Imidazo[1,2-*a*]pyridines. II.[1] Ozonolysis of Imidazo[1,2-*a*]pyridines and Synthesis of Cardiotonic Agents[2]

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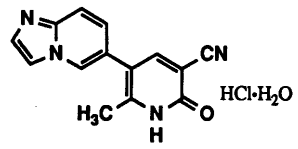
The metabolite of loprinone (E-1020) in dogs, 5-(2-aminopyridin-5-yl)-1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile (9), was prepared *via* ozonolysis of imidazo[1,2-*a*]pyridinylpyridines and evaluated for positive inotropic activity. Its potency was less than that of loprinone and milrinone. Among compounds related to loprinone which were synthesized using the versatile intermediates (10a, b) obtained during the preparation of 9, only 5-(2-aminoimidazo[1,2-*a*]pyridin-6-yl)-1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile (27) retained the activity of loprinone. The electron-withdrawing substituents at the 2-position of imidazo[1,2-*a*]pyridine reduced the activity of the parent compound. The ozonolysis of imidazo[1,2-*a*]pyridine derivatives under neutral conditions afforded 2-acylaminopyridine derivatives in a 30—55% yield independent of the substituents at the 2-position of imidazo[1,2-*a*]pyridine. It is possible to use imidazo[1,2-*a*]pyridines as protected 2-aminopyridines, and 2,3-unsubstituted imidazo[1,2-*a*]pyridines are convenient for that purpose from the viewpoint of ease of preparation of the starting material.

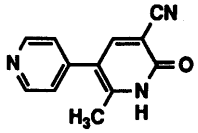
Keywords cardiotonic agent; positive inotropic activity; imidazo[1,2-*a*]pyridine; 5-imidazo[1,2-*a*]pyridinyl-2(1*H*)-pyridinone; loprinone; 5-(2-aminopyridin-5-yl)-2(1*H*)-pyridinone; structure–activity relationship; ozonolysis

Loprinone (E-1020, Chart 1) produced a dose-related intropic response with only a transient and slight increase in heart rate when administered intravenously to conscious dogs.[3] The drug is presently under development for the treatment of heart failure. It was shown in a pharmacokinetic study of loprinone in dogs that a small portion of 5-(2-aminopyridin-5-yl)-1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile (**9**) was detected in urine. During the early stage of our investigation, milrinone[4] (Chart 1) was reported to be a promising compound that possessed combined inotropic and vasodilator activities. Mechanistically, these drugs appear to drive their inotropic effects, at least in part, from selective inhibition of cyclic adenosine monophosphate (cAMP) specific phosphodiesterase (PDE III), resulting in an increase in cellular cAMP level. Since **9** structurally resembles milrinone, we intended to prepare it and evaluate its positive inotropic activity in dogs.

After several attempts, we found that ozonolysis of



loprinone (E-1020)



milrinone

Chart 1

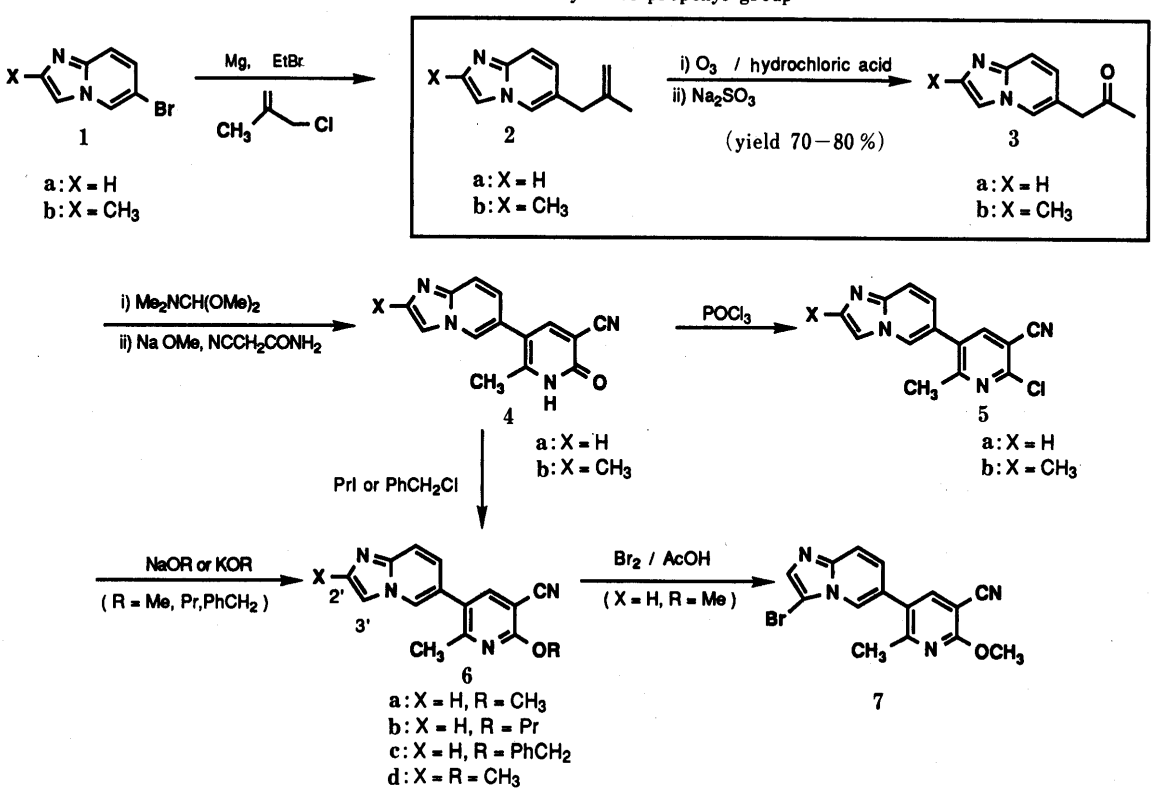


Chart 2

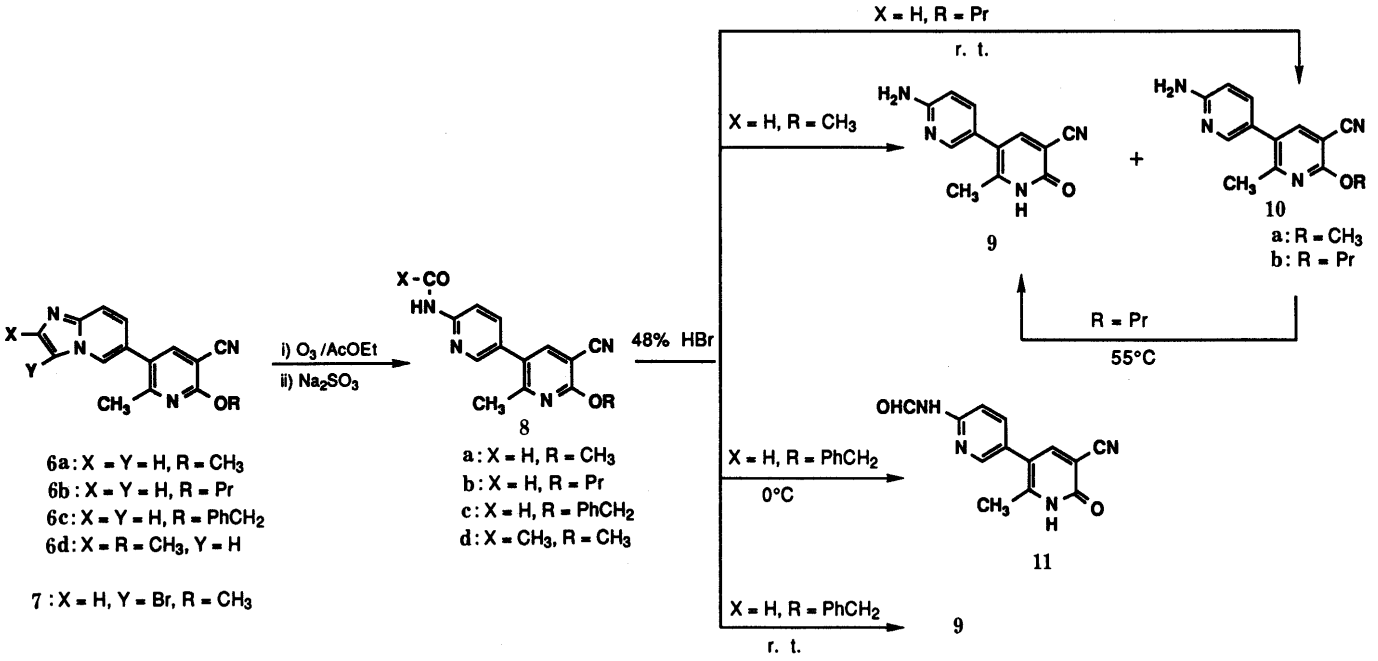


Chart 3

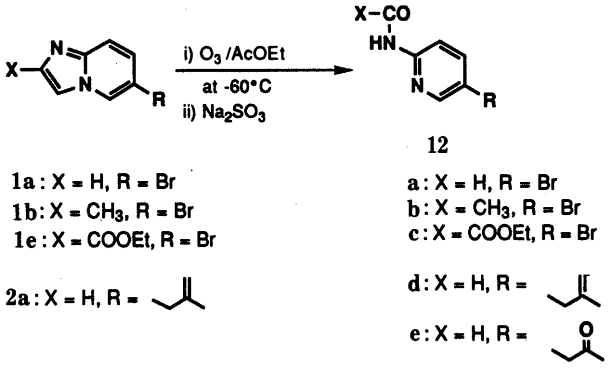


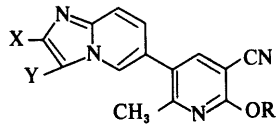
Chart 4

imidazo[1,2-*a*]pyridinylpyridines under neutral conditions, followed by reduction and hydrolysis, was an efficient method for the preparation of **9**. Namely, the imidazo[1,2-*a*]pyridine was used as the protected 2-aminopyridine. 2-Aminopyridinylpyridines **10a**, **c**, obtained during the preparation of this method, were attractive intermediate for the synthesis of compounds related to loprinone, which were difficult to synthesize by a previously reported method[1] *via* the Grignard cross-coupling reaction, *etc.* Those compounds contain suitable groups for the investigation of the effect of substituents at the carbon adjacent to heteroatom (nitrogen) which may act as a functional equivalent of a binding feature of the adenine fragment of the *anti* conformer of cAMP.[5]

