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Reaction of Aromatic N-Oxides with Dipolarophiles. III.[1] Cycloadditions of Substituted Phenyl Isocyanates to 3,5-Dimethyl and 3,5-Dibromopyridine N-Oxides and X-Ray Crystal Structures of the Isomeric Cycloadducts

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Three β-substituted pyridine N-oxides (I, II and III) were subjected to 1,3-dipolar cycloaddition with phenyl isocyanates having an *ortho*, *meta* or *para* substituent group. 3-Methyl- (I) and 3,5-dimethyl-pyridine N-oxide (II) afforded the 2,3-dihydropyridine derivatives, and the 3,5-dibromo compound (III) afforded a 2,3-dihydro-2-oxo-oxazolo-[4,5-*b*]pyridine (IX) by the elimination of hydrogen bromide from the 2,3-dihydropyridine thus formed. The presence of an *o*-substituent group or nitro group in the phenyl isocyanate resulted in a reduced cycloaddition yield. The structures of the 2,3-dihydropyridine adducts were determined by X-ray crystallographic analysis.

Keywords——1,3-dipolar cycloaddition; isomeric cycloadducts of 2,3- and 5,6-dihydropyridine; 2,3-dihydro-2-oxo-oxazolo[4,5-*b*]pyridines; substituent effects on cycloaddition; X-ray analyses of isomeric cycloadducts

In the course of studies on 1,3-dipolar cycloadditions, it was postulated that two cycloadducts isolated from the reaction of 3-picoline N-oxide (I) with phenyl isocyanate might be 1,2- and 1,6-dihydropyridine intermediates.[3] However, subsequent cycloadditions of phenyl isocyanate to β-bromopyridine N-oxides yielded the 2,3-dihydro-2-oxo-3-phenyl-oxazolo[4,5-*b*]pyridine structure.[4] Its formation may reasonably be explained in terms of cleavage of the N–O bond of an initial 1,2-dihydropyridine intermediate and concerted attack by the carbamate anion thus formed at the electron-deficient 3-position to give a 2,3-dihydropyridine skeleton, followed by the elimination of a hydrogen bromide molecule. In addition, it was reported by Abramovitch *et al.*[5] that the analogous reaction *via* 3,5-dimethylpyridine

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[1] Part II: T. Hisano, T. Matsuoka, and M. Ichikawa, *Chem. Pharm. Bull.* (Tokyo), 24, 533 (1976).

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[3] T. Hisano, S. Yoshikawa, and K. Muraoka, *Org. Prep. Proced. Int.*, 5, 95 (1973); T. Hisano, S. Yoshikawa, and K. Muraoka, *Chem. Pharm. Bull.* (Tokyo), 22, 1611 (1974).

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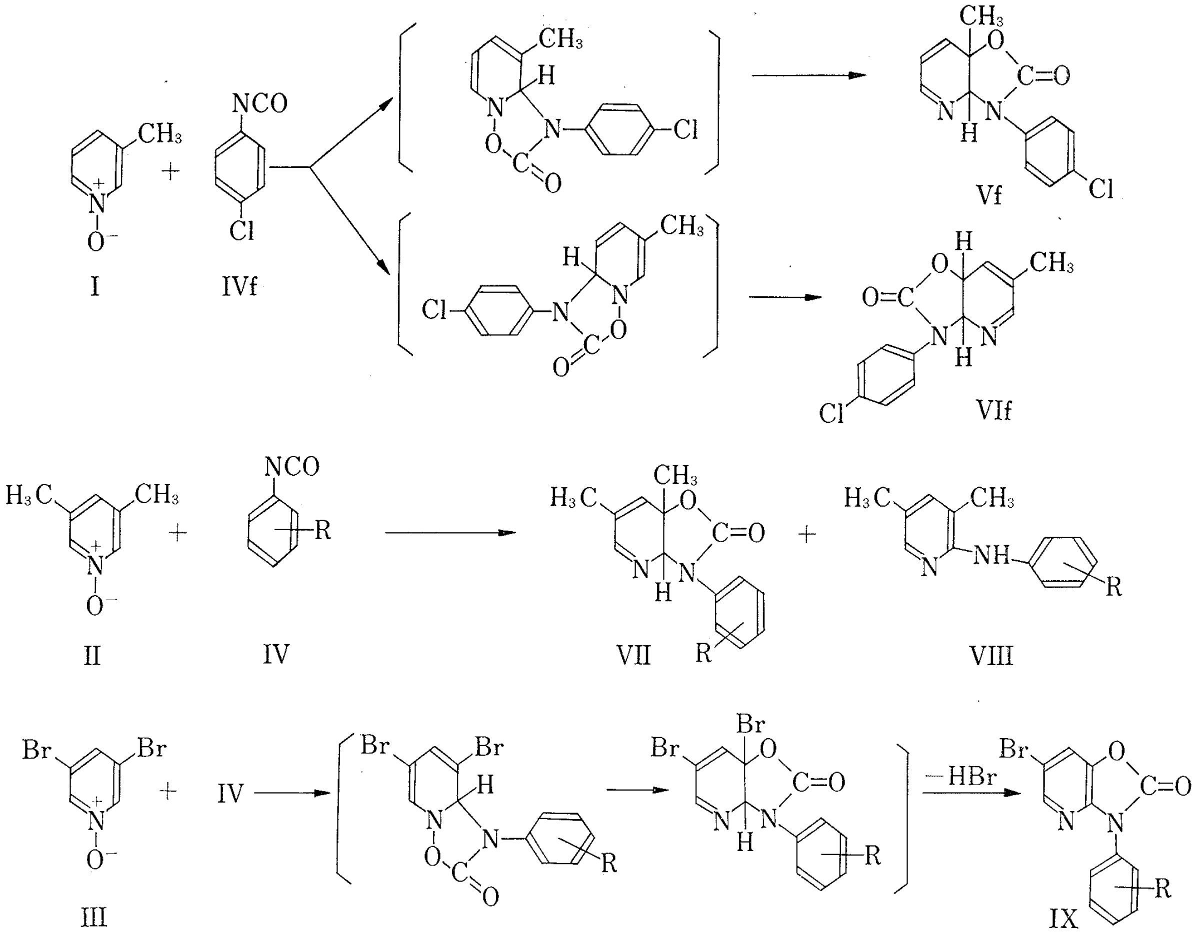
[5] R.A. Abramovitch, I. Shinkai, and R.V. Dahn, *J. Heterocycl. Chem.*, 13, 171 (1976).



