assumption. For example, 1-pyrroline *N*-oxide reacts at room temperature with phenyl isocyanate to afford the bicyclic adduct,[17] whereas a similar reaction of pyridine *N*-oxide could not be observed even in refluxing benzene. The difference may be ascribed to the energy difference of aromatic stabilization.

In 3-nitro- or 3-cyanopyridine *N*-oxide, electron delocalization is expected to be more extensive than in the parent dipole. Substitution by powerful acceptors causes effective donor–acceptor interaction between the π systems (mode 1′). In contrast, in 3,5-dimethylpyridine *N*-oxide[18c] or 3-methoxypyridine *N*-oxide,[1a] donor–acceptor interaction does not occur effectively, resulting in destabilization of the cyclic three-system interaction (mode 2). The localization of the electron diminishes the aromatic character of pyridine *N*-oxide and allows it to act as a reactive 1,3-dipole.

Previously, we showed that the cycloaddition reaction gave the 2,3-dihydropyridine derivative (IV) as the only cycloaddition product, so our interest has been focused on the possible existence of an intermediate in the reaction as shown in Chart 1.



$R_1 = H, CH_3$
$R_2 = H, CH_3$

Chart 1

To provide direct evidence for the rationalization of a series of pericyclic reactions involved in the formation of the 2,3-dihydropyridine-type compounds (IV), we tried to isolate the primary cycloadducts (III) by carrying out the reactions under various reaction conditions using less aromatic pyridine *N*-oxides such as 3,5-dimethylpyridine *N*-oxide; this work included a reexamination of previously reported reactions.

The cycloaddition of the various dipoles with a series of phenyl isocyanates was carried out in the usual manner as described in our previous papers.[18] Contrary to expectation, even under mild reaction conditions, no spot attributable to the primary adduct could be detected by thin-layer chromatography on silica gel. In the reaction of pyridine *N*-oxides substituted by donor groups (methyl, methoxy, and phenyl), 2,3-dihydropyridine-type compounds (IV) were obtained as the main products. In the case of halogeno substituted pyridine *N*-oxides, we could not obtain the 2,3-dihydropyridine-type products (IV), but isolated only the aromatized products (V). Pyridine *N*-oxides bearing halogeno groups at the 3 and 5 positions gave oxazolo[4,5-*b*]pyridine derivatives (V) in moderate yields together with small amounts of 2-anilinopyridine derivatives (VI).