In this paper, we describe the synthesis of the metabolite **9** and compounds to loprinone, and we also look at their cardiovascular profiles. In addition, we present which substituent is suitable for the ozonolysis of imidazo[1,2-*a*]pyridine ring and which is susceptible to ozonolysis, imidazole ring or vinyl group under neutral conditions.

Chemistry Imidazo[1,2-*a*]pyridinylpyridines required for the present study were prepared as shown in Chart 2. As mentioned in the preceding paper,[1] selective ozonolysis of the propenyl group of **2** occurred under acidic conditions,

TABLE I. Alkoxy and Benzyloxy Imidazo[1,2-*a*]pyridinylpyridines



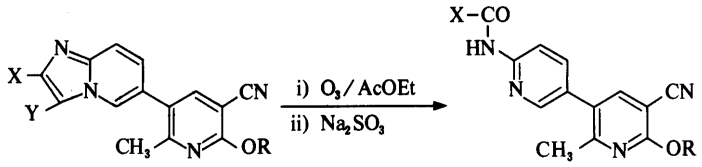
	X	Y	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
6a	H	H	CH_3	195—196	85	$C_{15}H_{12}N_4O$	68.16	4.59	21.20
							(68.38	4.55	20.95)
6b	H	H	Pr	119—121	85.5	$C_{17}H_{16}N_4O$	69.83	5.22	19.17
					43[a]		(69.89	5.51	19.29)
6c	H	H	CH_2Ph	153—154	88	$C_{21}H_{16}N_4O$	74.0	4.74	16.46
					46[a]		(74.18	4.93	16.44)
6d	CH_3	H	CH_3	231—215	92	$C_{16}H_{14}N_4O$ ·1/6H_2O	68.30 (68.52	5.14 5.14	19.92 19.89)
7	H	Br	CH_3	194—195	87	$C_{15}H_{11}BrN_4O$	52.49	3.24	16.33
							(52.53	3.26	16.15)

a) Prepared directly from **4**.

and successive reduction with Na_2SO_3 afforded **3a**, **b** in 70—80% yield. Treatment of **3a**, **b** with *N*,*N*-dimethylformamide (DMF) dimethylacetal followed by condensation with cyanoacetamide provided the pyridinones **4a**, **b**. Compounds **4a**, **b** were converted to chloropyridines **5a**, **b**, by treatment with $POCl_3$, which were then reacted with sodium alkoxide or potassium benzyloxide to yield **6a—d**. Compounds **6b**, **c** were also prepared direcly from **4a** by treatment with *n*-propyl iodide and benzyl bromide in the presence of K_2CO_3 in DMF in 43 and 46% yields, respectively. Treatment of **6a** with bromine in CH_2Cl_2 afforded **7**.

The ozonolysis of the imidazo[1,2-*a*]pyridine ring was carried out in AcOEt at varying temperatures; 0, −30, and −60 °C (Charts 3, 4). The amount of ozone consumed was not determined. The introduction of ozone was stopped when the color of the reaction mixture changed to bluish, or after a fixed period passed and the completion of the reac-

TABLE II. Ozonolysis of Imidazo[1,2-*a*]pyridinylpyridines



Run	Substrate				Reaction temp. (°C)	Product			Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
		X	Y	R			X	R				C	H	N
1	**6a**	H	H	CH_3	−60	**8a**	H	CH_3	39	235—237	$C_{14}H_{12}N_4O_2$	62.67	4.52	20.89
2					−30				48			(62.46	4.61	20.84)
3					0				37					
4	**6b**	H	H	Pr	−60	**8b**	H	Pr	35	167—169	$C_{16}H_{16}N_4O_2$	64.84	5.45	18.91
5					0				41			(64.68	5.48	18.91)
6	**6c**	H	H	CH_2Ph	−60	**8c**	H	CH_2Ph	42	201—203	$C_{20}H_{16}N_4O_2$	69.75	4.68	16.27
7					0				40			(69.46	4.74	16.17)
8	**6d**	CH_3	H	CH_3	0	**8d**	CH_3	CH_3	55	230—231	$C_{15}H_{14}N_4O_2$	63.80	5.01	19.85
												(63.60	4.98	19.99)
9	**7**	H	Br	CH_3	−60	**8a**	H	CH_3	13					
10					0				14					

TABLE III. Ozonolysis of Imidazo[1,2-*a*]pyridines

Run	Substrate			Product			Yield (%)	mp (°C)	Formula	Analysis (%) Calcd			Found		
		X	R		X	R				C	H	N	C	H	N
1	**1a**	H	Br	**12a**	H	Br	30	141—142	$C_6H_5BrN_2O$	35.85	2.51	13.94	35.87	2.59	14.08
2	**1b**	CH_3	Br	**12b**	CH_3	Br	37	174—175	$C_7H_7BrN_2O$	39.09	3.29	13.03	39.04	3.24	13.14
3	**1c**	COOEt	Br	**12c**	COOEt	Br	44	132—133	$C_9H_9BrN_2O_3$	39.58	3.33	10.26	39.60	3.26	10.29
4	**2a**	H		**12d**	H		8	79—80	$C_{10}H_{12}N_2O$	68.15	6.88	15.90	68.26	6.83	15.86
				12e	H		12	139—140	$C_9H_{10}N_2O_2$	60.65	5.67	15.72	60.65	5.68	15.62

TABLE IV. Hydrolysis of 5-(2-Formylaminopyridin-5-yl)pyridines

Run	Substrate	R	Conditions		Product	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
									C	H	N
1	**8a**	CH_3	r.t.	25 min	**9**	25	>300	$C_{12}H_{10}N_4O$	63.70	4.46	24.77
									(63.90	4.55	24.65)
					10a	59	199—200	$C_{13}H_{12}N_4O$	64.98	5.04	23.32
									(65.07	5.11	23.03)
2	**8a**	CH_3	r.t.	50 min	**9**	41					
					10a	34					
3	**8a**	CH_3	r.t.	150 min	**9**	83					
4	**8b**	Pr	r.t.	60 min	**10b**	71	117—119	$C_{15}H_{16}N_4O$	67.13	6.02	20.28
									(67.38	6.21	20.81)
5	**10b**	Pr	55 °C	190 min	**9**	79					
6	**8c**	CH_2Ph	0 °C	6 min	**11**	77	265—268	$C_{13}H_{10}N_4 \cdot 1/2H_2O$	59.30	4.22	21.29
									(59.47	4.22	21.18)
7	**8c**	CH_2Ph	r.t.	30 min	**9**	90					

tion was confirmed by thin layer chromatography (TLC). After expelling excess ozone by the introduction of N_2, Na_2SO_3 in H_2O was added. The ozonolysis of 2′,3′-unsubstituted imidazo[1,2-*a*]pyridinylpyridines **6a—c** produced 2-formylamino-5-pyridinylpyridines **8a—c**[6] in 30—50% yield independently of the reaction temperature. 2′-Methyl substituted derivative **6d** gave the acetylaminopyridine **8d** in 55% yield. In the case of the 3′-bromo derivative **7**, however, the reaction did not go smoothly and the yield of **8a** decreased (14%) (Table II). In the ozonolysis of simple imidazo[1,2-*a*]pyridines **1a, b, e**, 2-acylamino and 2-ethyl oxaloylaminopyridines were obtained in almost the same yield as **6a—d**. Compound **2a**, having a vinyl group, gave 2-formylamino-5-(2-methyl-3-propenyl)pyridine **12d** in ad-

dition to 1-(2-formylaminopyridin-5-yl)-2-propanone **12e**. Formation of **3a**, which was the main product from **2a** under acidic conditions, was not detected during the reaction. These results indicate that the 2,3-bond of imidazo[1,2-*a*]pyridine is more susceptible to ozone than the vinyl group (Chart 4 and Table III).

