ISOLATION OF THE INTERMEDIATES AND IMPROVED SYNTHESIS OF PYRIDO[1',2':1,2]IMIDAZO[4,5-*b*]PYRAZINES AND -QUINOXALINES

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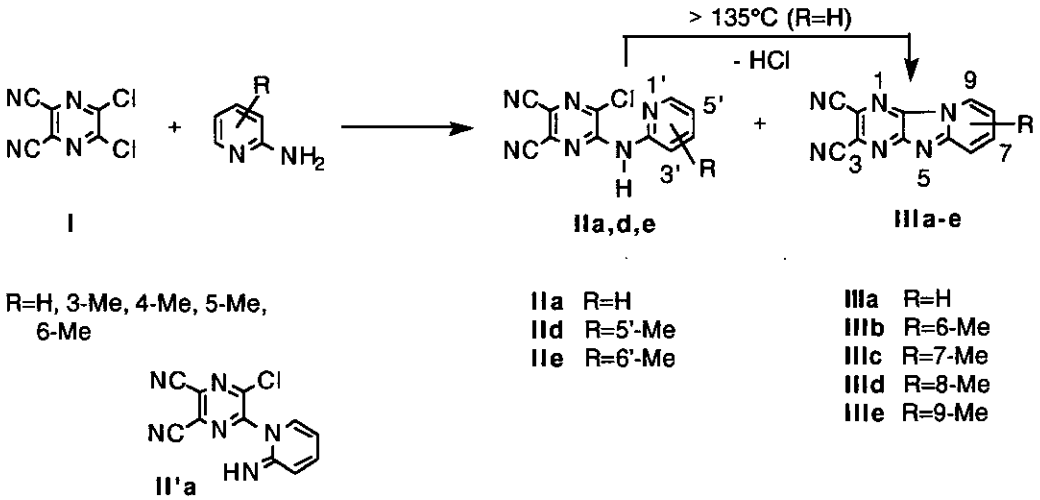
Abstract --- 2-(Pyrid-2'-yl)amino-3-chloro-5,6-dicyanopyrazines (**IIa, IId,** and **IIe**) and 2-(pyrid-2'-yl)amino-3-chloro-6-nitroquinoxalines (**Va-c**) were isolated for the first time in the course of the reaction of 2,3-dichloro-5,6-dicyanopyrazine (**I**) and 2,3-dichloro-6-nitroquinoxaline (**IVa**), respectively, with 2-aminopyridines. Furthermore, the yield of pyrido[1',2':1,2]imidazo[4,5-*b*]quinoxalines was remarkably improved due to the modification of the reaction conditions.

Nitrogen-containing fused polycyclic compounds have been paid much attention owing to the characteristic structure with a bridgehead nitrogen and pharmaceutical interest.[1,2] In 1986, we have published the novel synthesis of pyrido[1',2':1,2]imidazo[4,5-*b*]pyrazines by reaction of 2,3-dichloro-5,6-dicyanopyrazine with 2-aminopyridines or 2-amino-3-chloro-5,6-dicyanopyrazines with substituted pyridines.[3,4] In 1990, Tomoda has reported on the synthesis and the fluorescent property of pyridoimidazoquinoxalines.[5] Recently Tanaka has reported the extended synthesis of them bearing substituents on the pyridine and/or quinoxaline ring.[6] However, these methods gave the products in only low to moderate yields. Since these heterocyclic compounds particularly are of interest in chemiluminescence[7] as well as the fluoresent property, the improvement of the yield in the previous methods was undertaken. In this paper, we describe the improved synthesis of pyrido[1',2':1,2]-imidazo[4,5-*b*]pyrazines and -quinoxalines as well as the isolation of their intermediates.

