Imidazo[1,2-*a*]pyridines. III.[1] Synthesis and Bradycardic Activity of New 5-Imidazo[1,2-*a*]pyridin-6-ylpyridine Derivatives

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Structural modification of the cardiotonic agent, loprinone (E-1020, 1), suggested by data that it has a less positive chronotropic effect than milrinone (15), led us to find novel bradycardic agents that were structurally different from homoveratryl amine derivatives. Alkyl-oxy, -thio, and -amino derivatives at the 2-position of the pyridine ring of 1 produced bradycardic activity without a significant effect on blood pressure and myocardial contractility. Aryloxy analogues also decreased heart rate, and members with an electron-withdrawing group at the ortho position of the phenyl ring showed higher activity. Replacement of the imidazo[1,2-*a*]pyridine with pyridine resulted in diminished activity. The mechanism of bradycardic activity of these compounds seems to be direct action on the sinus node.

Keywords bradycardic agent; negative chronotropic effect; imidazo[1,2-*a*]pyridine; 5-imidazo[1,2-*a*]pyridin-6-ylpyridine derivative; structure–activity relationship; loprinone; sinus node

The prevention of myocardial hypoxia by reducing cardiac oxygen consumption is one of the main principles in the treatment of coronary heart disease.[2] In this context, heart rate is known to be a major determinant of myocardial energy demand,[3] and drugs that decrease heart rate are thus expected to reduce myocardial oxygen consumption.[4]

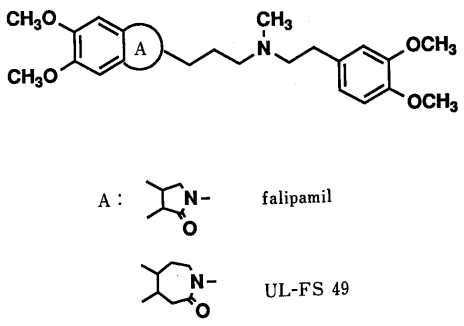


Chart 1

Although β-adrenoceptor antagonists[5] and calcium channel blockers[6] which induce bradycardia are frequently used in the treatment of ischemic heart disease, most of them may exert detrimental negative inotropic effects. Therefore, drugs that specifically decrease heart rate without affecting myocardial contractility are expected to be useful for the treatment of coronary heart disease. Homoveratrylamine derivatives[7] such as falipamil and UL-FS 49 are reported to exert specific bradicardic effects both in animal experiments and in a clinical setting.[8]

The purpose of the present study was to find selective bradycardic compounds with new chemical structures. Loprinone[9] (E-1020, **1**: a cardiotonic agent) was chosen as a lead compound for the following reasons. Although **1** had approximately the same potency in inhibiting phosphodiesterase III (PDE III) as milrinone[10] (**15**) *in vitro*, the positive chronotropic effect of **1** was less than that of milrinone in isolated guinea-pig atria.[11] Electrophysiological studies in isolated guinea-pig sinus nodes revealed

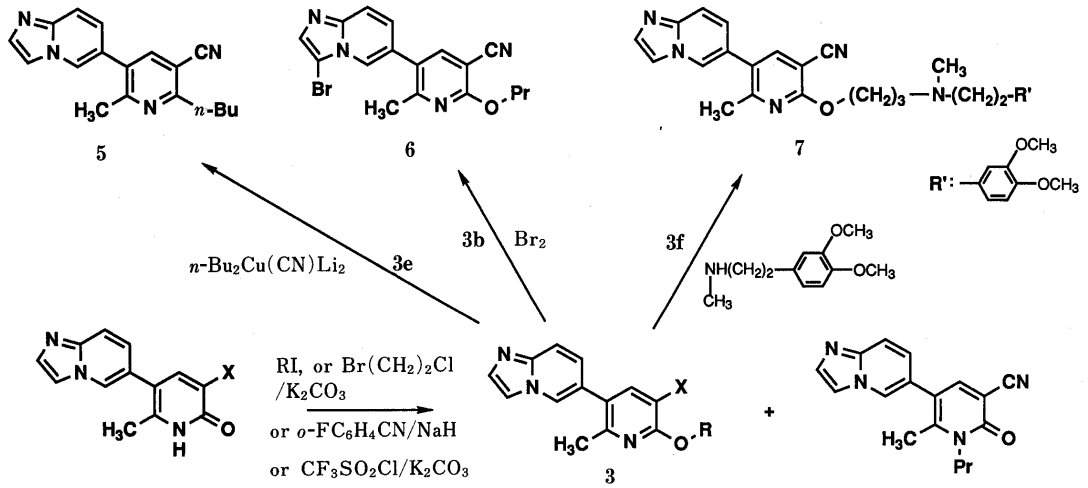


Chart 2

that **1** caused significantly less increase than milrinone in the slope of slow diastolic depolarization of nodal action potentials.[9] These results led us to postulate that **1** might have a bradicardic activity, which resulted in the suppression of the positive chronotropic effect induced by its inhibitory action of PDE III. We therefore thought that chemical modification of **1** might lead to a novel specific bradicardic agent. In this paper, we report the syntheses and bradycardic activities of 5-imidazo[1,2-*a*]pyridin-6-ylpyridine derivatives.