Hydrolysis of **8a—c** with 48% HBr afforded **9**, **10a**, **b** and **11** depending on the reaction time and temperature (Table IV). Treatment of **8a** at room temperature for 25 min gave **9** and **10a** in 25 and 59% yields, respectively, and for 150 min gave **9** in 83% yield. In the case of **8b**, treatment for 60 min gave **10b** in 71% yield, and formation of **9** from **10b** required higher temperature and a longer reaction time. On the other hand **8c** gave **11** in 86% yield by treatment at 0 °C for 6 min, while **9** was obtained in 77% yield at room temperature for 30 min.

The synthesis of the acetyl derivative (**13**) of **9** and compounds related to loprinone is outlined in Charts 5 and 6. Compounds **8a**, **c** were converted to **10a**, **c** by treatment with hydrazine hydrate in AcOH. Compound **13** was prepared by treatment of **10c** with acetic anhydride followed by hydrolysis at 0 °C with 48% HBr. Condensation of **10a** with 5-bromoacetyl-1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile[1] gave **14**, which on hydrolysis gave the bis(pyridinone) **15**. The reaction of **10a**, **c** with ethyl bromopyruvate in dimethoxyethane followed by refluxing in EtOH gave **16a** and **b**. Hydrolysis of **16b** with 48% HBr at 5 °C afforded the 2-ethoxycarbonylimidazo[1,2-*a*]-pyridinylpyridinone **19a**. On the other hand, **16a** was hydrolyzed with 1 N NaOH to the 2-imidazo[1,2-*a*]pyridinecarboxylic acid derivative, which was converted to the carbamoyl derivative **17** by treatment with of ethyl chloroformate followed by ammonia. Dehydration of **17** with trifluoroacetic anhydride provided the 2-imidazo[1,2-*a*]pyridinecarbonitrile **18**, which gave the dinitrile **19a** by treatment with 48% HBr. It was observed that the cyano group at the 2-position of imidazo[1,2-*a*]pyridine had a tendency to be more susceptible to hydrolysis under this condition than that on pyridine ring. That suceptibility caused the low yield of **19b**.

The 2-oxoimidazopyridine derivative **22** was prepared as follows. The bromoacetamide **20** obtained by treatment of **10c** with bromoacetyl bromide was converted to the 2,3-dihydro-2-oxoimidazo[1,2-*a*]pyridine **21** in an 80% yield by refluxing it in *n*-BuOH. Next, debenzylation was carried out by using 30% HBr–AcOH in order to obtain **22** as HBr salt.

2-Aminoimidazopyridine **27** was synthesized by using the procedure of Bochis *et al.*[7] Compound **10c** was reacted with *p*-toluenesulfonyl chloride to yield the sulfonamide **23**. Alkylation of **23** with 2-iodoacetamide afforded the carbamoylmethyl derivative **24** which was heated in trifluoroacetic anhydride under reflux to give the 2-trifluoroacetylaminoimidazo[1,2-*a*]pyridine derivative **25**. Hydrolysis of **25** with 2.5 N NaOH in MeOH at 50 °C gave the amino derivative **26**, which was converted to **27** with 30% HBr–AcOH.

Biological Results and Discussion Compounds **9**, **11**, **13** and the compounds in Table V were evaluated for inotropic activity intravenously in an acutely instrumented anesthetized dog model. The method was briefly reported in the previous paper.[1] Heart rate, myocardial contractility (derived by measuring d*P*/d*t* max of left venticular pressure), and systolic and diastolic blood pressure were recorded.

Cardiovascular data are summarized in Table VI.

Compound **9** produced dose-related increases in LVd*P*/d*t* max that were associated with increases in heart rate and decreases in blood pressure. Its potency was less than that of milrinone in spite of its structural resemblance. Robertson[8] reported that the presence and orientation of the

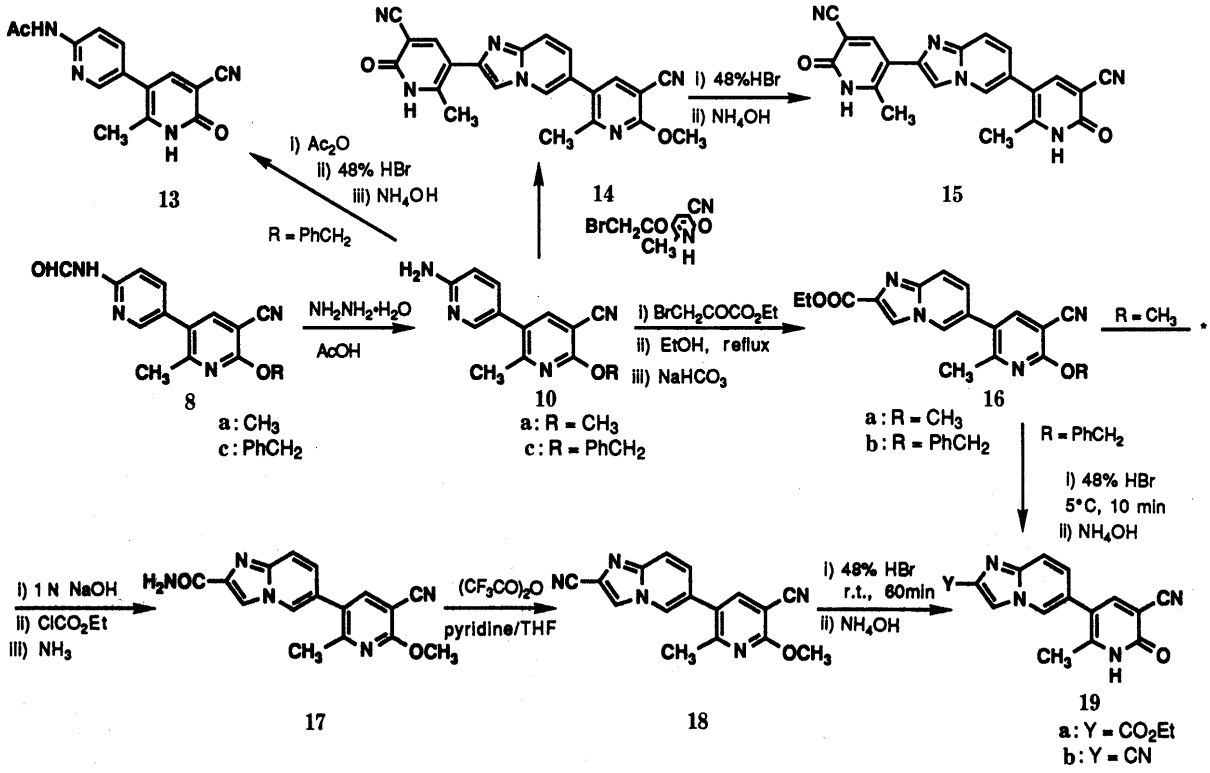


Chart 5

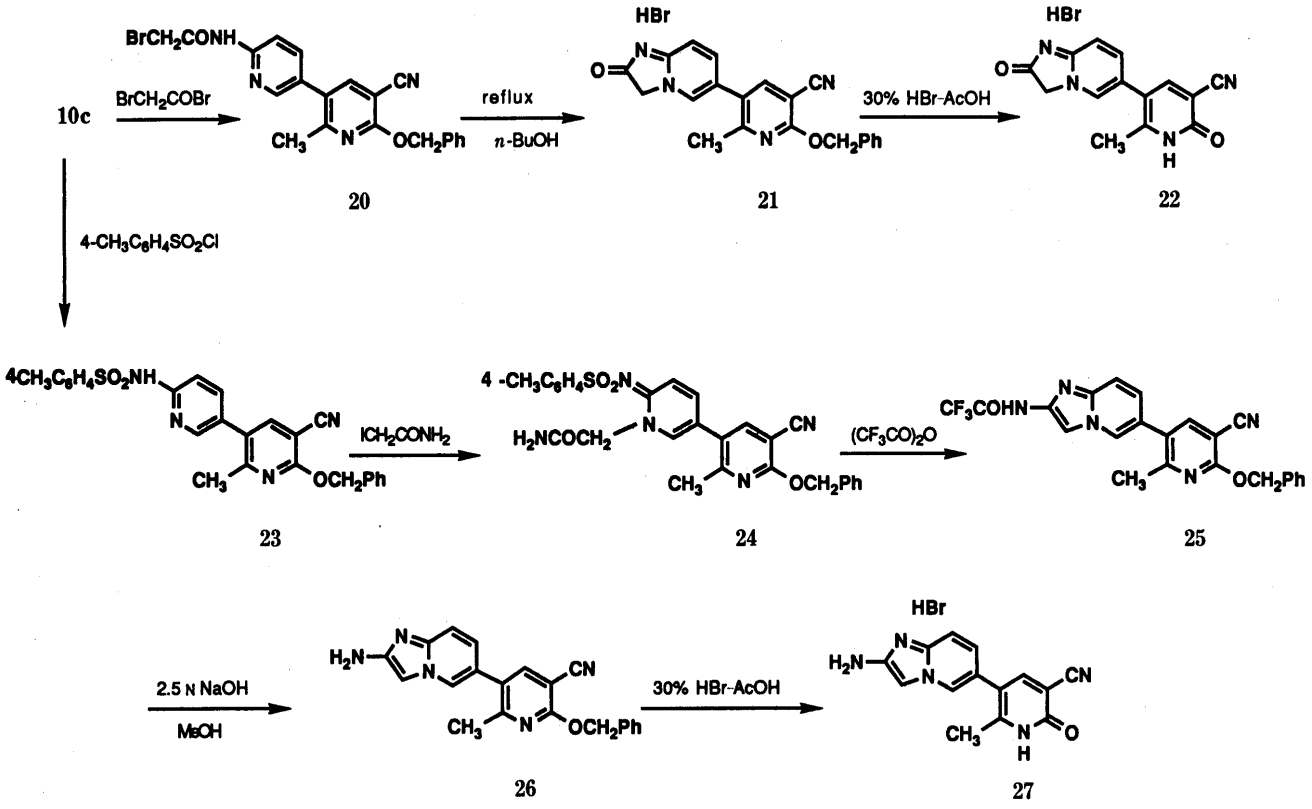
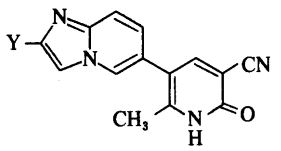