R=*o*-CH_3, (a); *m*-CH_3, (b); *p*-CH_3, (c); *o*-Cl, (d); *m*-Cl, (e); *p*-Cl, (f); *o*-NO_2, (g); *m*-NO_2, (h)

Chart 1

N-oxide afforded the 2,3-dihydropyridine adduct. The question arises as to whether the initial intermediate is a 1,2-dihydro or 2,3-dihydropyridine. Therefore, we reinvestigated this reaction; X-ray structure analysis established the intermediates to be 2,3-dihydropyridine intermediates and not the 1,2-dihydropyridine ones which were proposed in our previous reports.3)

This paper reports the X-ray structure analysis of two crystalline adducts isolated from the reaction of 3-picoline N-oxide (I) with *p*-chlorophenyl isocyanate (IVf), together with the isolation of cycloadducts from the reaction of 3,5-disubstituted pyridine N-oxides with phenyl isocyanates having a substituent group.

Cycloadditions of Phenyl Isocyanates (IV) to I, II and III

Heating of 3-picoline N-oxide (I) with *p*-chlorophenyl isocyanate (IVf) in dimethylformamide (DMF) resulted in the formation of two cycloadducts, Vf, mp 167° and VIf, mp 129—130°, assigned the formula $C_{13}H_{11}Cl\,N_2O_2$, which contain the dihydropyridine structure, as is the case with the 1:1 adducts of 3-picoline N-oxide and phenyl isocyanate3): the infrared (IR) spectra of these adducts, Vf and VIf, exhibited carbonyl absorptions at 1727 and 1730 cm^{-1}; neither compound displayed bands ascribable to a carboxyl moiety in the 3300 and 2700—2500 cm^{-1} regions. In addition to the methyl hydrogen peaks at τ 8.37 (singlet) for Vf and τ 8.08 (narrow doublet) for VIf, of which the latter appears to be split by allylic coupling in agreement with the results of Abramovitch,5) nuclear magnetic resonance (NMR) spectra showed a single hydrogen peak at τ 4.59 (doublet) for Vf, and signals at τ 4.36 and τ 5.12 as a doublet of doublets for VIf; the remaining seven hydrogens for Vf appeared at

τ 2.20—4.05 as complex multiplets, and the remaining six hydrogens for VIf at τ 2.30—4.20 as complex multiplets. On the basis of these data, we deduced Vf and VIf to be isomeric cycloadducts of *p*-chlorophenyl isocyanate (IVf) to 3-picoline N-oxide (I).

Next, the substituent effects of *ortho*, *meta* and *para*-substituted phenyl isocyanates on the cycloaddition were examined under the conditions of the above reaction.

First, 3,5-dimethylpyridine N-oxide (II) was reacted with the *o*, *m* or *p*-substituted phenyl isocyanate (IV) to afford a cycloadduct which in each case gave the elemental analysis results expected for a 1:1 adduct of the two reactants, as well as spectral data consistent with the 2,3-dihydropyridine structure [IR, NMR and mass (MS) spectra]. The cycloadducts (VII) were easily converted in high yields to the corresponding anilinopyridines (VIII), with the elimination of carbon dioxide, on reflux in alcoholic potassium hydroxide. The structural assignment of VIII is based on the satisfactory elemental analyses, and MS, IR and NMR spectra in accord with those described in the previous reports.[3]

The reactions of *o*-substituted phenyl isocyanates offer considerably lower yields of the cycloadducts, probably because of steric interactions among the atoms around the isocyanate

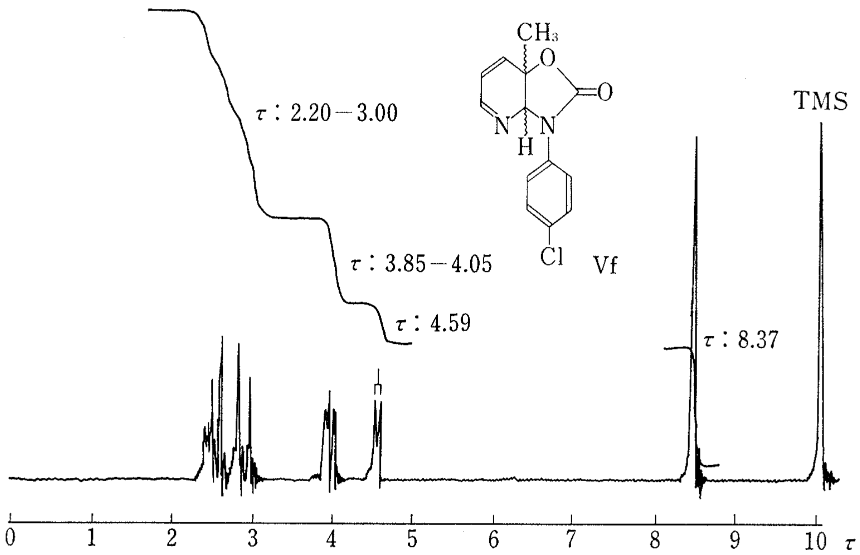


Fig. 1. NMR Spectrum of Vf (in $CDCl_3$, 60 MHz, TMS)

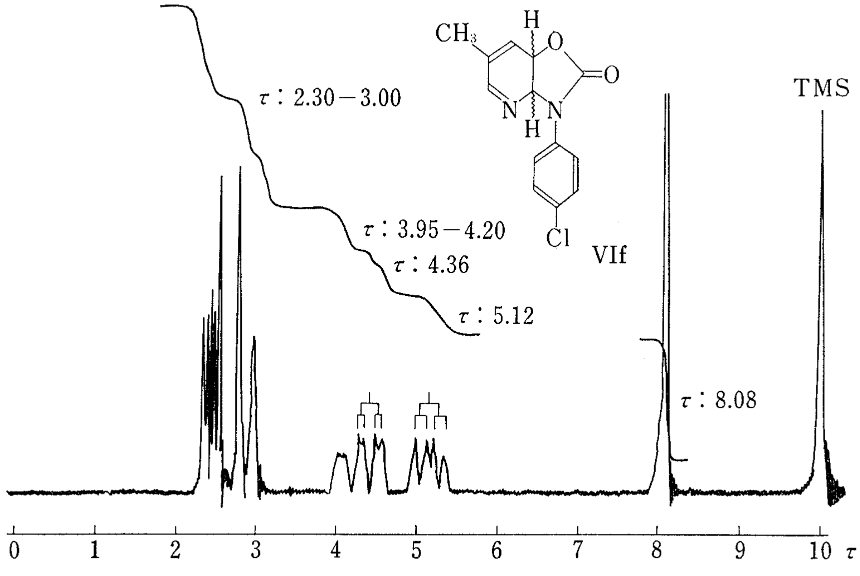
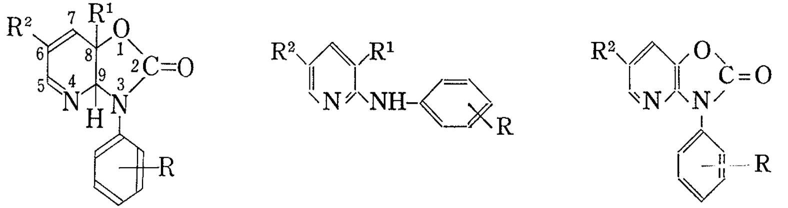