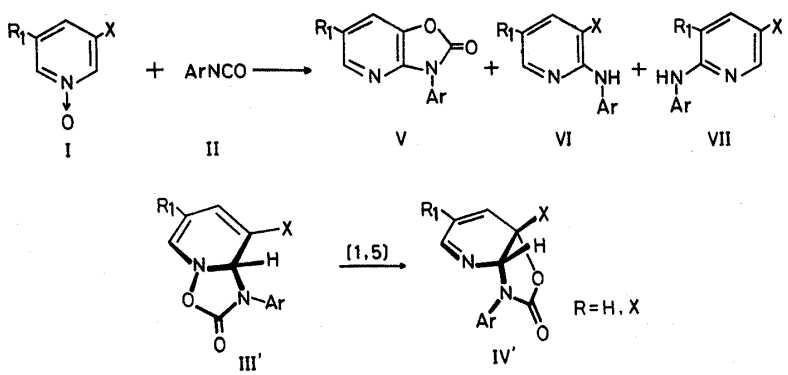


Chart 2

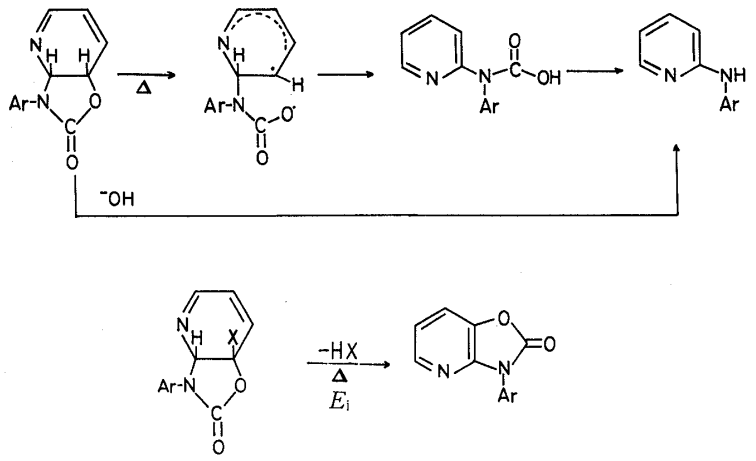


Chart 3

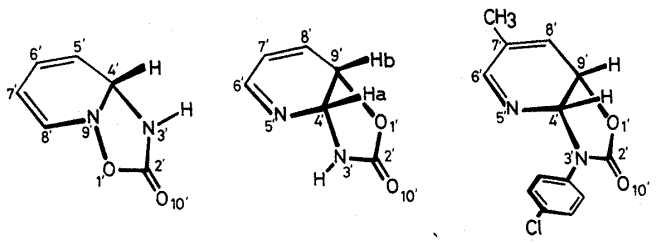
In the reaction of 3-bromo- and 3-chloropyridine *N*-oxides, the oxazolopyridine derivatives (V), formed from the primary cycloadduct attacked at O and C_2, were formed predominantly. The formation of these adducts is considered to be sterically unfavorable because of the higher degree of crowding in the transition state as compared with the alternative. In this connection, we have made the reasonable assumption that the ratio of the products reflects the substituent effect upon the FMO coefficients of the 1,3-dipole moieties:[1a] the periselectivity for 3-picoline *N*-oxide can be explained by taking into consideration the interaction of the HOMO of phenyl isocyanate and the next lowest unoccupied molecular orbital (NLUMO) of 3-picoline *N*-oxide stabilized by secondary orbital interactions. The same argument seems to be applicable to the observed site selectivity for the cycloaddition studied here. These considerations together with previous experimental data indicate that the primary cycloadducts are thermally unstable.

It would be of great interest to know the nature of the structure and the inherent stability of the transient intermediary of the primary cycloadduct. For this purpose, a quantum mechanical treatment of molecular structure seems to be suitable and might be reliable enough to serve as a practical tool in cases at present inaccessible to experimental study. Abramovich *et al.* tried to estimate the relative stability of the primary adduct and the 1,5-shifted product by using the MINDO/2′ method combined with geometrical optimization by the SIMPLEX method, and suggested the former to be much less stable than the latter.[19] However, as they stated, the results were unreliable because MINDO/2′ is unable to take into account satisfactorily bonds containing hetero atoms such as N–O.[20] In this respect, improved calculations were considered to be desirable and were performed for a pair of model compounds **A** and **B** using the MINDO/3 approximation combined with geometrical optimization by the Fletcher–Powell method.[7]

To save computation time, the calculation were performed for the simplest models using geometries taken from the X-ray geometry of **C**.[18c] The optimized geometry of the rearranged product (**B**) was then used as input data for the optimization of the model of the primary adduct (**A**). The optimized structures for **A** and **B** are shown in Table III.

As can be seen in Table III, the structure of **B** agrees well with the observed crystal structure of **C**. The O_1–C_9 bond is calculated to be considerably shorter than the observed bond length of **C**. The relative energies ($\Delta\Delta H_f$) for the two structures and the addends appear in Table IV.

The MINDO/3 calculated heats of formation (ΔH_f) for **A** and **B** are −44.3 and −71.5 kcal/mol, respectively, **A** thus being less stable than **B** by 27.2 kcal/mol. This value is 7.8 kcal/mol less than the corresponding MINDO/2′ value. Inspection of these values reveals



A B C

Fig. 3. Model Structures (**A** and **B**) for the MINDO/3 Calculation and the X-Ray Structure (**C**) with the Numbering Sequence Used in This Paper

TABLE III. MINDO/3 Calculated Bond Lengths of **A** and **B** with Observed Structure of **C**[a]