Isolation of the Intermediates. 2,3-Dichloro-5,6-dicyanopyrazine (**I**) was allowed to react with 2-aminopyridine at room temperature to give 2-(pyrid-2'-yl)amino-3-chloro-5,6-dicyanopyrazine (**IIa**)

together with the reported product,[3] 2,3-dicyanopyrido[1',2':1,2]imidazo[4,5-*b*]pyrazine (**IIIa**). (Scheme 1)



Scheme 1

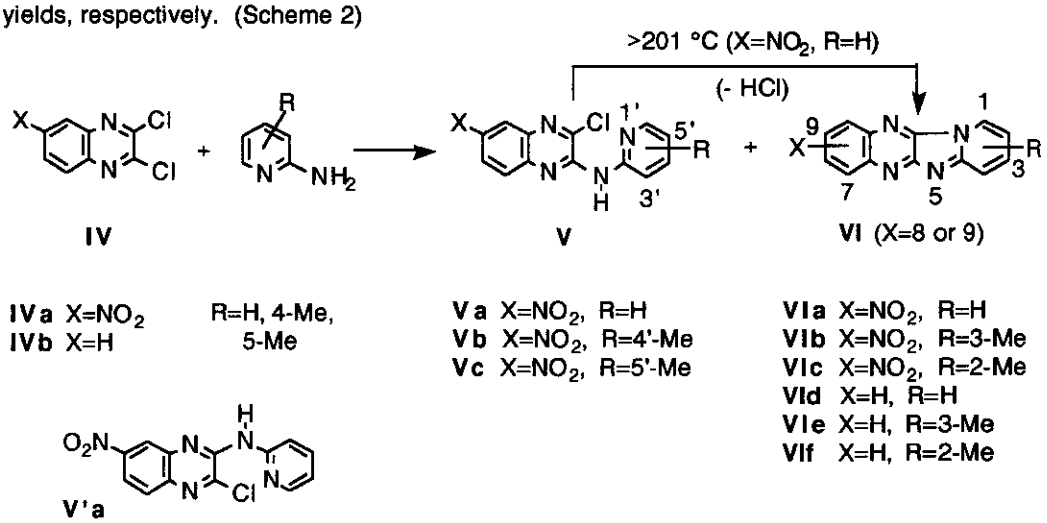
Ir spectrum of the product (**IIa**) shows absorption bands at 3360 and 2230 cm^{-1}, attributed to N-H and C=N stretching vibrations, respectively. ^1H Nmr spectrum shows the proton signals between 7.2 and 8.4 ppm similarly to those of 2-aminopyridine and a broad singlet at 8.5 ppm due to N-H proton. The possibility of the isomer (**II'a**) was ruled out by the fact that the proton signals of 1-substituted pyridine-2(1*H*)-imines usually appear at higher field than 7 ppm. Further, **IIa** was converted into pyridoimidazopyrazine (**IIIa**) in quantitative yield on heating over 135 °C, indicating that **IIa** obtained for the first time is the intermediate of pyridoimidazopyrazine (**IIIa**). The reaction of pyrazine (I) with other substituted 2-aminopyridines was carried out, and the results are summarized in Table 1. In two cases (R=3-Me and R=4-Me), the intermediate could not be isolated under the present conditions.

Table 1 Reaction of 2,3-Dichloro-5,6-dicyanopyrazine with Substituted 2-Aminopyridines

R[a]	Reaction time (h)	Product	Yield (%)	Mp (°C)	Product[b]	Yield (%)
H	4	IIa	23	135	IIIa	50
3-Me	5	—	—	—	IIIb	70
4-Me	4	—	—	—	IIIc	90
5-Me	4	IId	13	150	IIId	38
6-Me	21	IIe	14	160	IIIe	60

a) The substituents in 2-aminopyridines. b) The structure of compounds (**IIIa-e**) was identified by comparison with authentic samples.[3]

When 2,3-dichloro-6-nitroquinoxaline (**IVa**) was treated with 2-aminopyridine in dioxane under reflux for 6 h, a new compound, 2-(pyrid-2'-yl)amino-3-chloro-6-nitroquinoxaline (**Va**) and a mixture of 8-nitro- and 9-nitropyrido[1',2':1,2]imidazo[4,5-*b*]quinoxaline (**VIa**, in the ratio of 4:6) were obtained in 18 and 33% yields, respectively. (Scheme 2)



Scheme 2

The newly obtained product (**Va**) was found to be a single component from the fact that **Va** was converted into only the 9-nitro derivative in quantitative yield on heating over 201 °C. The structure of 9-nitro derivative was identified by comparison with an authentic sample prepared from 2-amino-3-chloro-6-nitroquinoxaline and pyridine.[6] Another intermediate (**V'a**), which would afford the 8-nitro derivative, could not be isolated in this reaction. The reaction of quinoxaline (**IVa**) with other substituted 2-aminopyridines was carried out, and the results are presented in Table 2.