Fig. 2. NMR Spectrum of VIf (in $CDCl_3$, 60 MHz, TMS)

Table I. Yields of Cycloadducts in the Cycloadditions of Substituted Phenyl Isocyanates (IV) to I, II and III


VII-type VIII-type IX-type

Starting materials		R^1	R^2	R	Product yields (%)		
IVa—h	Pyridine N-oxides				VII	VIII	XI
f	I	CH_3	H	p-Cl	40.7[a]	—	—
a	II	CH_3	CH_3	o-CH_3	20.3	—	—
b	II	CH_3	CH_3	m-CH_3	47.8	—	—
c	II	CH_3	CH_3	p-CH_3	49.6	—	—
d	II	CH_3	CH_3	o-Cl	23.4	—	—
e	II	CH_3	CH_3	m-Cl	47.7	—	—
f	II	CH_3	CH_3	p-Cl	51.7	—	—
g	II	CH_3	CH_3	o-NO_2	10.9	5.6	—
h	II	CH_3	CH_3	m-NO_2	4.5	13.9	—
c	III	Br	Br	p-CH_3	—	—	43.3
f	III	Br	Br	p-Cl	—	—	41.7
h	III	Br	Br	m-NO_2	—	—	17.7

a) The sum of Vf (R^1=CH_3, R^2=H) in 29.6% yield and VIf (R^1=H, R^2=CH_3) in 11% yield.

Table II. Analytical Data for the Cycloadducts

Compd. No.	mp (°C)	Appearance [ ]: recryst. solvent	Formula	Analysis (%) Calcd. (Found)		
				C	H	N
Vf	167	Colorless needles [benzene]	$C_{13}H_{11}ClN_2O_2$	59.44 (59.70	4.22 4.20	10.66 10.58)
VIf	129—130	Colorless prisms [n-hexane–benzene]	$C_{13}H_{11}ClN_2O_2$	59.44 (59.65	4.22 4.15	10.66 10.66)
VIIa	134—136	Colorless prisms [ether–acetone]	$C_{15}H_{16}N_2O$	70.29 (70.51	6.29 6.15	10.93 10.71)
VIIb	122—123	Colorless needles [ether–acetone]	$C_{15}H_{16}N_2O$	70.29 (70.35	6.29 6.15	10.93 11.02)
VIIc	123—124.5	Colorless prisms [ether–acetone]	$C_{15}H_{16}N_2O$	70.29 (70.18	6.29 6.41	10.93 10.98)
VIId	163—164	Colorless prisms [ether–acetone]	$C_{14}H_{13}ClN_2O_2$	60.77 (60.71	4.74 4.88	10.12 10.44)
VIIe	138—139	Colorless needles [ether–acetone]	$C_{14}H_{13}ClN_2O_2$	60.77 (60.86	4.74 4.67	10.12 10.21)
VIIf	137—138.5	Colorless prisms [ether–acetone]	$C_{14}H_{13}ClN_2O_2$	60.77 (61.03	4.74 4.72	10.12 10.31)
VIIg	156—157	Yellow prisms [ether–acetone]	$C_{14}H_{13}N_3O_4$	58.53 (58.51	4.56 4.53	14.63 14.76)
VIIh	148—150	Yellow prisms [ether-acetone]	$C_{14}H_{13}N_3O_4$	58.53 (58.32	4.56 4.53	14.63 14.76)
VIIIg	111—112.5	Orange needles [petr. benzine]	$C_{13}H_{13}N_3O_2$	64.19 (64.32	5.39 5.32	17.27 17.38)
VIIIh	138—140.5	Orange–yellow needles [ether]	$C_{13}H_{13}N_3O_2$	64.19 (64.18	5.39 5.44	17.27 17.55)
IXc	187—188	Colorless needles [ether]	$C_{13}H_9BrN_2O_2$	51.17 (50.96	2.93 2.98	9.18 9.45)
IXf	167—169	Colorless needles [ether]	$C_{12}H_6BrClN_2O_2$	44.27 (44.29	1.86 1.81	8.61 8.66)
IXh	149—151	Light yellow prisms [ether]	$C_{12}H_6BrN_3O_4$	42.88 (42.66	1.80 1.98	12.50 12.64)

group. Phenyl isocyanates bearing an electron-attracting function such as NO_2 tended to give anilinopyridines; *p*-nitrophenyl isocyanate itself was unreactive.

Next, the cycloaddition of IV to 3,5-dibromopyridine N-oxide (III) was carried out under the same conditions using *p*-methyl (IVc), *p*-chloro (IVf) and *m*-nitrophenyl isocyanate (IVh). Attempts to separate the corresponding 2,3-dihydro intermediates from the reaction mixture were unsuccessful. The product (IX) was assigned as the 6-bromo-2,3-dihydro-2-oxo-3-(substituted-phenyl)oxazolo[4,5-*b*]pyridine in the manner described in our earlier reports,[4] *i. e.*, the analytical value was in agreement with the empirical formula for the