From	To	Bond lengths		
		Primary adduct	1,5-Shifted product	
		A	**B**	**C**
1′	2′	1.348	1.356	1.361 (2)
1′	9′	1.395	1.386	1.463 (2)
2′	3′	1.375	1.371	1.364 (2)
2′	10′	1.220	1.218	1.204 (2)
3′	4′	1.425	1.432	1.462 (2)
3′	11′	1.019	1.020	
4′	5′	1.502	1.436	1.458 (2)
4′	9′	1.456	1.566	1.523 (2)
4′	12′	1.153	1.139	
5′	6′	1.355	1.276	1.269 (2)
5′	13′	1.105		
6′	7′	1.458	1.474	1.475 (2)
6′	13′		1.116	
6′	14′	1.106		
7′	8′	1.365	1.350	1.311 (2)
7′	14′		1.106	
7′	15′	1.103		
8′	9′	1.377	1.509	1.482 (2)
8′	15′		1.106	
9′	16′	1.111	1.137	

a) X-Ray analysis data. See ref. 18*c*.

TABLE IV. Calculated Heat of Formation (ΔH_f)

Compound	ΔH_f (kcal/mol)	$\Delta\Delta H_f$ (kcal/mol)
Pyridine *N*-oxide	20.5	
Isocyanic acid (H–N=C=O)	−42.3	
Primary adduct **A**	−44.3	0.0
1,5-Shifted product **B**	−71.5	−27.2

that **A** is a higher energy species than **B** and hence a very unstable intermediate which could not be isolated under the reaction conditions studied.

In connection with the series of pericyclic reactions, the pyrolytic reaction behavior of the rearranged products (IV) was studied on the basis of the MINDO/3 calculation data. As

TABLE V. Net Charges and LUMO (NLUMO) Coefficients of **B** Calculated by the MINDO/3 MO Method

Atom	Net charge	Coefficients	
		LUMO (0.123 eV)	NLUMO (0.969 eV)
O(1)	−0.49		
C(2)	0.86		
N(3)	−0.28		
C(4)	0.21		
N(5)	−0.21		
C(6)	0.18		
C(7)	−0.05		
C(8)	−0.02		
C(9)	0.32		
O(10)	−0.56		
H(3)	0.11		
H(4) (Ha)	−0.05	0.081	0.313
H(6)	−0.01	−0.006	0.245
H(7)	0.01	−0.020	−0.038
H(8)	0.02	−0.020	0.081
H(9) (Hb)	−0.07	0.073	0.055

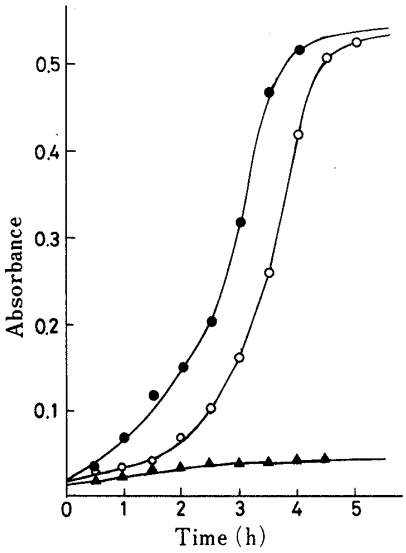


Fig. 4. Rate of Formation of 2-Anilinopyridine during Thermal Treatment of 3*H*-2-Oxo-3-phenyl-3a, 7a-dihydrooxazolo[4,5-*b*]pyridine at 110 °C

○, 1.87×10^{-2} mol/l in DMF; ●, 9.35×10^{-3} mol/l in DMF; ▲, 1.87×10^{-2} mol/l in sulfolane.

described in previous papers,[21] pyrolyses of the rearranged products at 150 °C gave the 2-anilinopyridine derivatives in nearly quantitative yields. Inspection of the FMO's of **B** indicates that the LUMO coefficient of Ha is slightly larger than that of Hb, while in the NLUMO, the coefficient of Ha is larger than that of Hb, indicating that the Ha proton becomes more reactive toward abstraction *via* a free radical mechanism (*trans*-elimination[22]). In fact, the formation of 2-anilinopyridine derivatives does not obey first-order rate laws and its rate was extremely sensitive to changes in solvent viscosity, indicating that the reactions probably have a considerable radical character (see Fig. 4).