Table 2 Reaction of 2,3-Dichloro-6-nitroquinoxaline with Substituted 2-Aminopyridines

X	R[a)]	Product	Yield (%)	Mp (°C)	Product[b)]	Yield (%)
NO_2	H	Va	18	201	VIa	33
	4-Me	Vb	23	179	VIb	35
	5-Me	Vc	9	182	VIc	18

a) The substituents in 2-aminopyridines. b) The structure of compounds (**VIa-c**) was identified by comparison with authentic samples.[6]

Improved Syntheses of Pyrido[1',2':1,2]imidazo[4,5-*b*]quinoxalines. A mixture of quinoxaline (**IVa**) and 2-aminopyridine was refluxed for 6 h in dioxane, and the solvent was evaporated

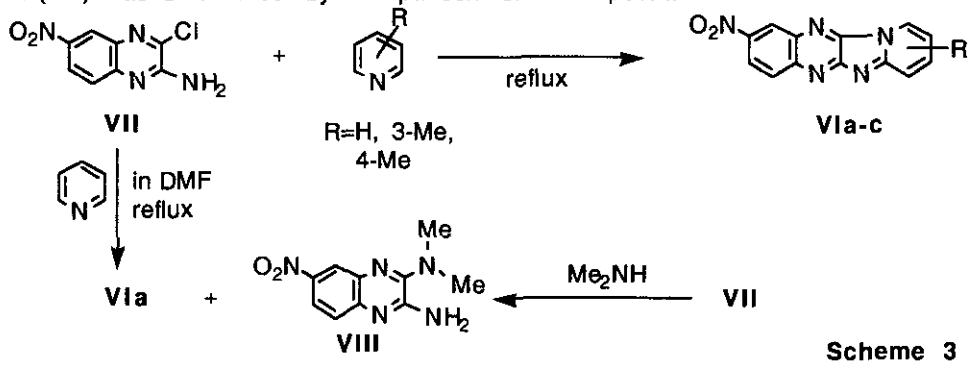
and then the residual solid was heated at 220 °C for 1 h without solvent to undergo the ring closure of the intermediate (**Va**) to give pyridoimidazoquinoxaline (**VIa**) in 85% yield. Heating at 220 °C results in the increase of the yield of **VIa** from 53% (33%+18%) up to 85%. Therefore an improved synthesis was achieved; quinoxaline (**IVa**) and 2-aminopyridine were homogenized well on a mortar, and then heated at 220 °C for 30 min without solvent to afford pyridoimidazoquinoxaline (**VIa**) in 80% yield. As a result, the yields of the desired products (**VIa-f**) remarkably increased compared with the previous method[6] as seen in Table 3.

Table 3 Improved Synthesis of Pyrido[1',2':1,2]imidazo[4,5-*b*]quinoxalines

			Yield (%)	
Compound	R[a)]	Product	The present method	The previous method[b)]
IVa	H	VIa	80	24
IVa	4-Me	VIb	90	45
IVa	5-Me	VIc	63	—
IVb	H	VId	15	3
IVb	4-Me	VIe	60	3
IVb	5-Me	VIf	47	5

a) The substituents in 2-aminopyridines. b) Ref. 6.

2,3-Dichloro-6-nitroquinoxaline (**IVa**) was treated with ammonium carbonate to give 2-amino-3-chloro-6-nitroquinoxaline (**VII**). The direction of the mono-amination was estimated by means of the MO calculation[6] and Eu(fod)$_3$ induced shift method. A mixture of quinoxaline (**VII**) and 3 equivalents of pyridine in DMF was refluxed for 12 h to afford 2-amino-3-dimethylamino-6-nitroquinoxaline (**VIII**) in 20% yield as well as the reported single isomer (**VIa**, 9-nitro). The structure of 3-dimethylamino derivative (**VIII**) was determined by comparison of the spectral data with those of a sample



Scheme 3

obtained separately from quinoxaline (**VII**) and dimethylamine. (Scheme 3) For suppression of the formation of 3-dimethylamino derivative (**VIII**), then pyridine was used as a reagent and a solvent in stead of DMF. This improved method results in an apparent increase of the yields of pyridoimidazoquinoxalines (**VIa-c**) as shown in Table 4.