Table III. NMR and IR Spectral Data for 2,3-Dihydropyridines

Compd. No.	NMR (in $CDCl_3$, 60 MHz): τ								IR (KBr): cm^{-1} (C=O)
	C_8–CH_3 (3H, s)	C_6–CH_3 (3H, d, $J=1.8$)	C_8–H	C_9–H (d, $J_{9-5}=2.3$)	C_6–H	C_7–H (1H, m)	C_5–H	Others	
Vf	8.37	—	—	4.59 ($J=2.5$)	3.85—4.05 (2H, m)		2.20—3.00 (5H, m)[a]		1725
VIf	—	8.08	5.12 (d-d, $J_{8-9}=9$, $J_{8-7}=6$)	4.36 (d-d, $J_{9-8}=9$, $J_{9-5}=2.5$)	—	3.95—4.20	2.30—3.00 (5H, m)[a]		1730
VIIa	8.64	8.09	—	4.93	—	4.16—4.34	2.41—2.62 (1H, t)	7.70 (3H, s, aromatic C_2–CH_3), 2.95 (4H, s, aromatic C–H)	1720
VIIb	8.41	8.09	—	4.68	—	4.12—4.30	2.32—2.43 (1H, t)	7.66 (3H, s, aromatic C_3–CH_3), 2.43—3.26 (4H, m, aromatic C–H)	1728
VIIc	8.42	8.12	—	4.82	—	4.21—4.41	2.51—3.24 (5H, m)[a]		1720
VIId	8.30	8.08	—	4.74	—	4.17—4.32	2.40—2.51 (1H, t)	2.52—3.02 (4H, m, aromatic C–H)	1736
VIIe	8.51	8.10	—	4.69	—	4.13—4.31	2.39—3.10 (5H, m)[a]		1728
VIIf	8.41	8.08	—	4.72	—	4.15—4.36	2.31—2.96 (5H, m)[a]		1728
VIIg	8.28	8.10	—	4.68	—	4.07—4.20	1.90—2.90 (5H, m)[a]		1740
VIIh	8.73	8.01	—	4.56	—	4.09—4.24	1.40—1.60 (1H, t)	1.74—2.92 (4H, m, aromatic C–H)	1735

[a] Including the remaining four aromatic protons.

Table IV. Spectral Data for 2,3-Dihydro-2-oxo-oxazolo[4,5-*b*]pyridines (IX)

Compound No.	IR ν_{max}^{KBr} cm^{-1} >C=O	NMR (in $CDCl_3$, 60 MHz): τ C_5–H	MS (m/e) M^+ (relative intensity: 1:1)		M^+-CO_2	
IXc	1770	2.05 (d, $J_{5-7}=2.0$ Hz)	304	306	260	262
IXf	1800	1.98 (d, $J_{5-7}=2.0$ Hz)	324	328[a]	280	284[a]
IXh	1780	1.80—2.05 (m)	335	337	291	293

[a] Relative intensity 3:1, due to chlorine atom.

Table V. Final Positional Parameters and Anisotropic Temperature Factors of Vf with their Estimated Standard Deviations in Parentheses

Atom	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
O(1)	0.60221(25)	0.43518(20)	0.61976(16)	0.01267(29)	0.00916(20)	0.00449(13)	−0.00174(22)	−0.00065(17)	−0.00103(14)
C(2)	0.63939(32)	0.41918(25)	0.51245(23)	0.01022(32)	0.00630(20)	0.00486(17)	0.00036(24)	−0.00048(21)	−0.00028(17)
N(3)	0.53104(26)	0.35515(21)	0.46049(17)	0.00957(27)	0.00694(18)	0.00413(13)	−0.00072(22)	0.00081(17)	−0.00057(14)
N(4)	0.27591(30)	0.39781(28)	0.49371(23)	0.01054(33)	0.01270(32)	0.00629(19)	0.00077(28)	−0.00011(23)	−0.00106(22)
C(5)	0.20320(42)	0.45977(40)	0.56451(35)	0.01239(47)	0.01280(42)	0.00941(31)	0.00200(39)	0.00115(34)	−0.00105(32)
C(6)	0.24496(48)	0.47654(35)	0.67950(33)	0.01562(51)	0.01005(35)	0.00884(30)	0.00141(39)	0.00318(36)	−0.00299(28)
C(7)	0.37106(45)	0.43487(34)	0.71749(28)	0.01759(56)	0.01058(34)	0.00567(21)	−0.00072(41)	0.00214(31)	−0.00241(24)
C(8)	0.47197(36)	0.36156(29)	0.64620(22)	0.01245(38)	0.00833(25)	0.00427(16)	−0.00089(30)	0.00051(23)	−0.00058(18)
C(9)	0.40428(32)	0.33137(26)	0.53280(22)	0.00994(32)	0.00712(22)	0.00457(16)	−0.00103(24)	0.00125(21)	−0.00074(17)
Cl(10)	0.52468(15)	0.20795(10)	−0.00813(6)	0.02741(21)	0.01457(11)	0.00419(4)	−0.00434(14)	0.00136(9)	−0.00199(6)
C(11)	0.52832(40)	0.25061(28)	0.12962(22)	0.01569(46)	0.00808(25)	0.00386(15)	−0.00029(32)	0.00020(25)	−0.00062(17)
C(12)	0.43212(38)	0.19832(30)	0.20162(25)	0.01450(45)	0.00812(26)	0.00539(19)	−0.00285(31)	0.00018(25)	−0.00107(20)
C(13)	0.43524(36)	0.23271(29)	0.31174(23)	0.01251(40)	0.00850(26)	0.00484(17)	−0.00259(29)	0.00138(23)	−0.00037(18)
C(14)	0.53285(30)	0.32003(23)	0.34786(20)	0.00923(30)	0.00597(19)	0.00399(14)	0.00050(22)	0.00004(19)	−0.00014(14)
C(15)	0.63015(36)	0.37234(27)	0.27333(25)	0.01184(38)	0.00682(22)	0.00536(19)	−0.00140(27)	0.00042(24)	−0.00025(18)
C(16)	0.62726(39)	0.33672(30)	0.16298(24)	0.01428(44)	0.00853(27)	0.00499(18)	−0.00135(32)	0.00170(26)	0.00051(20)
O(17)	0.75441(24)	0.45618(21)	0.47559(18)	0.01050(26)	0.01008(22)	0.00642(16)	−0.00310(23)	−0.00026(18)	−0.00108(17)
C(18)	0.52729(44)	0.24923(33)	0.70351(26)	0.01584(50)	0.01048(32)	0.00594(20)	0.00082(38)	0.00118(31)	0.00203(22)

Table V-1. Final Positional Parameters and Isotropic Temperature Factors of Hydrogen Atoms of Vf with their Estimated Standard Deviations in Parentheses

	x	y	z	B		x	y	z	B
H(18)	0.44937(389)	0.19835(311)	0.72573(276)	2.59(79)	H(12)	0.36491(406)	0.13596(325)	0.17860(296)	2.97(84)
H(18)′	0.58996(421)	0.19881(332)	0.65874(286)	3.09(85)	H(13)	0.37062(355)	0.19848(280)	0.35876(252)	1.60(66)
H(18)″	0.58966(398)	0.27319(308)	0.76779(279)	2.67(81)	H(15)	0.70033(360)	0.43236(285)	0.29021(273)	1.79(70)
H(5)	0.10914(471)	0.50313(375)	0.53304(339)	4.62(106)	H(16)	0.70414(385)	0.37504(310)	0.11319(289)	2.59(81)
H(6)	0.17637(442)	0.51610(367)	0.72092(336)	4.17(104)					
H(7)	0.40245(474)	0.44479(361)	0.79007(345)	4.35(103)					
H(9)	0.37939(339)	0.24413(272)	0.53218(236)	1.11(63)					

The temperature factor is of the form $\exp[-(B_{11}h^2+B_{22}k^2+B_{33}l^2+2B_{12}hk+2B_{13}hl+2B_{23}kl)]$.