In the halogeno- or methoxy-substituted 2,3-dihydropyridine derivatives (IV′), the pyrolytic *cis*-elimination of hydrogen halide is considered to occur preferentially *via* a four center transition state[23] in competition with the decarboxylation. It is plausible that the reaction is assisted by the increase of aromaticity of the pyridine ring in harmony with the release of strain of the oxazolo ring system.

Experimental

All melting points are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken with JNM-MH-100 and JNM-C-60H spectrometers in *ca.* 10% (w/v) solution with tetramethylsilane as an internal standard; chemical shifts are expressed in τ values. Infrared (IR) spectra were recorded on a JASCO DS-301 infrared spectrophotometer equipped with a grating. Mass spectra (MS) were taken with a JEOL JMS-01SG double-focusing spectrometer operating at an ionization potential of 75 eV. Ultraviolet (UV) spectra were determined with a JASCO UVIDEC-220B digital spectrophotometer.

All the calculations were performed on a FACOM M-190 and M-200 computers in the computer center of Kyushu University.

Materials——The starting materials, 3,5-dibromopyridine *N*-oxide (Ia),[18c] 3,5-dichloropyridine *N*-oxide (Ib),[18c] 3-bromopyridine *N*-oxide (Ic),[17] and 3-chloropyridine *N*-oxide (Id),[18] were prepared according to the previously established methods. Phenyl isocyanates (IIa—g) were obtained from commercial suppliers and were used without further purification.

Reaction of Substituted Pyridine *N*-Oxides (I) with Phenyl Isocyanates (II)——Compound II (0.030 mol) was added slowly to a solution of I (0.015 mol) in 30 ml of dry DMF at room temperature, and the mixture was heated under the conditions indicated in Table VI.

TABLE VI. Reactions of Substituted Pyridine *N*-Oxides with Various Phenyl Isocyanates

Exp. No.	Reactants			Duration (h)	Products, compd. No., Yields (%)[a]		
	I		II				
	R_1	X	R_2		V	VI	VII
1	Br	Br	H	7	Va (66)		
2			*o*-Me			Trace[b]	
3			*m*-Me		Vb (18)	VIa (3)	
4[c]			*p*-Me		Vc (53)	VIb (4)	
5			*o*-Cl		Vd (5)	VIc (2)	
6			*m*-Cl		Ve (42)	VId (4)	
7[c]			*p*-Cl		Vf (41)	VIe (6)	
8	Cl	Cl	H	10	Vg (65)		
9			*o*-Me			Trace	
10			*m*-Me		Vh (19)	VIf (1)	
11			*p*-Me		Vi (42)	VIg (5)	
12			*o*-Cl		Trace	Trace	
13			*m*-Cl		Vj (20)	VIh (3)	
14			*p*-Cl		Vk (20)	VIi (3)	
15			H		Vl (66)	VIj (4)	VIIa (4)
16			*o*-Me		Trace	Trace	Trace
17			*m*-Me		Vm (20)	VIk (4)	Trace
18			*p*-Me		Vn (23)	IVl (3)	Trace
19			*o*-Cl		Trace	IVm (2)	VIIb (2)
20			*m*-Cl		Vo (18)	VIn (6)	Trace
21			*p*-Cl		Vp (28)	VIo (2)	Trace
22	H	Cl	H		Vl (43)	Trace	Trace
23			*o*-Me		Trace	Trace	Trace
24			*m*-Me		Vm (12)	Trace	Trace
25			*p*-Me		Vn (17)	VIp (5)	Trace
26			*o*-Cl		Trace	VIq (2)	Trace
27			*m*-Cl		Vo (16)	VIr (3)	Trace
28			*p*-Cl		Vp (19)	VIs (3)	Trace

a) Calcd on the basis of I.
b) Detectable on TLC analysis.
c) Previously reported data, see ref. 18*c*.