Chemistry The synthesis of most, but not all, compounds for this study follows basically the same pathway as that reported for **3b** and **9a** (Charts 2, 3) in our previous paper.[1] Treatment of loprinone (**1**) and **2**[9] with alkyl iodide and 1-bromo-3-chloropropane in the presence of K_2CO_3 in *N*,*N*-dimethylformamide (DMF) afforded *O*-alkyl derivatives **3a**—**c**, **f** as major products and *N*-alkyl derivatives (only the *N*-propyl derivative **4** of **1** shown) as minor products. Bromination of **3b** gave the 3-bromoimidazo[1,2-*a*]pyridine derivative **6**. Compound **3f** was reacted with *N*-methyl-2-(3,4-dimethoxyphenyl)ethylamine to give **7**. Compound **5** with directly connected *n*-butyl group was prepared by applying the method of McMurry *et al.*[12] Namely, pyridinyl triflate **3e**, obtained from **1** and trifluoromethanesulfonyl chloride, was treated with the higher mixed cuprate of Lipshutz[13] to give **5** in 16% yield. The other *O*-alkyl, *N*-alkyl and *O*-aryl derivatives were prepared *via* 2-chloropyridine **8**,[1] prepared from **1** and $POCl_3$. Treatment of **8** with sodium alkoxides, alkylamines, and sodium phenoxides afforded **9a**—**c**, **9d**—**f**, and **10a**—**h**, respectively. 2-Pyridinyloxy derivative **11** was also obtained as the major product by treatment of **8** with 2-hydroxypyridine in the presence of sodium hydride. On the other hand, compound **3d**, the product of decyanation of the pyridine ring of **10b**, was directly prepared by treatment of **2** with 2-fluorobenzonitrile in the presence of sodium hydride due to the poor reactivity of the decyanated derivative of **8**. *S*-Alkyl derivatives were prepared by alkylation of 1,2-dihydro-5-imidazo[1,2-*a*]pyridin-6-yl-6-methyl-2-thioxo-3-pyridinecarbonitrile **13** which was synthesized by reaction of **12**[9] with 2-cyanothioacetamide.[14] The derivatives, **17a**, **b** of milrinone (**15**) were prepared *via* the 2-chloro derivative **16**.

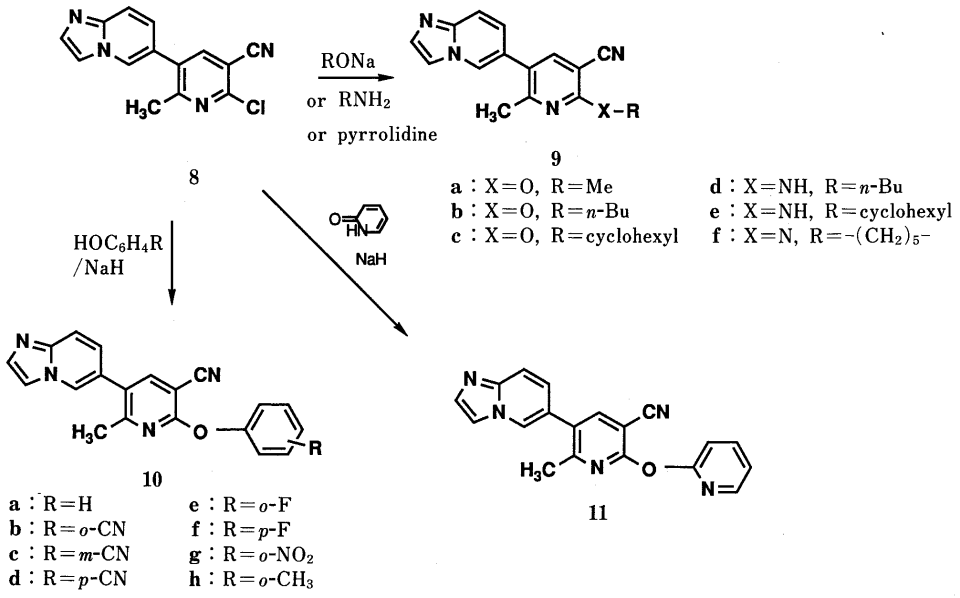


Chart 3

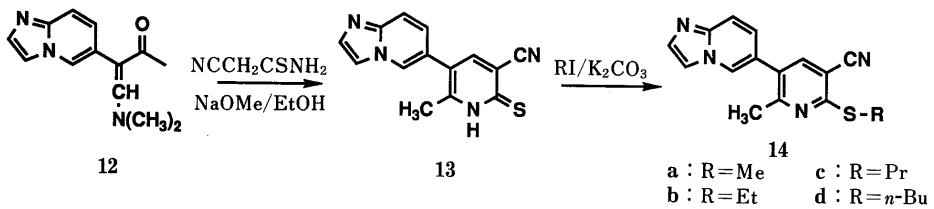


Chart 4

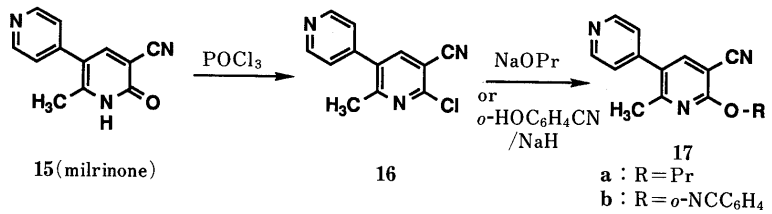
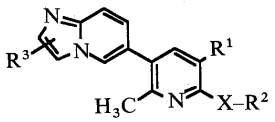


Chart 5

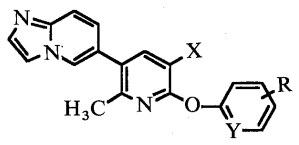
TABLE I. 5-Imidazo[1,2-*a*]pyridin-6-yl-pyridines (**3a—c**, **4—7**, **9a—f**, **14a—d**)