TABLE VI. Final Positional Parameters and Anisotropic Temperature Factors of VIf with their Estimated Standard Deviations in Parentheses ($R=0.048$).

Atom	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
O(1)	−0.25960(10)	−0.35226(12)	0.84568(12)	5.26(6)	4.00(6)	5.32(6)	−0.30(5)	2.41(5)	−0.03(4)
C(2)	−0.24067(14)	−0.21570(18)	0.83591(16)	4.45(8)	4.13(8)	4.22(7)	0.12(7)	1.46(6)	0.02(6)
N(3)	−0.14056(10)	−0.19440(13)	0.79804(13)	3.78(6)	3.48(6)	4.11(6)	0.35(5)	1.22(5)	−0.26(5)
N(4)	−0.08944(11)	−0.33072(14)	0.60838(13)	4.77(7)	4.05(6)	3.92(6)	0.35(6)	1.53(5)	−0.16(5)
C(5)	−0.11747(14)	−0.44334(19)	0.55378(18)	4.88(9)	4.94(9)	3.55(7)	0.61(7)	0.89(6)	−0.28(7)
C(6)	−0.15777(13)	−0.56544(17)	0.62281(18)	3.60(7)	4.03(7)	4.47(8)	0.19(6)	0.17(6)	−0.57(6)
C(7)	−0.18039(14)	−0.55421(18)	0.75217(18)	4.94(9)	3.56(8)	4.40(8)	−0.07(7)	0.50(7)	0.32(6)
C(8)	−0.16034(15)	−0.42544(18)	0.82873(17)	5.25(9)	3.99(8)	3.25(7)	0.28(7)	0.35(6)	0.33(6)
C(9)	−0.09137(13)	−0.32238(16)	0.75757(16)	3.59(7)	3.57(7)	4.06(7)	0.47(6)	0.41(6)	−0.29(6)
Cl(10)	0.09249(4)	0.33028(5)	0.81316(5)	6.02(2)	4.71(2)	4.99(2)	−1.42(2)	0.33(2)	−0.40(2)
C(11)	0.01962(13)	0.17868(17)	0.80388(16)	4.29(7)	3.83(7)	3.95(7)	−0.23(6)	0.07(6)	−0.02(6)
C(12)	0.04166(14)	0.08280(20)	0.70552(18)	4.46(8)	5.33(10)	4.50(8)	−0.88(7)	1.54(7)	−0.75(7)
C(13)	−0.01382(14)	−0.03913(19)	0.70168(18)	4.53(8)	4.60(8)	4.53(8)	−0.47(7)	1.58(7)	−1.21(7)
C(14)	−0.08993(12)	−0.06507(16)	0.79567(15)	3.72(7)	3.51(7)	3.48(6)	0.39(6)	0.66(5)	−0.04(5)
C(15)	−0.11239(14)	0.03433(17)	0.89180(17)	4.67(8)	3.93(7)	3.72(7)	0.47(6)	1.43(6)	0.09(6)
C(16)	−0.05746(15)	0.15611(17)	0.89574(17)	5.09(8)	3.62(7)	3.76(7)	0.54(6)	0.75(6)	−0.23(6)
O(17)	−0.30707(10)	−0.13341(13)	0.86706(15)	4.65(6)	4.80(6)	7.97(8)	0.58(5)	2.77(6)	−0.64(6)
C(18)	−0.17401(21)	−0.69279(25)	0.53912(26)	6.22(12)	5.28(11)	6.29(12)	0.96(10)	0.65(10)	1.89(9)

TABLE VI-1. Final Positional Parameters and Isotropic Temperature Factors of Hydrogen Atoms of VIf with their Estimated Standard Deviations in Parentheses

	x	y	z	B		x	y	z	B
H(18)	−0.20543(172)	−0.76756(224)	0.58788(210)	8.96(58)	H(12)	0.09622(137)	0.10125(171)	0.64239(173)	5.47(42)
H(18)′	−0.21971(192)	−0.67270(213)	0.45598(222)	8.48(64)	H(13)	−0.00068(136)	−0.10483(166)	0.63013(175)	5.20(41)
H(18)″	−0.10738(181)	−0.72020(220)	0.49950(201)	9.20(60)	H(15)	−0.16483(126)	0.01518(159)	0.95594(160)	4.35(37)
H(5)	−0.11654(128)	−0.44771(172)	0.45466(175)	5.10(41)	H(16)	−0.07321(127)	0.22209(172)	0.96364(149)	4.77(40)
H(7)	−0.21138(134)	−0.62442(166)	0.79775(165)	4.53(40)					
H(8)	−0.13094(123)	−0.44041(165)	0.91634(176)	4.12(39)					
H(9)	−0.01862(117)	−0.32714(140)	0.79175(141)	3.01(31)					

The temperature factor is of the form $\exp[-1/4(B_{11}h^2a^{*2}+B_{22}k^2b^{*2}+B_{33}l^2c^{*2}+2B_{12}hka^*b^*+2B_{13}hla^*c^*+2B_{23}klb^*c^*)]$.

oxazolo-pyridine structure, and the MS spectra of IXc and IXh showed two sorts of characteristic parent peaks with a relative intensity of 1:1, two fragment peaks for the elimination of carbon dioxide from these parent peaks and one fragment peak for the elimination of carbon dioxide and bromine. These data show that one mol of hydrogen bromide was lost from the 1:1 adduct of IV and III during the reaction. The IR spectra exhibited a carbonyl absorption at 1770—1800 cm^{-1}, but did not display any band ascribable to a carboxyl group. The NMR spectra showed an α-proton of pyridine as a narrow doublet around τ 2.00 and the remaining aromatic protons as complex multiplets at τ 2.30—3.00, while the characteristic hydrogen peaks ascribable to C_7– and C_9–H at τ 4.00—5.00 had disappeared. In this case, it seems reasonable to assume the 2,3-dihydropyridine as a transient intermediate.