TABLE VII. Analytical Data for Products[a]

Compd.	mp (°C)	IR ν_{max}^{KBr}: cm^{-1}	Formula	Analysis (%) Calcd (Found)		
				C	H	N
Vb	121—121.5[b]	1780[e]	$C_{13}H_9BrN_2O_2$	51.15	2.95	9.18
				(51.45	2.70	9.00)
Vd	124—125[c]	1780[e]	$C_{12}H_6BrClN_2O_2$	44.24	1.84	8.60
				(44.50	1.70	8.44)
Ve	124—125.5[b]	1780[e]	$C_{12}H_6BrClN_2O_2$	44.24	1.84	8.60
				(44.48	1.76	8.37)
Vg	151—152[b]	1790[e]	$C_{12}H_7ClN_2O_2$	58.43	2.86	11.36
				(58.21	2.81	11.33)
Vh	117—118[b]	1790[e]	$C_{13}H_9ClN_2O_2$	59.88	3.45	10.75
				(60.02	3.34	10.64)
Vi	185—186[b]	1772[e]	$C_{13}H_9ClN_2O_2$	59.88	3.45	10.75
				(59.98	3.16	10.74)
Vj	167—168[b]	1795[e]	$C_{12}H_6Cl_2N_2O_2$	51.25	2.14	9.96
				(51.54	1.97	9.98)
Vk	156—157[b]	1800[e]	$C_{12}H_6Cl_2N_2O_2$	51.25	2.14	9.96
				(51.55	2.02	9.89)
Vl	151.5—152.5[b]	1760[e]	$C_{12}H_8N_2O_2$	67.92	3.80	13.20
				(67.82	3.67	13.16)
Vm	134—135[b]	1784[e]	$C_{13}H_{10}N_2O_2$	69.03	4.42	12.39
				(68.99	4.37	12.34)
Vn	108—109[b]	1788[e]	$C_{13}H_{10}N_2O_2$	69.03	4.42	12.39
				(68.92	4.45	12.35)
Vo	131—132[b]	1788[e]	$C_{12}H_7ClN_2O_2$	58.42	2.84	11.36
				(58.35	2.86	11.48)
Vp	176—177[b]	1775[e]	$C_{12}H_7ClN_2O_2$	58.42	2.84	11.36
				(58.71	2.79	11.39)
VIa	39—40.5[c]	3370[f,g]	$C_{12}H_{10}Br_2N_2$	42.11	2.92	8.19
				(42.41	3.11	8.23)
VIb	41—42[b]	3370[e]	$C_{12}H_{10}BrN_2$	42.11	2.92	8.19
				(42.26	3.08	8.05)
VIc	97—98[b]	3330[f]	$C_{11}H_7Br_2ClN_2$	36.41	1.93	7.72
				(36.68	2.15	7.44)
VId	93—94[b]	3340[f]	$C_{11}H_7Br_2ClN_2$	36.41	1.93	7.72
				(36.42	2.04	7.66)
VIe	62—63[b]	3360[f]	$C_{11}H_7Br_2ClN_2$	36.41	1.93	7.72
				(36.64	2.23	7.61)
VIf	46—47[b]	3370[f]	$C_{12}H_{10}Cl_2N_2$	56.92	3.95	11.07
				(57.15	4.02	10.77)
VIg	34—35[b]	3340[f]	$C_{13}H_{10}Cl_2N_2$	56.92	3.95	11.07
				(57.20	3.87	10.88)
VIh	80—81[b]	3380[f]	$C_{11}H_7Cl_3N_2$	48.26	2.56	10.24
				(48.46	2.52	10.30)
VIi	71—72[b]	3380[f]	$C_{11}H_7Cl_3N_2$	48.26	2.56	10.24
				(48.56	2.57	10.03)
VIj	147—148[d]	3450[f,g]	$C_{11}H_9BrN_2 + C_6H_3N_3O_7$	42.70	2.53	14.64
				(42.75	2.61	14.35)
VIk	150—151[d]	3380[f]	$C_{12}H_{11}BrN_2 + C_6H_3N_3O_7$	43.90	2.85	14.23
				(43.98	2.68	13.96)
VIl	165—166[d]	3370[f]	$C_{12}H_{11}BrN_2 + C_6H_3N_3O_7$	43.90	2.85	14.23
				(43.65	2.83	14.15)
VIm	58—59[b]	3340[f]	$C_{11}H_8BrClN_2$	46.56	2.82	9.88
				(46.83	3.14	9.84)