Table 4 Improved Synthesis of Pyridoimidazoquinoxalines (**VIa-c**) from 2-Amino-3-chloro-6-nitroquinoxaline (**VII**)

R[a)]	Product	Yield (%) The present method	Yield (%) The previous method[b)]
H	VIa	75	51
4-Me	VIb	67	27
3-Me	VIc	51	42

a) The substituents in pyridines. b) Ref. 6.

EXPERIMENTAL

Melting points were recorded on a Mel-Temp apparatus in open capillaries and are uncorrected. Ir spectra were recorded on a JASCO A-100 Infrared Spectrophotometer. ^{1}H Nmr spectra were recorded on a JEOL GX-270 NMR Spectrometer in $CDCl_3$ and DMSO-d_6 and are reported in ppm (δ) downfield from internal Me_4Si. Thin layer chromatographic (tlc) analyses were performed on silica gel 60F-254 with a 0.2 mm layer thickness. Column chromatography was carried out with Merck Kieselgel 60 (230-400 mesh). Combusion analyses were performed on a Yanaco MT-3 CHN CORDER.

2,3-Dichloro-5,6-dicyanopyrazines (**I**) and 2,3-dichloroquinoxalines (**IVa,b**) were prepared according to the literature methods.[3,6]

General Procedure for Isolation of Intermediates (IIa, IId, and IIe): a Typical Example, 2-(Pyrid-2'-yl)amino-3-chloro-5,6-dicyanopyrazine (IIa): A mixture of 2,3-dichloro-5,6-dicyanopyrazine (**I**,1.03 g, 5 mmol) and 2-aminopyridine (1.41 g, 15 mmol) in dioxane (50 ml) was stirred for 4 h at room temperature. The resulting precipitate was filtered and then recrystallized from MeOH to give pyrido[1',2':1,2]imidazo[4,5-*b*]pyrazine (**IIIa**, 0.51 g, 50%) as pale yellow needles which was identical with an authentic sample.[6] The filtrate was carefully evaporated and the residue was chromatographed on silica gel with $CHCl_3$:acetone:EtOH (200:5:1 v/v) to give the product (**IIa**) (0.3 g, 23%); ir ($CHCl_3$) υ_{max}: 3360 and 2230 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 7.23 (1H, t, J=4.8 Hz), 7.85 (1H, t,

J=8.0 Hz), 8.28 (1H, d, J=8.0 Hz), 8.40 (1H, d, J=4.8 Hz), and 8.53 ppm (1H, br s). Anal. Calcd for $C_{11}H_5N_5Cl$: C, 51.34; H, 2.22; N, 32.61. Found: C, 51.46; H, 1.95; N, 32.75.

2-(5'-Methylpyrid-2'-yl)amino-3-chloro-4,6-dicyanopyrazine (IId): Similar reaction of compound (**I**) with 2-amino-5-methylpyridine gave the product (**IIId**) in 38% yield and the product (**IId**)[8] in 13% yield; ir ($CHCl_3$) υ_{max}: 3360 and 2230 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 2.40(3H, s), 7.68 (1H, d, J=2.2 and 8.5 Hz), 8.18 (1H, d, J=8.5 Hz), and 8.23 ppm (1H, d, J=2.2 Hz).

2-(6'-Methylpyrid-2'-yl)amino-3-chloro-5,6-dicyanopyrazine (IIe): Similar reaction of compound (**I**) with 2-amino-6-methylpyridine gave the product (**IIIe**) in 60% yield and the product (**IIe**)[8] in 14% yield; ir ($CHCl_3$) υ_{max}: 3370 and 2240 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 2.53 (3H, s), 7.06 (1H, d, J=8.4 Hz), 7.75 (1H, t, J=8.4 Hz), and 8.09 ppm (1H, d, J=8.4 Hz).