Structure Determinations of Vf and VIf by X-Ray Analysis

Taking into account the mechanism of the cycloaddition of IV to β-substituted pyridine N-oxides, the structures of the cycloadducts were assumed to be 2,3-dihydropyridine, although the spectroscopic data are not sufficient to establish the full structure. Vf and VIf were selected for X-ray crystallographic analysis, and their full structures were determined. The molecular structure of Vf, mp 167°, $C_{13}H_{11}ClN_2O_2$, orthorhombic crystals from ether–acetone, was solved by the direct method[6] using the MULTAN[7] series of programs and the UNICS-II system.[8] The structure of VIf, mp 129—130°, $C_{13}H_{11}ClN_2O_2$, monoclinic crystals from ether–petr. ether, was solved by the same direct method and also by the direct method using the SYNTEX-XTL program. From the E map calculated with a set of phases which gave a figure of merit of 1.008, 15 nonhydrogen atoms out of 18 independent ones in molecule Vf were located. Subsequent Fourier synthesis and gave refinement by the block-diagonal

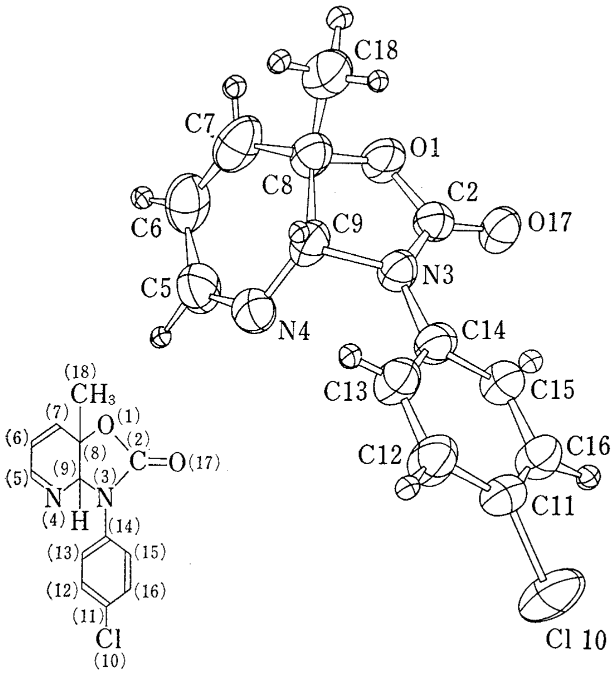


Fig. 3. Perspective View of the Molecular Structure of Vf

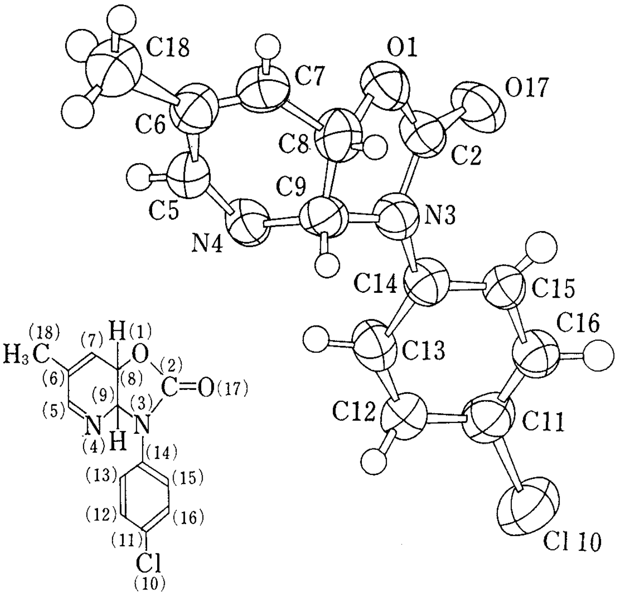


Fig. 4. Perspective View of the Molecular Structure of VIf

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6) All the calculations were performed on a FACOM M-190 computer in the Computer Center of Kyushu University.

7) P. Main, M.M. Woolfson, and G. Germin, *Acta Cryst.*, **B. 26**, 274 (1970); *idem, ibid.*, **A. 27**, 358 (1971).

8) The Universal Crystallographic Computation Program System UNICS-II (Sakurai, Iwasaka, Watanabe, Kobayashi, Bando and Nakamichi, 1974).

least-squares method gave the molecular structure. After an anisotropic refinement of nonhydrogen atoms (R=0.085) a difference Fourier map was calculated from which all the hydrogen atoms were located, and these were included in the final refinement, assuming isotropic temperature factors. The final R value was 0.054 using 2069 independent reflections. From the E map calculated with a set of phases which gave a figure of merit of 1.0890, 18 nonhydrogen atoms in VIf were easily located. The refinement of the molecular structures was carried out by the block-diagonal least-squares method (UNICS-II) and by the Gauss–Seidel block and full matrix least-squares methods (SYNTEX-XTL), and the R value fell to 0.066 with an anisotropic temperature factor. Calculated hydrogen atom coordinates were included in the final refinements and the final R value was 0.056 (UNICS-II) or 0.048 (SYNTEX-XTL). Both methods gave the same result.

In compound Vf, on the basis of the C(8)–CH_3(1.514 Å) bond length, the C(7)–C(8)(1.497 Å) and C(8)–C(9)(1.544 Å) distances are very similar and are both longer than C(6)–C(7)

Table VII. Bond Distances (Å) of Vf with Estimated Standard Deviations (ESD)

	Dist. (ESD)		Dist. (ESD)
Cl(10)–C(11)	1.740(4)	C(11)–C(12)	1.362(5)
C(11)–C(16)	1.369(5)	C(12)–C(13)	1.392(5)
C(16)–C(15)	1.398(5)	C(13)–C(14)	1.381(4)
C(15)–C(14)	1.388(4)	C(14)–N(3)	1.423(4)
N(3)–C(2)	1.363(4)	N(3)–C(9)	1.465(4)
C(2)–O(17)	1.202(4)	C(2)–O(1)	1.358(4)
O(1)–C(8)	1.466(4)	C(8)–C(18)	1.514(5)
C(8)–C(7)	1.497(5)	C(8)–C(9)	1.544(4)
C(7)–C(6)	1.311(6)	C(6)–C(5)	1.459(6)
C(5)–N(4)	1.282(5)	N(4)–C(9)	1.452(4)
H(12)–C(12)	0.962(37)	H(13)–C(13)	0.900(32)
H(15)–C(15)	0.942(33)	H(16)–C(16)	1.013(35)
H(5)–C(5)	1.047(43)	H(6)–C(6)	0.910(41)
H(7)–C(7)	0.933(43)	H(9)–C(9)	0.995(31)
H(18)–C(18)	0.941(35)	H(18)′–C(18)	0.964(38)
H(18)″–C(18)	0.998(36)		

Table VIII. Bond Distances (Å) of VIf with Estimated Standard Deviations (ESD)