TABLE VII. (continued)

Compd.	mp (°C)	IR ν_{max}^{KBr} cm^{-1}	Formula	Analysis (%) Calcd (Found)		
				C	H	N
VIn	57—58[b]	3390[f]	$C_{11}H_8BrClN_2$	46.56	2.82	9.88
				(46.59	2.81	9.94)
VIo	64—65[b]	3360[f]	$C_{11}H_8BrClN_2$	46.56	2.82	9.88
				(46.50	2.70	9.80)
VIp	159—160[d]	3380[f]	$C_{12}H_{11}ClN_2 + C_6H_3N_3O_7$	48.27	3.13	15.64
				(48.57	3.13	15.62)
VIq	60—62[b]	3340[f]	$C_{11}H_8Cl_2N_2$	55.23	3.35	11.72
				(55.20	3.37	11.57)
VIr	60—61[b]	3360[f]	$C_{11}H_8Cl_2N_2$	55.23	3.35	11.72
				(55.36	3.38	11.68)
VIs	58—59[b]	3370[f]	$C_{11}H_8Cl_2N_2$	55.23	3.35	11.72
				(55.18	3.30	11.70)
VIIa	111—112[c]	3230[f]	$C_{11}H_9BrN_2$	53.04	3.64	11.24
				(53.29	3.74	11.09)
VIIb	83—84[b]	3200[f]	$C_{11}H_8BrClN_2$	46.56	2.82	9.88
				(46.83	2.82	10.11)

a) Satisfactory MS data were obtained for all compounds.
b) Colorless needles recrystallized from ether.
c) Colorless prisms recrystallized from ether.
d) Colorless oil.
e) Absorption C=O.
f) Absorption N–H.
g) Neat.

a) Isolation of V: When the reaction was over, the reaction mixture was concentrated under reduced pressure below 60 °C to remove excess phenyl isocyanate. Approximately 20 ml of ether was added to the residue, and the mixture was allowed to stand overnight in a refrigerator. The resulting colorless crystals were collected by suction then washed with a small amount of pet. ether. The crystalline mass was recrystallized from ether to give a pure sample of V (Tables VI—VIII).

b) Isolation of VI—VII: The above ethereal filtrate was concentrated under reduced pressure and the residue was dissolved in a small amount of $CHCl_3$ and passed through a column of silica gel using $CHCl_3$ as an eluent. The solvent was evaporated off under reduced pressure and the crude product was recrystallized from *n*-hexane to give VI or VII (Tables VI—VIII).

The newly obtained results are summarized in Table III. The structures of the products were determined by comparison of ^{1}H-NMR spectral data with those of similar reaction products. The physical and spectral data are listed in Tables VI—VIII.

Hydrolysis of V——A mixture of Va (1.0 g) in 5 ml of 10% ethanolic potassium hydroxide was heated under reflux for 1 h. When the reaction was complete, the mixture was allowed to stand at room temperature. The resulting crystalline mass was recrystallized from ether to give the corresponding 2-anilino-3-hydroxypyridine, mp 175—176 °C, as colorless prisms in 96% yield.

Similarly, Vg—l were hydrolyzed to the corresponding 2-anilino-3-hydroxypyridines. The physical and spectral data are summarized in Table IX.