Compound No.	X	R^1	R^2	R^3	mp (°C)	Yield[a] (%)	Formula	Analysis (%) Calcd (Found)		
								C	H	N
3a	O	CN	Et	H	249—250	45	$C_{16}H_{14}N_4O \cdot HCl \cdot 1/6H_2O$	60.45 (60.43	4.55 4.81	17.63 17.37)
3b[1)]	O	CN	Pr	H	224 (dec.)	43	$C_{17}H_{16}N_4O \cdot HCl$	62.09 (61.72	5.22 5.01	17.04 16.99)
3c	O	H	Pr	H	104—106	48	$C_{16}H_{17}N_3O \cdot 1/2H_2O$	69.53 (69.37	6.58 6.23	15.20 14.96)
4	=O	CN	Pr[b]	H	194—195	11	$C_{17}H_{16}N_4O$	69.83 (69.77	5.53 5.68	19.17 18.90)
5	CH_2	CN	Pr	H	243—247 (dec.)	16	$C_{18}H_{18}N_4 \cdot HCl$	66.14 (66.21	5.87 6.12	17.15 17.16)
6	O	CN	Pr	3-Br	204—206	83	$C_{17}H_{15}BrN_4O \cdot HBr$	45.15 (45.22	3.57 3.55	12.39 12.24)
7	O	CN	A[c)]	H	216—218	32	$C_{28}H_{31}N_5O_3 \cdot 2HCl \cdot 1/2H_2O$	59.25 (59.00	6.05 5.90	12.34 12.21)
9a[1)]	O	CN	Me	H	195—196	85	$C_{15}H_{12}N_4O$	68.16 (68.38	4.59 4.55	21.20 20.95)
9b	O	CN	*n*-Bu	H	209—211 (dec.)	77	$C_{18}H_{18}N_4O \cdot HCl$	61.44 (61.52	5.74 5.68	15.93 16.01)
9c	O	CN	Cyclohexyl	H	270 (dec.)	73	$C_{20}H_{20}N_4O \cdot HCl$	65.11 (64.94	5.75 5.87	15.19 15.21)
9d	NH	CN	*n*-Bu	H	202—204	54	$C_{18}H_{19}N_5O \cdot HCl \cdot 1/2H_2O$	61.61 (61.41	6.04 6.02	19.96 19.91)
9e	NH	CN	Cyclohexyl	H	201—202 (dec.)	43	$C_{20}H_{21}N_5$	72.46 (72.33	6.40 6.38	21.13 20.98)
9f	N	CN	$-(CH_2)_5-$	H	122—124	44	$C_{19}H_{19}N_5$	71.89 (72.05	6.05 6.38	22.07 22.14)
14a	S	CN	Me	H	279—282 (dec.)	89	$C_{15}H_{12}N_4S \cdot HCl$	56.87 (56.77	4.14 4.05	17.68 17.68)
14b	S	CN	Et	H	261—263 (dec.)	60	$C_{16}H_{14}N_4S \cdot HCl$	58.09 (57.84	4.57 4.53	16.93 16.91)
14c	S	CN	Pr	H	268—270	44	$C_{17}H_{16}N_4S \cdot HCl$	66.20 (66.28	5.24 5.28	18.17 17.78)
14d	S	CN	*n*-Bu	H	227—229	79	$C_{18}H_{18}N_4S \cdot HCl \cdot H_2O$	57.36 (57.24	5.62 5.24	14.87 14.94)

a) Based on free base. Not optimized. *b*) N–Pr of pyridinone. *c*) A: -3-[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl.

TABLE II. 5-Imidazo[1,2-*a*]pyridin-6-yl-pyridines (**3d**, **10a—h**, **11**)



Compound No.	X	Y	R	mp (°C)	Yield[a] (%)	Formula	Analysis (%) Calcd			Found		
							C	H	N	C	H	N
3d	H	CH	*o*-CN	167.5—169.5	48	$C_{20}H_{14}N_4O$	73.60	4.33	17.17	73.57	4.46	17.05
10a	CN	CH	H	131—132 (dec.)	49	$C_{20}H_{14}N_4O \cdot 1/6H_2O$	72.92	4.37	17.01	72.97	4.56	16.75
10b	CN	CH	*o*-CN	>260 (dec.)	55	$C_{21}H_{13}N_5O \cdot HCl \cdot 1/4H_2O$	64.29	3.73	17.85	64.46	3.82	17.58
10c	CN	CH	*m*-CN	197—199	51	$C_{21}H_{13}N_5O \cdot 1/4H_2O$	70.86	3.97	19.68	71.03	4.12	19.48
10d	CN	CH	*p*-CN	119.5—121.5	46	$C_{21}H_{13}N_5O \cdot 1/3H_2O$	70.57	3.86	19.60	70.70	4.17	19.36
10e	CN	CH	*o*-F	149—151	33	$C_{20}H_{13}FN_4O$	69.75	3.81	16.27	69.89	3.98	16.22
10f	CN	CH	*p*-F	110—112	74	$C_{20}H_{13}FN_4O \cdot 1/6H_2O$	69.15	3.87	16.13	69.13	4.17	15.77
10g	CN	CH	*o*-NO_2	158—160	85	$C_{20}H_{13}N_5O_3$	64.69	3.53	18.86	64.98	3.62	18.66
10h	CN	CH	*o*-CH_3	273 (dec.)	56	$C_{21}H_{16}N_4O \cdot HCl$	66.92	4.55	14.87	66.81	4.61	15.12
11	CN	N	H	180—181	24	$C_{19}H_{13}N_5O$	69.70	4.01	21.40	69.70	4.09	21.21

a) Based on free base. Not optimized.