Chart 6

TABLE V. 5-Imidazo[1,2-*a*]pyridin-6-yl-2(1*H*)-pyridinones (**15**, **19a**, **b**, **22** and **27**)



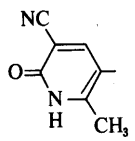
	Y	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
15		>300	57	$C_{21}H_{14}N_4O_2 \cdot 1/2H_2O$	64.43 (64.11)	3.90 (3.83)	21.48 (21.23)
19a	EtOOC	>300	60	$C_{17}H_{14}N_4O_3 \cdot HCl \cdot 1/6H_2O$	56.43 (56.27)	4.38 (4.23)	15.48 (15.32)
19b	NC	>300	6	$C_{15}H_9N_5O \cdot 1/6H_2O$	64.73 (64.87)	3.38 (3.57)	25.17 (24.83)
22	O= (2,3-Dihydro)	>300	47	$C_{14}H_{10}N_4O_2 \cdot HBr \cdot 4/3H_2O$	45.29 (45.40)	3.56 (3.60)	15.09 (14.77)
27	H_2N	>300	51	$C_{14}H_{11}N_5O \cdot HBr \cdot 3/2H_2O$	45.05 (45.43)	4.06 (3.85)	18.77 (18.39)

TABLE VI. Cardiovascular Profile of 2(1*H*)-Pyridinones in Anesthetized Dogs following i.v. Administration

Compd.	*n*[a]	Dose (mg/kg)	% change LVd*P*/d*t* max[b]	HR[c]	MAP[d]
9	4	0.100	42	15	−10
11	2	0.100	54	3	5
13	2	0.300	29	1	6
15	2	1.000	10	−5	−24
19a	2	1.000	23	0	−4
19b	2	0.100	32	11	−19
22	2	1.000	23	0	5
27	2	0.100	98	18	−12
28[e]	2	0.100	131	40	−21
Loprinone	6	0.100	99	28	−9
Milrinone	6	0.100	98	33	−18

a) Number of experiments. *b*) Maximum rate of rise in left ventricular pressure. *c*) Heart rate. *d*) Mean aortic pressure. *e*) 1,2-Dihydro-6-methyl-5-(2-methylimidazo[1,2-*a*]pyridin-6-yl)-2-oxo-3-pyridinecarbonitrile: Reference 1.

hydrogen-bond acceptor site appeared to be critical determinants of inotropic potency in dihydropyridazinone cardiotonics. A similar tendency was observed in a series of imidazo[1,2-*a*]pyridinylpyridinone cardiotonics.[1] 2-Aminopyridine has two nitrogens which may become hydrogen-bond acceptor sites. According to the calculation,[9] the nitrogen of the pyridine ring is more favorable to accepting a proton than that of amino group. Therefore, the lower potency of **9** than that of milrinone was presumably due to the improper orientation of its hydrogen-bond acceptor site. Robertson also reported that the introduction of an acetamido-like substituent into 6-phenyldihydropyridazinone provided potent cardiotonic activity owing to the newly-produced hydrogen-bond acceptor.[8,10] So we examined the inotropic activity of **11** and **13**, but the acyl groups in these compounds did not enhance the potency of **9**. This is probably due to the same reason mentioned above.

Among the imidazo[1,2-*a*]pyridines, compound **15** having a bis(pyridinone) group produced only vasodilator activity without any positive inotropic activity. Compounds **19a** and **b**, possessing electron-withdrawing groups at the 2-position of imidazo[1,2-*a*]pyridines, showed reduced

activity of loprinone. Compound **22**, which is a cyclic analog of **13** and whose hydrogen-bond acceptor site may be proper, produced only a 23% increase in LV$dP/dt$ max at 1 mg/kg. On the other hand, compound **27**, possessing an electron-donating group, was equipotent with the parent compound. 2-Methylimidazo[1,2-*a*]pyridine derivative **28**[1)] also retained the potency of loprinone. These results suggest that electron-donating groups as substituents adjacent to the hydrogen-bond acceptor site are favorable for positive inotropic activity in pyridinone cardiotonics, although an electron-withdrawing group (CN) was reported to also be acceptable in quinolinone cardiotonics.[11)]

In conclusion, the activity of the metabolite **9** in dogs was less potent and did not contribute to that of loprinone. Compound **27** was as potent as loprinone among related compounds which were prepared *via* ozonolysis of 2',3'-unsubstituted imidazo[1,2-*a*]pyridinylpyridines.

Experimental

Melting points were determined on a Yamato Model MP 12 capillary melting point apparatus and are uncorrected. Proton-nuclear magnetic resonance (^{1}H-NMR) spectra were obtained on a Varian Unity 400 or a JEOL JNM-GX 400 or a JEOL FX-90Q spectrometer with tetramethylsilane as an internal standard. Medium pressure liquid chromatography (MPLC) was performed with a Yamazen YFLC-5404-FC system. Elemental analyses were within ±0.4% of the calculated values, except where noted otherwise.

2-Chloro-5-imidazo[1,2-*a*]pyridin-6-yl-6-methyl-3-pyridinecarbonitrile (5a) A suspension of **4a** (17.8 g, 0.071 mol) in $POCl_3$ (150 ml) and DMF (1.0 ml) was refluxed for 2 h. After excess $POCl_3$ was evaporated under reduced pressure, a 20% NaOH solution was added to the residue under ice cooling until the pH of the solution was adjusted to 6. Then the solution was adjusted to pH 8 with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was separated, washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by silica-gel column chromatography (CH_2Cl_2 : MeOH = 98 : 2) to afford 11 g (58%) of **5a**, mp 185—186 °C. *Anal.* Calcd for $C_{14}H_9ClN_4$: C, 62.57; H, 3.38; N, 20.85. Found: C, 62.85; H, 3.50; N, 20.49. ^{1}H-NMR ($CDCl_3$, 90 MHz): 2.60 (3H, s, CH_3), 7.08 (1H, dd, J=2, 10 Hz, 7-H of imidazo[1,2-*a*]pyridine (IM)), 7.68, 7.72 (each 1H, each s, 2 and 3-H of IM), 7.74 (1H, d, J=10 Hz, 8-H of IM), 7.86 (1H, s, 4-H of pyridine (PN)), 8.16 (1H, br s, 5-H of IM). Compound **5b** was prepared similarly. **5b**: 37% yield, mp 158—159 °C. *Anal.* Calcd for $C_{15}H_{11}ClN_4$: C, 63.71; H, 3.93; N, 19.82. Found: C, 63.64; H, 4.05; N, 19.80. ^{1}H-NMR ($CDCl_3$, 90 HMz): 2.48 (3H, s, CH_3 of IM), 2.56 (3H, s, CH_3 of PN), 6.94 (1H, dd, J=2, 10 Hz, 7-H of IM), 7.34 (1H, s, 3-H of IM), 7.52 (1H, d, J=10 Hz, 8-H of IM), 7.78 (1H, s, 4-H of PN), 7.94 (1H, br s, 5-H of IM).

5-Imidazo[1,2-*a*]pyridin-6-yl-2-methoxy-6-methyl-3-pyridinecarbonitrile (6a) A solution of **5a** (7.8 g, 29 mmol) and 28% NaOMe in MeOH (11.2 ml, 58 mmol) in MeOH (100 ml) was refluxed for 4 h. The reaction mixture was then cooled and poured into cold water (1 l). The resulting precipitates were collected by filtration, washed with water and recrystallized from MeOH to give 6.5 g (85%) of **6a**, mp 195—196 °C. *Anal.* Calcd for $C_{15}H_{12}N_4O$: C, 68.16; H, 4.59; N, 21.20. Found: C, 68.38; H, 4.55; N, 20.95. ^{1}H-NMR ($CDCl_3$ 400 MHz): 2.41 (3H, s, CH_3), 4.10 (3H, s, OCH_3), 7.08 (1H, dd, J=1.8, 9.3 Hz, 7-H of IM), 7.65 (1H, dd, J=0.7, 1.3 Hz, 3-H of IM), 7.69 (1H, ddd, J=0.7, 0.9, 9.3 Hz, 8-H of IM), 7.73 (1H, d, J=1.3 Hz, 2-H of IM), 7.75 (1H, s, 4-H of PN), 8.07 (1H, dd, J=0.9, 1.8 Hz, 5-H of IM). Compound **6d** was prepared similarly, ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.48 (3H, s, CH_3), 2.49 (3H, s, CH_3), 4.09 (3H, s, OCH_3), 7.02 (1H, dd, J=1.8, 9.2 Hz, 6-H of IM), 7.39 (1H, d, J=0.7 Hz, 3-H of IM), 7.57 (1H, ddd, J=0.7, 0.9, 9.2 Hz, 8-H of IM), 7.73 (1H, s, 4-H of PN), 7.96 (1H, dd, J=0.9, 1.8 Hz, 5-H of IM). Compounds **6b, c** were prepared similarly by replacing NaOMe in MeOH with NaOPr in *n*-propanol, and $KOCH_2Ph$ prepared from benzylalcohol and potassium *tert*-butoxide in dimethoxyethane. They were purified by column chromatography on silica-gel and the results are listed in Table I. Compounds **6b, c** were also prepared as follows.