General Procedure for Isolation of Intermediates (Va-c): a Typical Example, 2-(Pyrid-2'-yl)amino-3-chloro-6-nitroquinoxaline (Va): A mixture of 2,3-dichloro-6-nitroquinoxaline (**IVa**, 2.42 g, 10 mmol) and 2-aminopyridine (2.82 g, 30 mmol) in dioxane (90 ml) was refluxed for 6 h. The resulting precipitate was filtered off, washed with hot water (1 l), and dried over anhydrous P_2O_5 for 3 h at 80 °C. The residual solid was chromatographed on silica gel with $CHCl_3$:acetone:EtOH (100:5:1 v/v) to give nitropyridoimidazoqinoxaline (**VIa**, R_f=0.2, 0.88 g, 33%) which was identical with an authentic sample[6] and the product (**Va**) (0.54 g, 18%); ir (KBr) υ_{max}: 3380, 1520, and 1345 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 7.23 (1H, dd, J=2.4 and 7.3 Hz), 7.95 (1H, dd, J=2.4 and 7.3 Hz), 8.01 (1H, d, J=9.2 Hz), 8.45-8.50 (2H, m), 8.46 (1H, dd, J=2.7 and 9.2 Hz), and 8.68 ppm (1H, d, J=2.7 Hz). Anal. Calcd for $C_{13}H_{18}N_5O_2Cl$: C, 51.76; H, 2.67; N, 23.22. Found: C, 51.46; H, 2.76; N, 23.06.

2-(4'-Methylpyrid-2'-yl)amino-3-chloro-6-nitroquinoxaline (Vb): Similar reaction of compound (**IVa**) with 2-amino-4-methylpyridine afforded the product (**VIb**) in 35 % yield and the product (**Vb**) in 23 % yield; ir (KBr) υ_{max}: 3370, 1515, and 1345 cm^{-1}; ^1H nmr (DMSO-d_6/$CDCl_3$) δ: 2.50 (3H, s), 6.98 (1H, d, J=5.1 Hz), 7.98 (1H, d, J= 9.1 Hz), 8.25 (1H, d, J=5.1 Hz), 8.48 (1H, dd, J=2.4 and 9.1 Hz), 8.58 (1H, s), and 8.79 ppm (1H, d, J=2.4 Hz). Anal. Calcd for $C_{14}H_{10}N_5O_2Cl$: C, 53.25; H, 3.17; N, 22.19. Found: C, 53.52; H, 3.22; N, 22.09.

2-(5'-Methylpyrid-2'-yl)amino-3-chloro-6-nitroquinoxaline (Vc): Similar reaction of compound (**IVa**) with 2-amino-5-methylpyridine afforded the product (**VIc**) in 18 % yield and the product (**Vc**) in 9 % yield; ir(KBr) υ_{max}: 3390, 1520, and 1345 cm^{-1}; ^1H nmr (DMSO-d_6/$CDCl_3$) δ: 2.37 (3H, s), 7.66 (1H, d, J=5.8 Hz), 7.94 (1H, d, J=7.4 Hz), 8.22 (1H, s), 8.46 (1H, d, J=7.4 Hz), 8.63 (1H, d, J=5.8 Hz), and 8.76 ppm (1H, s). Anal. Calcd for $C_{14}H_{10}N_5O_2Cl$: C, 53.25; H, 3.17; N, 22.19. Found: C, 53.41; H,

3.26; N, 22.35.

2-Amino-3-chloro-6-nitroquinoxalines (VII): Ammonium carbonate was used as the amination reagent instead of ammonia. To a solution of 2,3-dichloro-6-nitroquinoxaline (**IVa**, 1.22 g, 5 mmol) in DMF (50 ml) was added ammonium carbonate (30% as ammonia, 0.85 g, 15 mmol). The reaction mixture was stirred for 4 h at room temperature. After removal of DMF under reduced pressure, the crude product was recrystallized from acetone to give the product (**VII**) (0.52 g) in 46% yield; mp 285-287 °C (lit.,[6] mp 279-280 °C).