TABLE III. ^{1}H-NMR Spectra (400 MHz) of **3a—c**, **4—7**, **9b—f**, **10a—h**, **11**, **14a—d** and **17a—b**

Compd.	δ (ppm)
3a	(DMSO-d_6) 1.38 (3H, t, J=7.1 Hz, CH_3), 2.48 (3H, s, CH_3), 4.51 (2H, q, J=7.1 Hz, CH_2), 8.03 (1H, dd, J=1.5, 9.3 Hz, 7-H of IM), 8.06 (1H, dd, J=1.0, 9.3 Hz, 8-H of IM), 8.25 (1H, d, J=2.2 Hz, 3-H of IM), 8.27 (1H, s, 4-H of PN), 8.35 (1H, d, J=2.2 Hz, 2-H of IM), 9.03 (1H, dd, J=1.0, 1.5 Hz, 5-H of IM)
3b	(DMSO-d_6) 0.99 (3H, t, J=7.5 Hz, CH_3), 1.78 (2H, tq, J=6.5, 7.5 Hz, CH_2), 2.47 (3H, s, CH_3), 4.41 (2H, t, J=6.5 Hz, OCH_2), 8.00 (1H, dd, J=1.8, 9.5 Hz, 7-H of IM), 8.07 (1H, dd, J=1.1, 9.5 Hz, 8-H of IM), 8.24 (1H, d, J=2.2 Hz, 2-H of IM), 8.27 (1H, s, 4-H of PN), 8.37 (1H, d, J=2.2 Hz, 3-H of IM), 9.06 (1H, dd, J=1.1, 1.5 Hz, 5-H of IM)
3c	($CDCl_3$) 1.05 (3H, t, J=7.5 Hz, CH_3), 1.81 (2H, tq, J=6.8, 7.5 Hz, CH_2), 2.42 (3H, s, CH_3), 4.28 (2H, t, J=6.8 Hz, OCH_2), 6.63 (1H, d, J=8.4 Hz, 3-H of PN), 7.13 (1H, dd, J=1.8, 9.5 Hz, 7-H of IM), 7.44 (1H, d, J=8.4 Hz, 4-H of PN), 7.61 (1H, dd, J=0.7, 1.1 Hz, 3-H of IM), 7.66 (1H, ddd, J=0.7, 1.1, 9.3 Hz, 8-H of IM), 7.68 (1H, d, J=1.1 Hz, 2-H of IM), 8.03 (1H, dd, J=1.1, 1.7 Hz, 5-H of IM)
3d	($CDCl_3$) 2.36 (3H, s, CH_3), 6.96 (1H, dd, J=0.7, 8.2 Hz, 3-H of PN), 7.14 (1H, dd, J=1.8, 9.5 Hz, 7-H of IM), 7.30 (1H, ddd, J=0.9, 7.5, 8.6 Hz, 4-H of Ph), 7.34 (1H, ddd, J=0.7, 1.1, 8.4 Hz, 6-H of Ph), 7.62 (1H, d, J=8.2 Hz, 4-H of PN), 7.63 (1H, ddd, J=1.8, 7.5, 8.6 Hz, 5-H of Ph), 7.63 (1H, dd, J=0.7, 1.3 Hz, 3-H of IM), 7.68 (1H, ddd, J=0.7, 1.1, 9.5 Hz, 8-H of IM), 7.70 (1H, d, J=1.3 Hz, 2-H of IM), 7.71 (1H, dd, J=0.9, 7.5 Hz, 3-H of Ph), 8.08 (1H, dd, J=1.1, 1.8 Hz, 5-H of IM)
4	($CDCl_3$) 1.05 (3H, t, J=7.5 Hz, CH_3), 1.78 (2H, tq, J=7.5, 7.8 Hz, CH_2), 2.44 (3H, s, CH_3), 4.11 (2H, t, J=7.8 Hz, NCH_2), 7.00 (1H, dd, J=1.8, 9.2 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, 9.2 Hz, 8-H of IM), 7.71 (1H, s, 4-H of PN), 7.72 (1H, d, J=1.3 Hz, 2-H of IM), 8.08 (1H, dd, J=0.9, 1.8 Hz, 5-H of IM)
5	(DMSO-d_6) 0.93 (3H, t, J=7.3 Hz, CH_3), 1.38 (2H, tq, J=7.3, 7.8 Hz, CH_2), 1.73 (2H, tt, J=7.3, 7.8 Hz, CH_2), 2.53 (3H, s, CH_3), 2.96 (2H, t, J=7.8 Hz, CH_2), 7.97 (1H, dd, J=1.4, 9.2 Hz, 7-H of IM), 8.02 (1H, ddd, J=0.6, 1.0, 9.2 Hz, 8-H of IM), 8.18 (1H, dd, J=0.6, 2.0 Hz, 3-H of IM), 8.24 (1H, s, 4-H of PN), 8.30 (1H, d, J=2.0 Hz, 2-H of IM), 9.02 (1H, dd, J=1.0, 1.4 Hz, 5-H of IM)
6	(DMSO-d_6) 0.99 (3H, t, J=7.5 Hz, CH_3), 1.78 (2H, tq, J=7.3, 7.5 Hz, CH_2), 2.44 (3H, s, CH_3), 4.41 (2H, t, J=6.6 Hz, OCH_2), 7.90 (1H, dd, J=1.6, 9.3 Hz, 7-H of IM), 7.99 (1H, dd, J=0.9, 9.3 Hz, 8-H of IM), 8.27 (1H, s, 4-H of PN), 8.35 (1H, s, 2-H of IM), 8.71 (1H, dd, J=0.9, 1.5 Hz, 5-H of IM)