	Dist. (ESD)		Dist. (ESD)
Cl(10)–C(11)	1.749(2)	C(11)–C(12)	1.380(2)
C(11)–C(16)	1.372(2)	C(12)–C(13)	1.386(3)
C(16)–C(15)	1.381(2)	C(13)–C(14)	1.383(2)
C(15)–C(14)	1.390(2)	C(14)–N(3)	1.421(2)
N(3)–C(2)	1.364(2)	N(3)–C(9)	1.462(2)
C(2)–O(17)	1.204(2)	C(2)–O(1)	1.361(2)
O(1)–C(8)	1.463(2)	C(8)–C(7)	1.482(2)
C(8)–C(9)	1.523(2)	C(7)–C(6)	1.311(2)
C(6)–C(18)	1.500(3)	C(6)–C(5)	1.475(2)
C(5)–N(4)	1.269(2)	N(4)–C(9)	1.458(2)
H(12)–C(12)	0.968(17)	H(13)–C(13)	0.967(17)
H(15)–C(15)	0.951(16)	H(16)–C(16)	0.953(16)
H(5)–C(5)	0.968(17)	H(7)–C(7)	0.917(16)
H(8)–C(8)	0.928(17)	H(9)–C(9)	0.967(15)
H(18)–C(18)	0.968(22)	H(18)′–C(18)	0.994(23)
H(18)″–C(18)	0.981(23)		

(1.311 Å), whereas the N(4)–C(5)(1.282 Å) has more double bond character than N(4)–C(9)(1.452 Å) and C(9)–N(3)(1.465 Å). In compound VIf, which is isomeric with Vf, the N(4)–C(5) (1.269 Å) and C(6)–C(7)(1.311 Å) distances have more double bond character than C(5)–C(6) (1.475 Å), C(7)–C(8)(1.482 Å) and C(9)–C(8)(1.523 Å). The atomic configuration of C(8) in compounds Vf and VIf is thus sp^3 on the basis of these data. Molecular stereographic views

TABLE IX. Bond Angles (Degrees) of Vf with Estimated Standard Deviations (ESD)

	Angle (ESD)		Angle (ESD)
Cl(10)–C(11)–C(12)	119.32(28)	Cl(10)–C(11)–C(16)	119.17(28)
C(11)–C(12)–C(13)	119.18(32)	C(12)–C(11)–C(16)	121.50(33)
C(11)–C(16)–C(15)	119.59(32)	C(12)–C(13)–C(14)	120.75(29)
C(16)–C(15)–C(14)	119.68(29)	C(13)–C(14)–C(15)	119.29(27)
C(13)–C(14)–N(3)	119.40(25)	C(15)–C(14)–N(3)	121.31(25)
C(14)–N(3)–C(2)	125.48(24)	C(14)–N(3)–C(9)	122.42(23)
C(2)–N(3)–C(9)	112.01(23)	N(3)–C(2)–O(1)	109.66(24)
N(3)–C(2)–O(17)	128.59(28)	O(17)–C(2)–O(1)	121.73(27)
C(2)–O(1)–C(8)	109.56(23)	O(1)–C(8)–C(7)	108.02(27)
O(1)–C(8)–C(9)	104.00(24)	O(1)–C(8)–C(18)	107.30(26)
C(18)–C(8)–C(7)	112.50(30)	C(18)–C(8)–C(9)	111.18(27)
C(7)–C(8)–C(9)	113.26(28)	C(8)–C(7)–C(6)	120.99(37)
C(7)–C(6)–C(5)	121.04(40)	C(6)–C(5)–N(4)	125.41(40)
C(5)–N(4)–C(9)	117.44(32)	N(3)–C(9)–C(8)	100.84(23)
N(3)–C(9)–N(4)	109.46(24)	C(8)–C(9)–N(4)	119.74(26)
H(5)–C(5)–N(4)	114.57(235)	H(5)–C(5)–C(6)	119.97(235)
H(6)–C(6)–C(5)	114.59(260)	H(6)–C(6)–C(7)	124.36(261)
H(7)–C(7)–C(6)	123.64(266)	H(7)–C(7)–C(8)	115.30(265)
H(7)–C(6)–H(6)	101.36(287)	H(9)–C(9)–N(3)	110.30(178)
H(9)–C(9)–N(4)	108.26(178)	H(9)–C(9)–C(8)	107.91(178)

TABLE X. Bond Angles (Degrees) of VIf with Estimated Standard Deviations (ESD)

	Angle (ESD)		Angle (ESD)
Cl(10)–C(11)–C(12)	119.42(13)	Cl(10)–C(11)–C(16)	119.50(13)
C(11)–C(12)–C(13)	119.17(16)	C(12)–C(11)–C(16)	121.08(16)
C(11)–C(16)–C(15)	119.56(16)	C(12)–C(13)–C(14)	120.54(16)
C(16)–C(15)–C(14)	120.40(15)	C(13)–C(14)–C(15)	119.20(15)
C(13)–C(14)–N(3)	120.21(14)	C(13)–C(14)–N(3)	120.51(14)
C(14)–N(3)–C(2)	124.57(13)	C(14)–N(3)–C(9)	124.22(13)
C(2)–N(3)–C(9)	111.21(13)	N(3)–C(2)–O(1)	109.35(14)
N(3)–C(2)–O(17)	129.17(16)	O(17)–C(2)–O(1)	121.48(16)
C(2)–O(1)–C(8)	108.83(13)	O(1)–C(8)–C(7)	110.21(14)
O(1)–C(8)–C(9)	103.88(13)	C(7)–C(8)–C(9)	115.07(15)
C(8)–C(7)–C(6)	121.08(16)	C(7)–C(6)–C(5)	117.80(16)
C(7)–C(6)–C(18)	124.25(17)	C(18)–C(6)–C(5)	117.91(16)
C(6)–C(5)–N(4)	127.57(16)	C(5)–N(4)–C(9)	116.77(14)
N(3)–C(9)–C(8)	100.69(13)	N(3)–C(9)–N(4)	110.10(13)
C(8)–C(9)–N(4)	116.95(14)	H(5)–C(5)–N(4)	116.21(101)
H(5)–C(5)–C(6)	116.09(100)	H(7)–C(7)–C(8)	117.51(104)
H(7)–C(7)–C(6)	121.37(104)	H(8)–C(8)–O(1)	106.53(102)
H(8)–C(8)–C(9)	108.04(102)	H(8)–C(8)–C(7)	112.44(102)
H(9)–C(9)–N(3)	111.06(85)	H(9)–C(9)–N(4)	106.43(85)
H(9)–C(9)–C(8)	111.61(85)		

of Vf and VIf are shown in Figs. 3 and 4.[9] The bond lengths are given in Tables VI and VII, and bond angles in Tables VIII and IX, respectively.