2-Benzyloxy-5-imidazo[1,2-*a*]pyridin-6-yl-6-methyl-3-pyridinecarbonitrile (6c) A solution of benzylbromide (3.66 g, 21.4 mmol) in DMF (5 ml) was added to the mixture of **4a** (5 g, 20 mmol) and K_2CO_3 (4.15 g, 30 mmol) in DMF (60 ml) with stirring below 5 °C, then the mixture was heated at 90 °C for 30 min. After removal of the solvent *in vacuo*, water (50 ml) and $CHCl_3$ (100 ml) were added to the residue. The organic layer was separated, washed with brine and dried over $MgSO_4$. After the solvent was evaporated under reduced pressure, the residue was purified by column chromatography on silica-gel with $CHCl_3$–MeOH (99 : 1) to give 3.1 g (46%) of **6c**, mp 153—154 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.50 (3H, s, CH_3), 5.56 (2H, s, CH_2), 7.07 (1H, dd, J=1.8, 9.3 Hz, 7-H of IM), 7.32—7.55 (5H, m, C_6H_5), 7.64 (1H, dd, J=0.7, 1.3 Hz, 3-H of IM), 7.69 (1H, ddd, J=0.7, 0.9, 9.3 Hz, 8-H of IM), 7.72 (1H, d, J=1.3 Hz, 2-H of IM), 7.75 (1H, s, 4-H of PN), 8.05 (1H, dd, J=0.9, 1.8 Hz, 5-H of IM). Compound **6b** was prepared similarly, ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.07 (3H, t, J=7.5 Hz, CH_3), 1.87 (2H, tq, J=6.6, 7.5 Hz, CH_2), 4.43 (2H, t, J=6.6 Hz, OCH_2), 7.08 (1H, dd, J=1.8, 9.3 Hz, 7-H of IM), 7.64 (1H, dd, J=0.7, 1.3 Hz, 3-H of IM), 7.69 (1H, ddd, J=0.7, 0.9, 9.3 Hz, 8-H of IM), 7.71 (1H, d, J=1.3 Hz, 2-H of IM), 7.73 (1H, s, 4-H of PN), 8.06 (1H, dd, J=0.9, 1.8 Hz, 5-H of IM).

5-(3-Bromoimidazo[1,2-*a*]pyridin-6-yl)-2-methoxy-6-methyl-3-pyridinecarbonitrile (7) To a solution of **6a** (2 g, 7.57 mmol) in CH_2Cl_2 (200 ml) was added dropwise a solution of bromine (1.42 g, 8.89 mmol) in CH_2Cl_2 (5 ml) at room temperature with stirring. After 10 min, the solution was washed with 10% K_2CO_3 solution and brine, and dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized from MeOH to give 2.25 g (86.5%) of **7**, mp 194—195 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.50 (3H, s, CH_3), 4.11 (3H, s, OCH_3), 7.16 (1H, dd, J=1.8, 9.2 Hz, 7-H of IM), 7.70 (1H, dd, J=1.1, 9.2 Hz, 8-H of IM), 7.71 (1H, s, 4-H of PN), 7.78 (1H, s, 2-H of IM), 8.03 (1H, dd, J=1.1, 1.8 Hz, 5-H of IM).

2-Benzyloxy-5-(2-formylaminopyridin-5-yl)-6-methyl-3-pyridinecarbonitrile (8c) (Ozonolysis of 6c, General Procedure) To a solution of **6c** (9 g, 26.44 mmol) in AcOEt (1000 ml) was introduced ozone produced by an ozone generator (Nihon Ozone 0-10-2 : O_2 flow 150 ml/h at 90 mV) at −60 °C for 15 min. After expelling excess ozone by introducing N_2, a solution of sodium sulfite (3.5 g) in H_2O (200 ml) was added. The organic layer was separated, washed with brine, and dried over $MgSO_4$. After removal of the solvent *in vacuo*, the residue was purified by MPLC on silica-gel with AcOEt–hexane (6 : 4) to afford 3.86 g (42%) of **8c**, mp 201—203 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.47 (3H, s, CH_3), 5.56 (2H, s, CH_2), 6.95, 8.31 (together 1H, each d, J=8.2 Hz, *exo* and *endo* 3'-H), 7.31—7.54 (5H, m, C_6H_5), 7.59, 7.66 (together 1H, each dd, J=2.4, 8.2 Hz, *exo* and *endo* 4'-H), 7.71 (1H, s, 4-H), 8.23 (1H, d, J=2.4 Hz, 6'-H). 8.30, 8.57 (together 1H, each d, J=1.3, 10.8 Hz, *endo* and *exo* NH), 8.53, 9.37 (together 1H, each d, J=1,3, 10.8 Hz, *endo* and *exo* CHO). Compounds **6a, b, d** and **7** were treated similarly at the fixed temperature and afforded **8a, b, d** and **8a**, respectively. These results are listed in Table II. ^{1}H-NMR of **8a** ($CDCl_3$, 400 MHz): 2.47 (3H, s, CH_3), 4.07 (3H, s, OCH_3), 6.90, 8.30 (together 1H, each d, J=8.8 Hz, *exo* and *endo* 3'-H), 7.60, 7.66 (together 1H, each dd, J=2.2, 8.8 Hz, *exo* and *endo* 4'-H), 7.69, 7.70 (together 1H, each s, *exo* and *endo* 4-H), 8.00, 8.05 (together 1H, each d, J=0.9, 10.8 Hz, *exo* and *endo* NH), 8.22, 8.23 (together 1H, each d, J=2.2 Hz, *exo* and *endo* 6'-H), 8.53, 9.36 (together 1H, each d, J=1.6, 10.8 Hz, *endo* and *exo* CHO).

^{1}H-NMR of **8b** ($CDCl_3$, 400 MHz): 1.07 (3H, t, J=7.5 Hz, CH_3), 1.87 (2H, tq, J=6.6, 7.7 Hz, CH_2), 4.43 (2H, t, J=6.6 Hz, OCH_2), 2.45 (3H, s, CH_3), 6.94, 8.30 (together 1H, each d, J=8.4 Hz, *exo* and *endo* 3'-H), 7.60 7.66 (together 1H, each dd, J=2.4, 8.4 Hz, *exo* and *endo* 4'-H), 7.68 (1H, s, 4-H), 8.15, 8.23 (together 1H, each d, J=0.9, 10.8 Hz, *endo* and *exo* NH), 8.53, 9.36 (together 1H, each d, J=0.9, 10.8 Hz, *endo* and *exo* CHO). ^{1}H-NMR of **8d** ($CDCl_3$, 400 MHz): 2.26 (3H, s, $COCH_3$), 2.47 (3H, s, CH_3), 4.09 (3H, s, OCH_3), 7.64 (1H, dd, J=2.4, 8.6 Hz, 4'-H), 7.69 (1H, s, 4-H), 8.10 (1H, br s, NH), 8.18 (1H, dd, J=0.5, 2.4 Hz, 6'-H), 8.30 (1H, d, J=8.6 Hz, 3'-H).

Ozonolysis of 6-(2-Methyl-2-propenyl)imidazo[1,2-*a*]pyridine (2a) To a solution of **2a** (2 g, 11.6 mmol) in AcOEt (100 ml) was introduced ozone (O_2 flow 100 ml/h at 95 mV) at −60 °C for 7 min. After expelling excess ozone by introducing N_2, a solution of sodium sulfite (1.5 g) in water (50 ml) was added. The organic layer was separated, washed with brine and dried over $MgSO_4$. After removal of the solvent, MPLC on silica-gel, eluting with AcOEt–MeOH (98 : 2), gave 0.14 g (7%) of 2-formylamino-5-(2-methyl-3-propenyl)pyridine **12d**, mp 79—80 °C. ^{1}H-NMR ($CDCl_3$–D_2O, 90 MHz): 1.68 (3H, s, CH_3), 3.24 (2H, s, CH_2), 4.28 (1H, s, =CH), 4.98 (1H, s, =CH), 6.76, 8.08 (together 1H, each d, J=9 Hz, *exo* and *endo* 3-H), 7.18—7.26 (1H, m, 4-H), 8.06 (1H, d, J=2 Hz, 6-H), 7.68 (1H, s, 4-H), 8.40, 9.16 (together 1H, each s, *endo* and *exo* CHO), and 0.24 g (12%) of 1-(2-formylaminopyridin-5-yl)-2-propanone **12e**, mp 139—140 °C. ^{1}H-NMR ($CDCl_3$–D_2O, 90 MHz): 2.20 (3H, s, CH_3), 3.68 (2H, s, CH_2), 6.82,

8.16 (together 1H, each d, J=9 Hz, *exo* and *endo* 3-H), 7.42—7.64 (1H, m, 4-H), 8.10 (1H, d, J=2 Hz, 6-H), 8.44, 9.24 (together 1H, each s, *endo* and *exo* CHO). Compounds **1a**—**c** were treated similarly and afforded **12a**—**c**. These results are listed in Table III.