7	(DMSO-d_6) 2.29 (2H, tt, J=6.2, 8.4 Hz, CH_2), 2.48 (3H, s, CH_3), 2.82 (3H, d, (addition of D_2O: s), NCH_3), 2.99 (2H, t, J=8.4 Hz, CH_2), 3.18—3.40 (4H, m, 2 × CH_2: after addition of D_2O), 3.70 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 4.54 (2H, t, J=6.2 Hz, OCH_2), 6.79 (1H, dd, J=1.6, 8.2 Hz, 6-H of Ph), 6.88 (1H, d, J=8.2 Hz, 5-H of Ph), 6.91 (1H, d, J=1.6 Hz, 2-H of Ph), 7.95 (1H, dd, J=1.6, 9.2 Hz, 7-H of IM), 8.03 (1H, dd, J=0.7, 9.2 Hz, 8-H of IM), 8.20 (1H, d, J=2.0 Hz, 2-H of IM), 8.30 (1H, s, 4-H of PN), 8.34 (1H, d, J=2.0 Hz, 3-H of IM), 9.03 (1H, dd, J=0.7, 1.6 Hz, 5-H of IM)
9b	(DMSO-d_6) 0.95 (3H, t, J=7.5 Hz, CH_3), 1.45 (2H, tq, J=7.3, 7.5 Hz, CH_2), 1.75 (2H, tt, J=6.5, 7.3 Hz, CH_2), 2.47 (3H, s, CH_3), 4.56 (2H, t, J=6.5 Hz, OCH_2), 7.99 (1H, dd, J=1.5, 9.1 Hz, 7-H of IM), 8.04 (1H, dd, J=1.0, 9.1 Hz, 8-H of IM), 8.23 (1H, d, J=2.0 Hz, 2-H of IM), 8.26 (1H, s, 4-H of PN), 8.35 (1H, d, J=2.0 Hz, 3-H of IM), 9.03 (1H, dd, J=1.0, 1.5 Hz, 5-H of IM)
9c	(DMSO-d_6) 1.32—1.98 (10H, m, cyclo-C_6H_{10}), 2.45 (3H, s, CH_3), 5.24 (1H, m, OCH), 7.93 (1H, dd, J=1.8, 9.3 Hz, 7-H of IM), 8.00 (1H, dd, J=0.9, 9.3 Hz, 8-H of IM), 8.17 (1H, d, J=1.7 Hz, 3-H of IM), 8.24 (1H, s, 4-H of PN), 8.29 (1H, d, J=1.7 Hz, 2-H of IM), 8.97 (1H, dd, J=0.9, 1.8 Hz, 5-H of IM)
9d	(DMSO-d_6) 0.90 (3H, t, J=7.3 Hz, CH_3), 1.32 (2H, tq, J=7.3, 7.5 Hz, CH_2), 1.54 (2H, tt, J=7.3, 7.5 Hz, CH_2), 2.36 (3H, s, CH_3), 3.42 (2H, br s, NCH_2), 7.32 (1H, br s, NH), 7.88 (1H, s, 4-H of PN) 8.00, 8.01 (2H, s, 7-, 8-H of IM), 8.23, 8.32 (each 1H, each d, J=2.0 Hz, 2-, 3-H of IM), 8.97 (1H, dd, J=1.1, 1.3 Hz, 5-H of IM)
9e	(DMSO-d_6) 1.20—2.11 (10H, m, cyclo-C_6H_{10}), 2.40 (3H, s, CH_3), 4.05—4.14 (1H, m, NCH), 5.02 (1H, d, J=7.7 Hz, NH), 7.07 (1H, dd, J=1.8, 9.3 Hz, 7-H of IM), 7.50 (1H, s, 4-H of PN), 7.61 (1H, dd, J=0.7, 1.3 Hz, 3-H of IM), 7.65 (1H, ddd, J=0.7, 1.1, 9.3 Hz, 8-H of IM), 7.69 (1H, d, J=1.3 Hz, 2-H of IM), 8.01 (1H, dd, J=1.1, 1.8 Hz, 5-H of IM)
9f	($CDCl_3$) 1.72 (6H, br s, J=7.5 Hz, 3 × CH_2), 2.41 (3H, s, CH_3), 3.76—3.86 (4H, br s, $N(CH_2)_2$), 7.08 (1H, dd, J=1.8, 9.3 Hz, 7-H of IM), 7.60 (1H, s, 4-H of PN), 7.62 (1H, dd, J=0.7, 1.1 Hz, 3-H of IM), 7.66 (1H, ddd, J=0.7, 1.1, 9.3 Hz, 8-H of IM), 7.69 (1H, d, J=1.1 Hz, 2-H of IM), 8.03 (1H, dd, J=1.1, 1.8 Hz, 5-H of IM)
10a	($CDCl_3$) 2.38 (3H, s, CH_3), 7.09 (1H, dd, J=1.7, 9.1 Hz, 7-H of IM), 7.21—7.47 (5H, m, C_6H_5), 7.65 (1H, dd, J=0.7, 1.1 Hz, 3-H of IM), 7.72 (1H, ddd, J=0.6, 1.1, 9.3 Hz, 8-H of IM), 7.73 (1H, d, J=1.3 Hz, 2-H of IM), 7.85 (1H, s, 4-H of PN), 8.08 (1H, dd, J=1.1, 1.7 Hz, 5-H of IM)