Practically speaking, the 1,2- and 1,6-dihydropyridines appear to be unstable transient intermediates which cannot be isolated, and which rearrange with cleavage of the N–O bond to yield 2,3- and 5,6-dihydropyridines.

Experimental

All melting points are uncorrected. IR spectra were recorded on a Nippon Bunko DS-301 infrared spectrophotometer equipped with a grating. ^{1}H-NMR spectra were taken with JNM-MH-100 and JNM-C-60H spectrometers in *ca.* 5% (w/v) solution with tetramethylsilane as an internal standard, and chemical shifts are expressed as τ value. MS spectra were taken with a JEOL JMS-01SG spectrometer.

Reaction of 3-Picoline N-Oxide (I) with *p*-Chlorophenyl Isocyanate (IVf)——Compound IVf (7.68 g, 0.050 mol) was added dropwise to a solution of 2.73 g (0.025 mol) of I in 20 ml of DMF with stirring at room temperature, and the mixture was heated at 110° for 7 hr.

a) Separation of Vf: When the reaction was over, the reaction mixture was concentrated *in vacuo* below 70° and the residue was dissolved in 20 ml of ether. The ethereal solution was kept overnight below 5° and the resulting colorless crystals were collected by suction and washed with a small amount of cold ether. The crystalline mass was recrystallized from benzene to give an analytical sample of Vf, mp 167° as colorless needles, in 29.6% yield (Tables I, II and III). MS *m/e*: 262 and 264 (M^+; relative intensity, 3: 1), 218 and 220 (M^+-CO_2).

b) Separation of VIf: After removal of Vf, the filtrate was concentrated *in vacuo*. After the tarry residue had been treated with hot *n*-hexane, the residue was dissolved in 10 ml of ether and then kept overnight below 5°. The resulting crystals were collected by suction and recrystallized from *n*-hexane–benzene to give an analytical sample of VIf, mp 129—130° as colorless prisms, 11.1% yield (Tables I, II and III). MS *m/e*: 262 and 264 (M^+; relative intensity, 3: 1), 218 and 220 (M^+-CO_2).

Cycloadditions of IVa—f to II——Compound IV (0.025 mol) was added dropwise to a solution of 1.53 g (0.0125 mol) of II in 20 ml of DMF with stirring at room temperature, and the mixture was heated at 110° for 7 hr. When the reaction was over, the reaction mixture was treated as described above and the resulting crystals were collected by suction. Recrystallization from ether–acetone gave an analytical sample.

The ethereal filtrate was extracted with H_2O and the aqueous layer was concentrated *in vacuo* to recover unchanged II.

Cycloadditions of IVg and h to II——Compound IV (0.025 mol) was added dropwise to a solution of 1.53 g (0.0125 mol) of II in 20 ml of DMF, and the mixture heated at 110° for 7 hr. After cooling, the reaction mixture was concentrated *in vacuo* below 50° to give a tarry residue. The residue was dissolved in 15 ml of ether and the ethereal solution was extracted with 30 ml of H_2O to separate out unchanged II. The organic layer was allowed to stand overnight at 0—5° to deposit the cycloadduct. The resulting crystals were collected by suction and recrystallized. After separating the cycloadduct, the ethereal filtrate was concentrated and the residue was dissolved in a small amount of benzene for chromatography on Al_2O_3 (70 g), using CCl_4 as an eluant. From the first effluent fraction, VIII was obtained and purified by recrystallization (Table II). VIIIg: IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3300 (NH). NMR ($CDCl_3$, 60 MHz): τ 7.75 and 7.68 (3H, s, CH_3), 2.07 (1H, d, $J_{6-4}=$ 1.6 Hz, pyridine C_6–H), −0.10 (1H, broad s, NH). VIIIh: IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3355 (NH). NMR ($CDCl_3$, 60 MHz): τ 7.78 (6H, s, two CH_3), 2.12 (1H, d, $J_{6-4}=1.4$ Hz, pyridine C_6–H), 3.78 (1H, broad s, NH).

Cycloaddition of IVc, f and h to III——Compound IV (0.01 mol) was added dropwise to a solution of 1.2 g (0.005 mol) of III in 10 ml of DMF with stirring at room temperature, and the mixture was heated at 110° for 7 hr. The reaction mixture was then allowed to stand overnight at 0—5° and the precipitated solid was filtered off. The filtrate was concentrated *in vacuo* to give a crystalline residue which was washed with benzene. Recrystallization from ether afforded 2,3-dihydro-2-oxo-3-(substituted-phenyl)-6-bromo-oxazolo-[4,5-*b*]pyridines (IX) (Tables, I II and IV).

The benzene washings were extracted with 10% HCl and the aqueous layer was made basic to litmus with 3 N NaOH. The alkaline solution was reextracted with $CHCl_3$ and the extract was concentrated to recover unchanged III.

Crystallographic Analysis of Vf and VIf——The cell parameters and intensities were measured with a Syntex P_1^- automated diffractometer with Mo $K\alpha$ radiation monochromated with a graphite crystal. The cell parameters were determined by least-squares refinement from 15 reflections within a range of $6<2\theta<21°$ (Vf) and $10<2\theta<26°$ (VIIf). The values for Vf are $a=9.010$ (3), $b=11.113$ (4), $c=12.150$ (3) Å, $V=1216.6$ (7)Å^3, $Dm=1.41$ g/cm^3 (flotation in hexane–carbon tetrachloride solution), $Dc=1.439$ g/cm^3, $z=4$, space group $P2_12_12_1$. The values for VIf are $a=12.664$ (3), $b=9.797$ (6), $c=9.751$ (4) Å, $\beta=92.58$ (3)°, $V=1208.6$ (9)Å^3. $Dm=1.46$ g/cm^3 (flotation in hexane–carbon tetrachloride solution) $Dc=1.449$ g/cm^3, $z=4$, space

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9) C.K. Johnson, ORTEP, ORNL-379.

group $P2_1/A$. Intensity data were collected by the θ—2θ scan technique with a variable scan rate of 3.0 to 24.0°/min. Three standard reflections were monitored every 50 reflections, and their intensities showed good stability. A total of 2069 independent reflections of Vf with $2\theta < 60°$ were used for the structure analysis. On the other hand, 3522 reflections ($2\theta < 60°$) were processed with 2725 observed reflections [intensity greater than 1.96 sigma (I)] for the structure analysis of VIf. They were corrected for Lorenz and polarization effects, but corrections for absorption were not applied.

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