2-Amino-3-dimethylamino-6-nitroquinoxaline (VIII): A mixture of compound (**VII**) (0.5 g, 2.2 mmol) and pyridine (0.52 g, 6.6 mmol) in DMF (20 ml) was refluxed for 12 h. After evaporation of the solvent under reduced pressure, the residue was dissolved in $CHCl_3$ (200 ml). The organic phase was washed with H_2O (100 ml x 5), and dried over anhdrous Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel with $CHCl_3$:acetone:EtOH (200:5:1 v/v) to give compound (**VIa**) (R_f=0.13) in 22% yield and compound (**VIII**) (R_f=0.25, 0.15 g, 20%) as pale brown needles after recrystallization from MeOH; mp 228-232 °C; ir (KBr) υ_{max}: 3450, 1540, and 1330 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 3.00 (6H, s), 7.40 (2H, br s), 7.55 (1H, d, J=8.0 Hz), 8.00 (1H, d, J=8.0 Hz), and 8.30 ppm (1H, s). Anal. Calcd for $C_{10}H_{11}N_5O_2$: C, 51.50; H, 4.72; N, 30.04. Found: C, 51.66; H, 4.79; N, 29.81. This product (**VIII**) was identical with a sample obtained from 2-amino-3-chloro-6-nitroquinoxaline (**VII**) and dimethylamine in DMF.

Measurement of Eu(fod)$_3$ Induced Shift: To a solution of 2-amino-3-chloro-6-nitroquinoxaline (**VII**) (2 mg) in $CDCl_3$ (0.6 ml) was added Eu(fod)$_3$ (2 mg), and ^1H nmr was measured. The magnitude of the induced shift was in the order of 8-H>5-H=7-H.

Improved Syntheses of Pyrido[1',2':1.2]imidazo[4,5-*b*]quinoxalines: From the Reaction of 2,3-Dichloroqinoxalines and 2-Aminopyridines, A General Procedure: 2,3-Dichloroquinoxalines (**IV**, 1 mmol) and 2-aminopyridines (3 mmol) were homogenated on a mortar, and then heated at 220 °C for 30 min without solvent, while the vigorous evolution of HCl gas was observed. The residual solid was washed with hot water (300 ml) and then dried over anhydrous P_2O_5. The crude products were purified by column chromatography on silica gel with $CHCl_3$:acetone:EtOH (100:5:1 v/v). The yields of pyridoimidazoquinoxalines (**VI**) are presented in Table 3. In this reaction new compounds

(**VIc**), a mixture of 2-methyl-8-nitro- and -9-nitropyrido[1',2':1,2]imidazo[4,5-*b*]quinoxaline (4:6), were obtained in 63% yield; mp 319-322 °C (decomp.); ir υ_{max}(KBr) 1538 and 1344 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 2.45 (s, 1.8H), 2.55 (s, 1.2H), 7.75 (d, 0.4H, J=8.7 Hz), 7.83 (d, 0.6H, J=6.8 Hz), 7.87 (d, 0.4H, J=8.7 Hz), 7.96 (d, 0.6H, J=8.9 Hz), 8.42 (d, 0.6H, J=9.9 Hz), 8.44 (d, 0.4H, 9.2 Hz), 8.48 (dd, 0.4H, J=2.2 and 9.2 Hz), 8.57 (dd, 0.6H, J=2.8 and 9.9 Hz), 8.90-8.93 (m, 0.4H), 9.0-9.03 (m, 0.6H), 9.01 (d, 0.6H, J=2.2 Hz), and 9.06 ppm (d, 0.4H, J=2.8 Hz). Anal. Calcd for $C_{14}H_9N_5O_2 \cdot 0.2H_2O$: *C*, 59.57; H, 3.32; N, 24.77. Found: C, 59.77; H, 3.35; N, 24.63.

From the Reaction of 2-Amino-3-chloro-6-nitroquinoxaline and Pyridines; A general Procedure: A solution of compound (**VII**) (0.23 g, 1 mmol) in pyridines (10 ml) was refluxed for 12 h. After evaporation of the solvent, the residual solid was washed well with hot water (300 ml) and dried over anhydrous P_2O_5. The residue was chromatographed on silica gel with $CHCl_3$:acetone:EtOH (100:5:1 v/v) to give the pure products (**VI**). The yields of pyridoimidazoquinoxalines (**VI**) are presented in Table 4.

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8. Attempts to purify the intermediates (**IId**) and (**IIe**) by column chromatography or recrystallization were unsuccessful due to the partial ring closure to pyridoimidazopyrazines even at room temperature.

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