10b	(DMSO-d_6) 2.42 (3H, s, CH_3), 7.56 (1H, ddd, J=0.7, 7.7, 8.6 Hz, 4-H of Ph), 7.62 (1H, dd, J=0.7, 7.7 Hz, 6-H of Ph), 7.89 (1H, ddd, J=1.7, 7.7, 8.6 Hz, 5-H of Ph), 8.04 (1H, dd, J=1.7, 7.7 Hz, 3-H of Ph), 8.05 (1H, dd, J=1.7, 9.3 Hz, 7-H of IM), 8.09 (1H, dd, J=1.1, 9.3 Hz, 8-H of IM), 8.26 (1H, d, J=2.0 Hz, 2-H of IM), 8.38 (1H, d, J=2.0 Hz, 3-H of IM), 8.54 (1H, s, 4-H of PN), 9.10 (1H, dd, J=1.1, 1.7 Hz, 5-H of IM)
10c	($CDCl_3$) 2.41 (3H, s, CH_3), 7.09 (1H, dd, J=1.8, 9.3 Hz, 7-H of IM), 7.48—7.61 (4H, m, C_6H_4), 7.73 (1H, d, J=9.1 Hz, 8-H of IM), 7.74 (1H, s, 2-H of IM), 7.77 (1H, s, 3-H of IM), 7.91 (1H, s, 4-H of PN), 8.10 (1H, d, J=1.5 Hz, 5-H of IM)
10d	($CDCl_3$) 2.42 (3H, s, CH_3), 7.09 (1H, dd, J=1.8, 9.3 Hz, 7-H of IM), 7.38 (2H, d, J=8.8 Hz, 2-, 6-H of Ph), 7.66 (1H, dd, J=0.7, 1.1 Hz, 3-H of IM), 7.73 (1H, ddd, J=0.7, 1.1, 9.3 Hz, 8-H of IM), 7.74 (1H, d, J=1.3 Hz, 2-H of IM), 7.76 (2H, d, J=8.8 Hz, 3-, 5-H of Ph), 7.92 (1H, s, 4-H of PN), 8.10 (1H, dd, J=1.1, 1.8 Hz, 5-H of IM)
10e	($CDCl_3$) 2.36 (3H, s, CH_3), 7.08 (1H, dd, J=1.8, 9.3 Hz, 7-H of IM), 7.18—7.31 (4H, m, C_6H_4), 7.65 (1H, dd, J=0.5, 1.3 Hz, 3-H of IM), 7.70 (1H, ddd, J=0.5, 0.9, 9.3 Hz, 8-H of IM), 7.72 (1H, d, J=1.3 Hz, 2-H of IM), 7.87 (1H, s, 4-H of PN), 8.09 (1H, dd, J=0.9, 1.8 Hz, 5-H of IM)
10f	($CDCl_3$) 2.38 (3H, s, CH_3), 7.08 (1H, dd, J=1.8, 9.3 Hz, 7-H of IM), 7.10—7.21 (4H, m, C_6H_4), 7.65 (1H, dd, J=0.6, 1.3 Hz, 3-H of IM), 7.71 (1H, ddd, J=0.6, 0.9, 9.3 Hz, 8-H of IM), 7.72 (1H, d, J=1.3 Hz, 2-H of IM), 7.87 (1H, s, 4-H of PN), 8.08 (1H, dd, J=0.9, 1.8 Hz, 5-H of IM)
10g	($CDCl_3$) 2.29 (3H, s, CH_3), 7.06 (1H, dd, J=1.8, 9.3 Hz, 7-H of IM), 7.42 (1H, dd, J=1.3, 8.2 Hz, 6-H of Ph), 7.47 (1H, ddd, J=1.7, 7.8, 8.2 Hz, 4-H of Ph), 7.65 (1H, dd, J=0.6, 1.1 Hz, 3-H of IM), 7.70 (1H, ddd, J=0.6, 1.1, 9.3 Hz, 8-H of IM), 7.72 (1H, d, J=1.1 Hz, 2-H of IM), 7.75 (1H, ddd, J=1.7, 7.8, 8.2 Hz, 5-H of Ph), 7.90 (1H, s, 4-H of PN), 8.08 (1H, dd, J=1.1, 1.8 Hz, 5-H of IM), 8.17 (1H, dd, J=1.7, 8.2 Hz, 3-H of Ph)
10h	(DMSO-d_6) 2.30 (3H, s, CH_3), 7.18—7.38 (4H, m, C_6H_4), 8.00 (1H, dd, J=1.3, 9.3 Hz, 7-H of IM), 8.05 (1H, dd, J=0.5, 9.3 Hz, 8-H of IM), 8.22 (1H, d, J=2.0 Hz, 2-H of IM), 8.35 (1H, d, J=2.0 Hz, 3-H of IM), 8.44 (1H, s, 4-H of PN), 9.05 (1H, dd, J=0.5, 1.7 Hz, 5-H of IM)
11	($CDCl_3$) 2.46 (3H, s, CH_3), 7.11 (1H, dd, J=1.7, 9.3 Hz, 7-H of IM), 7.18—7.23 (2H, m, 2-, 4-H of 2-PN), 7.66 (1H, dd, J=0.5, 1.1 Hz, 3-H of IM), 7.72 (1H, ddd, J=0.5, 1.1, 9.3 Hz, 8-H of IM), 7.73 (1H, d, J=1.1 Hz, 2-H of IM), 7.85 (1H, ddd, J=1.7, 7.4, 9.3 Hz, 4-H of 2-PN), 7.91 (1H, s, 4-H of PN), 8.10 (1H, dd, J=1.1, 1.7 Hz, 5-H of IM), 8.31 (1H, ddd, J=0.7, 2.0, 4.9 Hz, 3-H of 2-PN)