Hydrolysis of 8c (General Procedure) 5-(2-Aminopyridin-5-yl)-1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile (9) A suspension of **8c** (0.2 g, 0.58 mmol) in 48% HBr (2 ml) was stirred at room temperature for 30 min, and then adjusted to pH 8 with 28% NH_4OH. The precipitates were collected by filtration, washed with water and recrystallized from DMF to give 0.11 g (84%) of **9**, mp > 300 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.22 (3H, s, CH_3), 6.04 (2H, s, NH_2), 6.45 (1H, d, J=8.4 Hz, 3'-H), 7.34 (1H, dd, J=2.4, 8.4 Hz, 4'-H), 7.84 (1H, d, J=2.4 Hz, 6'-H), 7.99 (1H, s, 4-H).

5-(2-Formylaminopyridin-5-yl)-1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile (11) A suspension of **8c** (0.3 g, 0.87 mmol) in 48% HBr (3 ml) was stirred at 0 °C for 6 min and then adjusted to pH 8 with 28% NH_4OH. The precipitates were collected by filtration, washed with water and recrystallized from MeOH to give 0.16 g (77%) of **11**, mp 265—268 °C (dec.). ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.24 (3H, s, CH_3), 6.96, 8.10 (together 1H, each d, J=8.6 Hz, *exo* and *endo* 3'-H), 7.77, 7.80 (together 1H, each d, J=8.6 Hz, *exo* and *endo* 4'-H), 8.09 (1H, s, 4-H), 8.23, 8.29 (together 1H, each s, 6'-H), 8.30, 9.29 (together 1H, s and d, J=10.2 Hz, *endo* and *exo* CHO), 10.67—10.71 (1H, br d, *exo* and *endo* NH), 12.73 (1H, br s, NH).

Hydrolysis of 8a: A suspension of **8a** (1.68 g, 6.26 mmol) in 48% HBr (16 ml) was stirred at room temperature for 25 min and adjusted to pH 8 with 28% NH_4OH. Then, CH_2Cl_2 was added to the solution. The organic layer was separated, washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by silica-gel column chromatography with AcOEt to give 0.84 g (59%) of 5-(2-aminopyridin-5-yl)-2-methoxy-6-methyl-3-pyridinecarbonitrile **10a**, mp 199—200 °C. ^{1}H-NMR ($CDCl_3$, 90 MHz): 2.42 (3H, s, CH_3), 4.02 (3H, s, OCH_3), 4.52 (2H, br s, NH_2), 6.50 (1H, d, J=9 Hz, 3'-H), 7.26 (1H, dd, J=2, 9 Hz, 4'-H), 7.56 (1H, s, 4-H), 7.90 (1H, d, J=2 Hz, 6'-H). In addition, the precipitate separated from the aqueous layer on standing was collected by filtration, washed with water and dried to give 0.35 g (25%) of **9**. The results of the treatment of **8a**, **b** and **10b** with 48% HBr for a longer time were listed in Table IV. ^{1}H-NMR ($CDCl_3$, 90 MHz) of **10b**: 1.06 (3H, t, J=7 Hz, CH_3), 1.86 (2H, sextet, J=7 Hz, CH_2), 2.44 (3H, s, CH_3), 4.40 (2H, t, J=7 Hz, OCH_2), 4.64 (2H, br s, NH_2), 6.58 (1H, d, J=9 Hz, 3'-H), 7.36 (1H, dd, J=2, 9 Hz, 4'-H), 7.64 (1H, s, 4-H), 7.98 (1H, d, J=2 Hz, 6'-H).

5-(2-Aminopyridin-5-yl)-2-benzyloxy-6-methyl-3-pyridinecarbonitrile (10c) A mixture of **8c** (1.74 g, 5 mmol) and 80% $NH_2NH_2 \cdot H_2O$ (1.3 ml) in AcOH (25 ml) was heated at 100 °C for 2 h. The cooled solution was adjusted to pH 8 with 28% NH_4OH and extracted with CH_2Cl_2. The extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by MPLC on silica-gel with $CHCl_3$–MeOH (98:2) to give 1.35 g (85%) of **10c**, mp 162—163 °C. *Anal.* Calcd for $C_{19}H_{16}N_4O$: C, 72.13; H, 5.10; N, 17.71. Found: C, 72.20; H, 5.27; N, 17.45. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.47 (3H, s, CH_3), 4.60 (2H, s, NH_2), 5.54 (2H, s, CH_2), 6.57 (1H, dd, J=0.9, 8.6 Hz, 3'-H), 7.30—7.54 (6H, m, C_6H_5 and 4'-H), 7.67 (1H, s, 4-H), 7.98 (1H, dd, J=0.9, 2.4 Hz, 6'-H). Similar treatment of **8a** (3.3 g) gave 2.0 g (68%) of **10a**.

5-(2-Acetylaminopyridin-5-yl)-1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile (13) A solution of (0.54 g, 1.7 mmol), Ac_2O (0.5 ml, 4.9 mmol) in pyridine (5 ml) was heated at 45 °C for 4 h. After removal of the solvent *in vacuo*, saturated aqueous $NaHCO_3$ and CH_2Cl_2 were added to the residue. The organic layer was separated, washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from MeOH to give 0.53 g (87%) of 5-(2-acetylaminopyridin-5-yl)-2-benzyloxy-6-methyl-3-pyridinecarbonitrile, mp 157—158 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.25 (3H, s, $COCH_3$), 2.47 (3H, s, CH_3), 5.56 (2H, s, CH_2), 7.31—7.54 (5H, m, C_6H_5), 7.63 (1H, dd, J=2.4, 8.6 Hz, 4'-H), 7.70 (1H, s, 4-H), 8.13 (1H, br s, NH), 8.18 (1H, d, J=2.4 Hz, 6'-H) 8.29 (1H, d, J=8.6 Hz, 3'-H). To 48% HBr (4 ml) was added portionwise 5-(2-acetylamino-pyridin-5-yl)-2-benzyloxy-6-methyl-3-pyridinecarbonitrile (0.4 g, 1.12 mmol) at 0 °C and stirred for 5 min. After the reaction mixture was adjusted to pH 8 with 28% NH_4OH, the precipitates were collected by filtration, washed with water and EtOH, and recrystallized from DMF–MeOH to afford 0.2 g (67%) of **13**, mp > 300 °C. *Anal.* Calcd for $C_{14}H_{12}N_4O_2$: C, 62.67; H, 4.52; N, 20.89. Found: C, 62.49; H, 4.63, N, 20.75. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.09 (3H, s, $COCH_3$), 2.25 (3H, s, CH_3), 7.75 (1H, dd, J=2.4, 8.6 Hz, 4'-H), 8.08 (1H, d, J=8.6 Hz, 3'-H), 8.11 (1H, s, 4-H), 8.27 (1H, d, J=2.4 Hz, 6'-H), 10.57 (1H, s, NH), 12.54 (1H, br s, NH).

2,6-Bis(3-cyano-1,2-dihydro-6-methyl-2-oxopyridin-5-yl)imidazo[1,2-*a*]pyridine (15) To a boiling clean solution of 5-bromoacetyl-1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile[1] (0.53 g, 2.1 mmol) in acetonitrile (150 ml) was added portionwise **10a** (0.5 g, 2.1 mmol). After refluxing for 2.5 h, the precipitates were collected by filtration while hot and recrystallized from DMF to give 0.3 g (36%) of 5-[6-(3-cyano-2-methoxy-6-methylpyridin-5-yl)imidazo[1,2-*a*]pyridin-2-yl]-1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile **14**, mp > 300 °C. *Anal.* Calcd for $C_{22}H_{16}N_6O_2 \cdot 0.7H_2O$: C, 64.60; H, 4.30; N, 20.55. Found: C, 64.94; H, 4.30; N, 20.20. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.50 (3H, s, CH_3), 2.62 (3H, s, CH_3), 4.04 (3H, s, OCH_3), 7.35 (1H, dd, J=1.8, 9.3 Hz, 7-H of IM), 7.66 (1H, d, J=9.3 Hz, 8-H of IM), 8.17 (1H, s, 3-H of IM), 8.25 (1H, s, 4-H of PN), 8.52 (1H, s, 4-H of pyridinone (PNO)), 8.68 (1H, dd, J=0.9, 1.8 Hz, 5-H of IM), 12.60 (1H, br s, NH). A mixture of **14** (0.22 g, 0.56 mmol) in 48% HBr (4 ml) was stirred at room temperature for 2.5 h and was adjusted to pH 8 with 28% NH_4OH. The precipitates were collected by filtration, washed with water and recrystallized from DMF to afford 0.12 g (57%) of **15**, mp > 300 °C. ^{1}H-NMR (DMSO-d, 400 MHz): 2.30 (3H, s, CH_3 of PNO at 6-position of IM (6-PNO)), 2.62 (3H, s, CH_3 of 2-PNO), 7.29 (1H, dd, J=1.8, 9.3 Hz, 7-H of IM), 7.62 (1H, ddd, J=0.7, 1.8 9.3 Hz, 8-H of IM), 8.15 (1H, d, J=0.5 Hz, 3-H of IM), 8.18 (1H, s, 4-H of 6-PNO), 8.54 (1H, s, 4-H of 2-PNO), 8.57 (1H, dd, J=0.9, 1.8 Hz, 5-H of IM), 12.76 (1H, br s, NH), 12.80 (1H, br s, NH).