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TABLE VIII. ^{1}H-NMR Spectral Data for Products Va—VIIb

Compd.	^{1}H-NMR: Chemical shifts
Vb	7.65 (3H, s, –Me), 2.30—2.97 (5H, m, C_7–H and –C_6H_4), 1.81 (1H, d, $J_{5,7}=2$ Hz, C_5–H)
Vd	2.17—2.80 (5H, m, C_7–H and –C_6H_4Cl), 1.85 (1H, d, $J_{5,7}=2$ Hz, C_5–H)
Vg	2.05 (1H, d, $J=2$ Hz, C_5–H), 2.27—2.82 (6H, m, C_7–H and –Ph)
Vh	7.56 (3H, s, –Me), 2.33—2.98 (5H, m, C_7–H and –C_6H_4–), 1.92 (1H, d, $J_{5,7}=2$ Hz, C_5–H)
Vi	7.57 (3H, s, –Me), 2.28—3.16 (5H, m, C_7–H and –C_6H_4–), 1.92 (1H, d, $J_{5,7}=2$ Hz, C_5–H)
Vj	2.06—2.86 (5H, m, C_7–H and –C_6H_4–), 1.87 (1H, d, $J_{5,7}=2$ Hz, C_5–H)
Vk	2.10—2.82 (5H, m, C_7–H and –C_6H_4–), 1.92 (1H, d, $J_{5,7}=1.9$ Hz, C_5–H)
Vl	2.25—3.20 (7H, m, C_6–H, C_7–H and Ph), 2.03 (1H, dd, $J_{5,6}=5$ Hz, $J_{5,7}=2$ Hz, C_5–H)
Vm	7.59 (3H, s, Me), 2.20—3.06 (6H, m, C_6–H, C_7–H and –C_6H_4–), 1.89 (1H, dd, $J_{5,6}=5$ Hz, $J_{5,7}=2$ Hz, C_5–H)
Vn	7.56 (3H, s, Me), 2.33—3.10 (6H, m, C_6–H, C_7–H and –C_6H_4–), 1.88 (1H, dd, $J_{5,6}=5$ Hz, $J_{5,7}=2$ Hz, C_5–H)
Vo	1.98—3.02 (6H, m, C_4–H, C_6–H and –C_6H_4–), 1.87 (1H, dd, $J_{5,6}=5$ Hz, $J_{5,4}=2$ Hz, C_5–H)
Vp	2.00—3.06 (6H, m, C_6–H, C_7–H and –C_6H_4–), 1.87 (1H, dd, $J_{5,6}=5$ Hz, $J_{5,7}=2$ Hz, C_5–H)
VIa	7.65 (3H, s, Me), 2.43—3.37 (5H, m, N–H and –C_6H_4–), 2.21 (1H, d, $J_{4,6}=2$ Hz, C_4–H), 1.85 (1H, d, $J_{6,4}=2$ Hz, C_6–H)
VIb	7.69 (3H, s, Me), 2.40—3.50 (5H, m, –C_6H_4– and N–H), 2.23 (1H, d, $J_{4,6}=2$ Hz, C_4–H), 1.88 (1H, d, $J_{6,4}=2$ Hz, C_6–H)
VIc	2.00—3.28 (5H, m, C_4–H, N–H and –C_6H_4–), 1.82 (1H, d, $J_{6,4}=2$ Hz, C_6–H), 1.51 (1H, dd, $J_{4,6}=2$ Hz, $J=8$ Hz, C_4–H and –C_6H_4–)
VId	2.00—3.20 (6H, m, N–H, C_4–H and –C_6H_4–), 1.82 (1H, d, $J_{6,4}=2$ Hz, C_6–H)
VIe	2.23—3.20 (5H, m, N–H and aromatic H), 2.17 (1H, d, $J_{4,6}=2$ Hz, C_4–H), 1.85 (1H, d, $J_{6,4}=2$ Hz, C_6–H)
VIg	7.68 (3H, s, Me), 2.38—3.27 (6H, m, C_4–H, N–H and –C_6H_4–), 1.98 (1H, d, $J_{6,4}=2$ Hz, C_6–H)
VIh	2.13—3.27 (6H, m, N–H, C_5–H and –C_6H_4–), 1.94 (1H, d, $J_{6,4}=2$ Hz, C_6–H)
VIj	3.54 (1H, dd, $J_{5,6}=5$ Hz, $J_{5,4}=7$ Hz, C_5–H), 2.04 (1H, dd, $J_{6,5}=5$ Hz, $J_{6,4}=2$ Hz, C_6–H), 2.35—3.28 (7H, m, Ph, C_4–H and N–H)
VIk	7.67 (3H, s, Me), 3.46 (1H, dd, $J_{5,4}=8$ Hz, $J_{5,6}=5$ Hz, C_5–H), 2.20—3.30 (6H, m, C_4–H, N–H and –C_6H_4–), 1.89 (1H, dd, $J_{6,5}=5$ Hz, $J_{6,4}=1.9$ Hz, C_6–H)
VIm	2.00—3.60 (6H, m, C_4–H, C_5–H, N–H and –C_6H_4–), 1.84 (1H, dd, $J_{6,5}=5$ Hz, $J_{6,4}=2$ Hz, C_6–H), 1.41 (1H, dd, $J_{6,5}=8.5$ Hz, $J_{6,4}=2$ Hz, *ortho* C–H of –C_6H_4Cl)
VIo	3.38 (1H, dd, $J_{5,6}=5$ Hz, $J_{5,4}=8$ Hz, C_5–H), 2.17—3.18 (6H, m, C_4–H, N–H and –C_6H_4–), 1.88 (1H, dd, $J_{6,5}=5$ Hz, $J_{6,4}=2$ Hz, C_6–H)
VIp	7.67 (3H, s, Me), 2.32—3.56 (7H, m, C_4–H, C_5–H, N–H and –C_6H_4–), 1.93 (1H, dd, $J_{6,5}=5$ Hz, $J_{6,4}=2$ Hz, C_6–H)
VIq	2.00—3.44 (6H, m, C_5–H, C_4–H, N–H and C–$_6H_4$–), 1.85 (1H, dd, $J_{6,4}=2$ Hz, $J_{6,5}=5$ Hz, C_6–H), 1.37 (1H, dd, $J=8$ Hz, *ortho* C–H of –C_6H_4–)
VIr	2.03—3.44 (7H, m, C_4–H, C_5–H, N–H and –C_6H_4–), 1.88 (1H, dd, $J_{6,5}=5$ Hz, $J_{6,4}=2$ Hz, C_6–H)
VIIa	2.44—3.46 (8H, m, N–H aromatic H), 1.90 (1H, d, $J=2.5$ Hz, C_2–H)
VIIb	1.88—3.50 (7H, m, C_4–H, N–H and –C_6H_4–), 1.75 (1H, d, $J=2$ Hz, C_2–H)