TABLE III. (continued)

Compd.	δ (ppm)
14a	(DMSO-d_6) 2.55 (3H, s, CH_3), 2.66 (3H, s, SCH_3), 7.98 (1H, dd, J=1.4, 9.2 Hz, 7-H of IM), 8.03 (1H, d, J=9.2 Hz, 8-H of IM), 8.20 (1H br s, 2-H of IM), 8.22 (1H, s, 4-H of PN), 8.33 (1H, br s, 3-H of IM), 9.02 (1H, br s, 5-H of IM)
14b	(DMSO-d_6) 1.35 (3H, t, J=7.3 Hz, CH_3), 2.54 (3H, s, CH_3), 3.30 (2H, q, J=7.3 Hz, CH_2), 8.00 (1H, dd, J=1.6, 9.2 Hz, 7-H of IM), 8.04 (1H, ddd, J=0.6, 1.1, 9.3 Hz, 8-H of IM), 8.21 (1H, d, J=2.0 Hz, 2-H of IM), 8.21 (1H, s, 4-H of PN), 8.33 (1H, dd, J=0.6, 2.0 Hz, 3-H of IM), 9.30 (1H, dd, J=1.1, 1.6 Hz, 5-H of IM)
14c	(DMSO-d_6) 1.00 (3H, t, J=7.5 Hz, CH_3), 1.72 (2H, tq, J=7.1, 7.3 Hz, CH_2), 2.54 (3H, s, CH_3), 3.29 (2H, t, J=7.3 Hz, SCH_2), 7.99 (1H, d, J=9.3 Hz, 7-H of IM), 8.03 (1H, d, J=9.5 Hz, 8-H of IM), 8.20 (1H, d, J=1.7 Hz, 2-H of IM), 8.21 (1H, s, 4-H of PN), 8.32 (1H, d, J=1.7 Hz, 3-H of IM), 9.02 (1H, br s, 5-H of IM)
14d	(DMSO-d_6) 0.92 (3H, t, J=7.5 Hz, CH_3), 1.43 (2H, tq, J=7.3, 7.5 Hz, CH_2), 1.68 (2H, tt, J=7.3, 7.5 Hz, CH_2), 2.54 (3H, s, CH_3), 3.31 (2H, t, J=7.3 Hz, SCH_2), 8.00 (1H, d, J=9.3 Hz, 7-H of IM), 8.05 (1H, d, J=9.3 Hz, 8-H of IM), 8.21 (1H, s, 4-H of PN), 8.22 (1H, d, J=2.0 Hz, 2-H of IM), 8.34 (1H, d, J=2.0 Hz, 3-H of IM), 9.04 (1H, br s, 5-H of IM)
17a	(DMSO-d_6) 0.99 (3H, t, J=7.5 Hz, CH_3), 1.78 (2H, tq, J=6.6, 7.5 Hz, CH_2), 2.49 (3H, s, CH_3), 4.42 (2H, t, J=6.6 Hz, OCH_2), 8.00 (2H, d, J=6.6 Hz, 3-, 5-H of 4-PN), 8.34 (1H, s, 4-H of PN), 8.92 (2H, d, J=6.6 Hz, 2-, 6-H of 4-PN)
17b	($CDCl_3$) 2.35 (3H, s, CH_3), 7.24 (2H, dd, J=1.8, 6.2 Hz, 3-, 5-H of 4-PN), 7.35 (1H, dd, J=1.1, 8.4 Hz, 6-H of Ph), 7.41 (1H, ddd, J=1.1, 7.6, 7.7 Hz, 4-H of Ph), 7.71 (1H, ddd, J=1.6, 7.6, 8.4 Hz, 6-H of ph), 7.75 (1H, dd, J=1.6, 7.7 Hz, 3-H of Ph), 7.88 (1H, s, 4-H of PN), 8.73 (2H, dd, J=1.8, 4.4 Hz, 2-, 6-H of 4-PN)

The HCl salts were measured in DMSO-d_6 and free bases in $CDCl_3$. IM: imidazo[1,2-*a*]pyridine ring. PN: pyridine ring. 4-PN: pyridine ring connected at 4-position.

Biological Results and Discussion

The imidazo[1,2-*a*]pyridine derivatives in Tables I, II and the pyridines were evaluated for bradycardic, hypotensive and inotropic activities following intravenous administration in an acutely instrumented anesthetized dog model. The method is briefly reported in our previous paper.[9] The *in vitro* bradycardic effects of some compounds were also evaluated in isolated guinea-pig atria. The electrophysiological studies were performed on isolated guinea-pig sinus nodes and right ventricular papillary muscles. Cardiovascular data are summarized in Table IV. In this study the values of heart rate (HR), mean aortic blood pressure (MAP) and contractile force (CF) are the maximum changes for 10 min after administration.