Ethyl 6-(3-Cyano-2-methoxy-6-methylpyridin-5-yl)-2-imidazo[1,2-*a*]-pyridinecarboxylate (16a) A solution of **10a** (1.8 g, 7.5 mmol) and ethylbromopyruvate (1.6 g, 8.2 mmol) in dimethoxyethane (25 ml) was stirred at room temperature for 2 h. The precipitates were collected by filtration and refluxed in EtOH (50 ml) for 3 h. After removal of the solvent, the residue was dissolved in water. The solution was adjusted to pH 8 with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$ and concentrated. The residue was washed with AcOEt to give 1.03 g (41%) of **16a**, mp 234—235 °C. *Anal.* Calcd for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79; N, 16.66. Found: C, 64.13; H, 4.67; N, 16.60. ^{1}H-NMR (DMSO-d_6, 90 MHz): 1.30 (3H, t, J=8 Hz, CH_3), 2.44 (3H, s, CH_3), 4.00 (3H, s, OCH_3), 4.28 (2H, q, J=8 Hz, CH_2), 7.34 (1H, dd, J=2, 9 Hz, 7-H of IM), 7.64 (1H, d, J=9 Hz, 8-H of IM), 8.16 (1H, s, 4-H of PN), 8.44 (1H, s, 3-H of IM), 8.56 (1H, br s, 5-H of IM). **16b** was prepared similarly in 43% yield after purification by silica-gel chromatography with CH_2Cl_2–MeOH (99:1), mp 198— 199 °C. *Anal.* Calcd for $C_{24}H_{20}N_4O_3$: C, 69.89; H, 4.89; N, 13.58. Found: C, 69.77; H, 4.99; N, 13.56. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.43 (3H, t, J=7.3 Hz, CH_3), 2.50 (3H, s, CH_3), 4.48 (2H, q, J=7.3 Hz, CH_2), 5.57 (2H, s, CH_2), 7.76 (1H, ddd, J=0.7, 0.9, 9.3 Hz, 8-H of IM), 7.76 (1H, s, 4-H of PN), 8.05 (1H, dd, J=0.9, 1.6 Hz, 5-H of IM), 8.23 (1H, d, J= 0.7 Hz, 3-H of IM).

6-(3-Cyano-2-methoxy-6-methylpyridin-5-yl)-2-imidazo[1,2-*a*]pyridinecarboxamide (17) A mixture of **16a** (1.02 g, 3 mmol), 1 N NaOH solution (9 ml) in EtOH (80 ml) was stirred at room temperature for 3h and 1 N HCl solution (8.9 ml) was added under cooling. The precipitates were collected by filtration, washed with cold water and dried to give 0.86 g (93%) of 6-(3-cyano-2-methoxy-6-methylpyridin-5-yl)-2-imidazo[1,2-*a*]-pyridinecarboxylic acid, mp 240—242 °C, which was without further purification. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.49 (3H, s, CH_3), 4.04 (3H, s, OCH_3), 7.43 (1H, dd, J=1.8, 9.3 Hz, 7-H of IM), 7.70 (1H, ddd, J=0.7, 0.9, 9.3 Hz, 8-H of IM), 8.26 (1H, s, 4-H of PN), 8.47 (1H, d, J=0.4 Hz, 3-H of IM), 8.66 (1H, dd, J=1.1, 1.8 Hz, 5-H of IM). Ethylchloroformate (0.3 g, 2.8 mmol) was added to a mixture of the acid (0.78 g, 2.5 mmol) and Et_3N (0.28 g, 2.8 mmol) in DMF (30 ml) at 0 °C. The reaction mixture was stirred at 0—5 °C for 50 min and then NH_3 was introduced at 0 °C. After stirring for 40 min at that temperature, DMF was removed *in vacuo*. To the residue was added water (120 ml) and the precipitates were collected by filtration, washed with water, dried and purified by silica-gel column chromatography with $CHCl_3$–MeOH (9:1) to afford 0.41 g (53%) of **17**, mp > 290 °C. Anal. Calcd for $C_{16}H_{13}N_5O_2$: C, 62.52; H, 4.27; N, 22.79. Found: C, 62.32; H, 4.40; N, 22.62. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.49 (3H, s, CH_3), 4.04 (3H, s, OCH_3), 7.42 (1H, dd, J=1.8, 9.3 Hz, 7-H of IM), 7.46 (1H, br s, NH), 7.67 (1H, ddd, J=0.7, 0.9, 9.3 Hz, 8-H of IM). 7.76 (1H, br s, NH), 8.26 (1H, s, 4-H of PN), 8.34 (1H, d, J=0.7 Hz, 3-H of IM), 8.68 (1H, dd, J=0.9, 1.8 Hz, 5-H of IM).

6-(3-Cyano-2-methoxy-6-methylpyridin-5-yl)-2-imidazo[1,2-*a*]pyridinecarbonitrile (18) To a mixture of **17** (0.12 g, 0.71 mmol) and pyridine (0.113 g, 1.43 mmol) in dioxane (15 ml) was added trifluoroacetic anhydride (0.45 g, 2.14 mmol). The mixture was stirred at room temperature for 2.5 d and concentrated. Ice and 28% NH_4OH were added to the residue,

which was extracted with $CHCl_3$, washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica-gel with CH_2Cl_2–MeOH (96:4) to give 0.14 g (71%) of **18**, mp 261—262 °C. *Anal.* Calcd for $C_{16}H_{11}N_5O \cdot 1/4H_2O$: C, 65.41; H, 3.95; N, 23.84. Found: C, 65.66; H, 3.95; N, 23.78. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.50 (3H, s, CH_3), 4.11 (3H, s, OCH_3), 7.26 (1H, dd, J=1.8, 9.3 Hz, 7-H of IM), 7.74 (1H, s, 4-H of PN), 7.74 (1H, ddd, J=0.7, 0.9, 9.3 Hz, 8-H of IM), 8.07 (1H, dd, J=0.9, 1.8 Hz, 5-H of IM), 8.10 (1H, d, J=0.7 Hz, 3-H of IM).

Ethyl 6-(3-Cyano-1,2-dihydro-6-methyl-2-oxopyridin-5-yl)-2-imidazo[1,2-*a*]pyridinecarboxylate Hydrochloride (19a) A suspension of **16b** (0.39 g, 0.95 mmol) in 48% HBr (8 ml) was stirred at 0 °C for 10 min and adjusted to pH 8 with 28% NH_4OH. The precipitates were collected by filtration, washed with water and EtOH, recrystallized from DMF and converted to HCl salt **19a** (0.2 g, 60%) by treatment of HCl–EtOH in DMF, mp > 300 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz): 1.33 (3H, t, J=7.1 Hz, CH_3), 2.30 (3H, s, CH_3), 4.37 (3H, q, 7.1 Hz, OCH_2), 7.70 (1H, d, J=9.3 Hz, 7-H of IM), 7.80 (1H, d, J=9.3 Hz, 8-H of IM), 8.17 (1H, s, 4-H of PN), 8.74 (1H, s, 3-H of IM), 8.79 (1H, s, 5-H of IM), 12.87 (1H, br s, NH).

6-(3-Cyano-1,2-dihydro-6-methyl-2-oxopyridin-5-yl)-2-imidazo[1,2-*a*]pyridinecarbonitrile (19b) A mixture of **18** (0.18 g, 0.62 mmol) in 48% HBr (4 ml) was stirred at room temperature for 1 h and adjusted to pH 8 with 28% NH_4OH. The precipitates were collected by filtration, washed with water and recrystallized from DMF–MeOH to give 10.5 mg (6%) of **19b**, mp > 300 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.31 (3H, s, CH_3), 7.49 (1H, dd, J=1.8, 9.3 Hz, 7-H of IM), 7.77 (1H, ddd, J=0.7, 0.9, 9.3 Hz, 8-H of IM), 8.18 (1H, s, 4-H of PN), 8.66 (1H, dd, J=0.9, 1.8 Hz, 5-H of IM), 8.76 (1H, d, J=0.7 Hz, 3-H of IM), 12.83 Hz (1H, br s, NH).