TABLE IX. Yields, Analytical and Spectral Data for Products of the Hydrolysis of Oxazolopyridines

Starting materials		Products						
Compd. No.	X	Compd. No.	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
						C	H	N
Va	Br	VIIIa	80	175—176	$C_{11}H_9BrN_2O$	49.81	3.40	10.57
						(50.06	3.58	10.52)
Vg	Cl	VIIIg	62	163—164	$C_{11}H_9ClN_2O$	59.86	4.08	12.70
						(60.06	4.37	12.95)
Vl	H	VIIIl	41	177—178	$C_{11}H_{10}N_2O$	70.97	5.38	15.05
						(71.23	5.45	15.15)

^{1}H-NMR (in DMSO-d_6)		IR (KBr): cm^{-1}	
OH (1H, br s)	Others	N–H	O–H
−0.67	2.36—3.34 (6H, m, N–H, Ph), 2.12 (1H, d, J=1.8 Hz, C_4–H), 1.92 (1H, d, J=1.8 Hz, C_6–H)	3380	3040—2300
−0.75	2.18—3.35 (6H, m, N–H, Ph), 2.12 (1H, d, J=2 Hz, C_4–H), 1.92 (1H, d, J=2 Hz, C_6–H)	3380	3040—2300
−0.10	2.54—3.50 (5H, m, others), 1.92—2.42 (4H, m, C_6–H, N–H, and ortho H of Ph)	3380	3040—2300

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