2-Benzyloxy-5-(2-bromoacetylaminopyridin-5-yl)-6-methyl-3-pyridinecarbonitrile (20) To a solution of **10c** (0.95 g, 3 mmol) and *N*,*N*-diisopropylethylamine (0.86 g, 6.65 mmol) in CH_2Cl_2 (50 ml) was added dropwise bromoacetylbromide (1.13 g, 5.6 mmol) at 0 °C. The reaction mixture was stirred for 2 h, then saturated aqueous $NaHCO_3$ was added. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified twice by MPLC on silica-gel with CH_2Cl_2–AcOEt (9:1) to give 0.8 g (61%) of **20**, mp 212—214 °C (dec.). *Anal.* Calcd for $C_{21}H_{17}BrN_4O_2$: C, 57.67; H, 3.93; N, 12.81. Found: C, 57.75; H, 3.91; N, 12.61. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.47 (3H, s, CH_3), 4.05 (2H, s, CH_2), 5.55 (2H, s, OCH_2), 7.30—7.53 (5H, m, C_6H_5), 7.66 (1H, dd, J=2.4, 8.6 Hz, 4′-H), 7.71 (1H, s, 4-H), 8.24 (1H, d, J=2.4 Hz, 6′-H), 8.27 (1H, d, J=8.6 Hz, 3′-H), 8.78 (1H, br s, NH).

2-Benzyloxy-5-(2,3-dihydro-2-oxoimidazo[1,2-*a*]pyridin-6-yl)-6-methyl-3-pyridinecarbonitrile Hydrobromide (21) A suspension of **20** (0.75 g, 1.71 mmol) in *n*-buthanol was heated at reflux for 30 min. After cooling, the precipitates, which were newly separated, were collected by filtration, washed with CH_2Cl_2 and dried to give 0.6 g (80%) of **21**, mp 242—244 °C (dec.). *Anal.* Calcd for $C_{21}H_{17}BrN_4O_2$: C, 57.76; H, 3.93; N, 12.81. Found: C, 57.59; H, 3.94; N, 12.58. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.48 (3H, s, CH_3), 5.25 (2H, s, CH_2), 5.55 (2H, s, OCH_2), 7.35—7.52 (5H, m, C_6H_5), 7.68 (1H, d, J=8.8 Hz, 8-H of IM), 8.27 (1H, s, 4-H of PN), 8.45 (1H, d, J=8.8 Hz, 7-H of IM), 8.91 (1H, s, 5-H of IM).

5-(2,3-Dihydro-2-oxoimidazo[1,2-*a*]pyridin-6-yl)-1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile Hydrobromide (22) A solution of **21** (0.13 g, 0.3 mmol) in 30% HBr–AcOH (1.5 ml) was stirred at 15 °C for 5 min. To the mixture was added diethyl ether (15 ml) and the precipitaes were collected by filtration and washed with diethyl ether. This hygroscopic solid was dissolved in EtOH. To the mixture was added diethyl ether and the precipitates were collected by filtration to give 48 mg (47%) of **22**. mp > 300 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.30 (3H, s, CH_3), 5.25 (2H, s, CH_2), 7.58 (1H, d, J=9.0 Hz, 8-H of IM), 8.18 (1H, s, 4-H of PNO), 8.38 (1H, dd, J=1.8, 9.0 Hz, 7-H of IM), 8.82 (1H, d, J=1.8 Hz, 5-H of IM), 12.94 (1H, br s, NH).

2-Benzyloxy-6-methyl-5-[2-(4-methylbenzenesulfonylamino)pyridin-5-yl]-3-pyridinecarbonitrile (23) A cooled solution of **10c** (5.0 g, 15.8 mmol) in pyridine (30 ml) was treated portionwise with *p*-toluenesulfonyl chloride (6 g, 31.6 mmol). The mixture was stirred at room temperature overnight. The reaction mixture was poured into cold water. The precipitates were collected by filtration, washed with water, dried and recrystallized from EtOH to afford 6.1 g (82%) of **23**, mp 184—185 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.41 (3H, s, CH_3), 2.45 (3H, s, CH_3), 5.53 (2H, s, CH_2), 7.47 (1H, dd, J=0.9, 8.8 Hz, 3′-H), 7.28, 7.80 (each 2H each, d, J=8.2 Hz, $SO_2C_6H_4$), 7.30—7.52 (5H, m, C_6H_5), 7.57 (1H, dd, J=2.4, 8.8 Hz, 4′-H), 7.64 (1H, s, 4-H of CN-substituted PN), 8.37 (1H, dd, J=0.9, 2.4 Hz, 6′-H), 11.60 (1H, s, NH).

2-Benzyloxy-[1-(carbamoylmethyl)-1,2-dihydro-2-(4-methylbenzenesulfonylamino)pyridin-5-yl]-6-methyl-3-pyridinecarbonitrile (24) To a suspension of a 60% NaH oil dispersion (0.13 g, 3.25 mmol) in dry DMF (15 ml) was added **23** (1.4 g, 2.97 mmol) portionwise. After the mixture was stirred at 60 °C for 30 min, 2-iodoacetamide (0.6 g, 3.24 mmol) was added in one portion. The reaction mixture was stirred at 60 °C for 2.5 h and then the solvent was evaporated *in vacuo*. To the residue was added water and the precipitates were collected by filtration, washed with water, dried and suspended in CH_2Cl_2. The precipitates were collected by filtration, and dried to give 1.1 g (70%) of **24**, mp 236—238 °C (dec.), which was used without further purification. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.33 (3H, s, CH_3), 2.47 (3H, s, CH_3), 4.83 (2H, s, NCH_2), 5.51 (2H, s, OCH_2), 7.28, 7.68 (each 2H each, d, J=8.2 Hz, $SO_2C_6H_4$), 7.31—7.50 (6H, m, C_6H_5 and NH), 7.38 (1H, d, J=9.5 Hz, 3′-H), 7.77 (1H, br s, NH), 7.84 (1H, dd, J=2.4, 9.5 Hz, 4′-H), 8.15 (1H, s, 4-H of CN-substituted PN), 8.17 (1H, d, J=2.4 Hz, 6′-H).

2-Benzyloxy-[2-(trifluoroacetylamino)imidazo[1,2-*a*]pyridin-6-yl]-6-methyl-3-pyridinecarbonitrile (25) A suspension of **24** (1 g, 1.9 mmol) in trifluoroacetic anhydride (50 ml) was heated at reflux for 5 h. The solid product was collected by filtration and recrystallized from MeOH to give 0.34 g (40%) of **25**, mp 249—250 °C. *Anal.* Calcd for $C_{23}H_{10}F_3N_5O_2$: C, 61.19; H, 3.58; N, 15.52. Found: C, 61.28; H, 3.73; N, 15.74. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.51 (3H, s, CH_3), 5.57 (2H, s, CH_2), 7.18 (1H, dd, J=1.8, 9.2 Hz, 7-H of IM), 7.32—7.54 (5H, m, C_6H_5), 7.56 (1H, d, J=9.2 Hz, 8-H of IM), 7.77 (1H, s, 4-H of PN), 8.07 (1H, dd, J=0.9, 1.8 Hz, 5-H of IM), 8.22 (1H, s, 3-H of IM), 11.06 (1H, s, NH).

5-(2-Aminoimidazo[1,2-*a*]pyridin-6-yl)-2-benzyloxy-6-methyl-3-pyridinecarbonitrile (26) A solution of **25** (0.31 g, 0.69 mmol) and 2.5 N NaOH (5 ml) in MeOH (40 ml) was stirred at 50 °C for 17 h. After removal of the solvent, the residue was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica-gel with CH_2Cl_2–MeOH (98:2) to afford 0.19 g (78%) of **26**, mp 150—152 °C. Anal. Calcd for $C_{21}H_{17}N_5 0.1/2H_2O$: C, 69.22; H, 4.98; N, 19.22. Found: C, 69.56, H, 4.93; N, 19.56. ^{1}H-NMR: ($CDCl_3$, 400 MHz): 2.48 (3H, s, CH_3), 5.55 (2H, s, CH_2), 6.95 (1H, d, J=0.4 Hz, 3-H of IM), 6.95 (1H, dd, J=0.9 Hz, 1.8 Hz, 7-H of IM), 7.31—7.54 (6H, m, C_6H_5 and 8-H of IM), 7.73 (1H, s, 4-H of PN), 7.84 (1H, dd, J=1.8, 9.2 Hz, 5-H of IM).

5-(2-Aminoimidazo[1,2-*a*]pyridin-6-yl)-1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile Hydrobromide (27) To a solution of **26** (0.11 g, 0.31 mmol) in MeOH (10 ml) was added 30% HBr–AcOH (3 ml) under cooling and the reaction mixture was stirred for 6 min at room temperature. The mixture was added to diethyl ether (150 ml), then the precipitates were collected by filtration and recrystallized from MeOH to give 60 mg (57%) of **27**, mp 226—230 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.27 (3H, s, CH_3), 7.18 (1H, s, 3-H of IM), 7.63 (1H, dd, J=1.6, 9.1 Hz, 7-H of IM), 7.66 (1H, dd, J=0.9, 9.1 Hz, 8-H of IM), 8.15 (1H, s, 4-H of PNO), 8.65 (1H, dd, J=0.9, 1.6 Hz, 5-H of IM), 12.85 (1H, s, NH).

References and Notes

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