In anesthetized dogs, bradycardic effects were observed depending on the number of alkyl carbons in the *O*- and *S*-alkyl groups at the 2-position of the pyridine ring of **1**. Methoxy derivative **9a** exerted positive chronotropic and inotropic effects. Ethoxy derivative **3a** slightly decreased the heart rate. The three carbon derivative **3b**, however, produced a definite dose-related decrease in heart rate without a significant effect on blood pressure and contractile force. The activity of *S*-alkyl derivatives appeared clearly from the ethyl derivative **14b**. *N*-Alkyl derivatives, **9d**—**f**, also decreased the heart rate. Bromination and decyanation of **3b** did not offer any advantage and only resulted in a decrease in bradycardic potency (**6**) and in an increase in heart rate (**3c**), respectively. Compound **5** in which the pyridine ring is connected directly with a *n*-butyl group showed bradycardic activity, though weak. On the other hand, the *N*-propyl derivative **4** which has a propyl group at the 1-position of the pyridinone ring showed only positive inotropic activity and did not give any decrease in heart rate. Compound **7** containing *N*-methylhomoveratryl amine as in falipamil and UL-FS 49 had no activity.

Interesting structure–activity relationships were observed with *O*-aryl derivatives. Phenoxy derivative **10a** had moderate activity. Introduction of electron-withdrawing groups into the *ortho* position of the phenyl group enhanced the activity of **10a**. *o*-Cyano and *o*-nitro derivatives (**10b**, **g**) produced potent activities without causing any change in blood pressure or contractile force. Above all, the introduction of a fluoro group resulted in the most potent compound **10e** in this series. Movement of these groups to the *meta* or *para* position resulted in reduced potency, and especially in the case of the cyano group, diminished the bradycardic activity (**10c**, **d**). Decyanation of the pyridine ring of **10b** resulted in the product (**3d**) which, like **3c**, did not decrease heart rate.

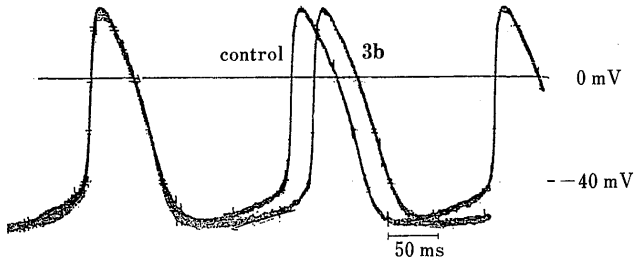


Fig. 1. Effect of Compound **3b** (10^{-4} M) on Action Potential of Isolated Guinea-Pig Sinus Node

Although alkyl derivatives showed somewhat higher *in vivo* activity than aryl derivatives compared to their *in vitro* effect, the *in vivo* bradycardic activity of these compounds correlated approximately to their *in vitro* effects. In order to confirm the difference in the effect on heart rate between the imidazo[1,2-*a*]pyridine and pyridine ring as examined in the parent cardiotonic compounds, loprinone (E-1020, **1**) and milrinone (**15**), *n*-propyloxy and *o*-cyanophenoxy derivatives, **17a**, **b**, of **15** were also evaluated for bradycardic activity. Both of them only produced positive inotropic activity without bradycardic effect *in vivo*, and the *in vitro* effect of **17b** was much less than that of the similar analogue **10b**. These results suggest that the imidazo[1,2-*a*]pyridine ring plays an important role in bradycardic activity for which the pyridine ring is not able to substitute, although these are bioisoster for cardiotonic activity.

The bradycardic activity of **10e** in mice was not affected by pretreatment with scopolamine, a blocker of cholinergic muscarinic receptors (data not shown). The effects of **3b** on isolated guinea-pig sinus node and right ventricular papillary muscle are shown in Figs. 1 and 2, respectively. Compound **3b** decreased the slope of slow diastolic

TABLE IV. Cardiovascular Activities of Imidazo[1,2-*a*]pyridinylpyridines and Pyridinylpyridines in Anesthetized Dogs after i.v. Administration and in Isolated Guinea-Pig Right Atria

Compd.	Anesthetized dogs (% change)					Isolated guinea-pig right atria
	$n^{a)}$	Dose (mg/kg)	HR[b]	MAP[c]	CF[d]	$-\log(EC_{30})^{e)}$
9a	2	1.0	+8	NA[f]	+32	NT[g]
3a	2	1.0	−9	NA	NA	NT
3b	4	0.1	−8±1	NA	NA	5.3
	5	0.3	−18±2	NA	NA	
	4	1.0	−28±2	−8±2	NA	
9b	2	0.1	−6	NA	NA	NT
	2	0.3	−11	NA	NA	
	2	1.0	−20	NA	NA	
9c	2	1.0	−12	−8	−12	NT
3c	2	1.0	+13	NA	NA	NT
4	2	1.0	NA	NA	+13	NT
14a	2	1.0	NA	NA	+10	NT
14b	2	1.0	−18	−7	−7	NT
14c	2	0.3	−17	NA	NA	5.6
	2	1.0	−17	NA	NA	
14d	2	1.0	−19	−7	NA	NT
5	2	1.0	−10	NA	NA	4.9
6	2	1.0	−8	−10	+15	NT
7	2	1.0	NA	NA	NA	NT
9d	2	1.0	−16	NA	+7	5.7
9e	2	1.0	−7	NA	NA	NT
9f	2	1.0	−22	−8	NA	6.2
10a	2	0.3	−10	NA	−10	6.2
	2	1.0	−19	NA	−8	
10b	3	0.3	−14±3	NA	NA	6.4
	3	1.0	−25±3	NA	NA	
10c	2	1.0	NA	NA	NA	<4
10d	2	1.0	+6	NA	NA	<4
10e	2	0.1	−7	NA	NA	7.0
	2	0.3	−26	−6	NA	
	2	1.0	−30	−16	NA	
10f	2	1.0	−6	NA	−14	5.1
10g	3	0.1	−8±2	NA	NA	6.7
	3	0.3	−17±3	NA	NA	
	3	1.0	−28±2	NA	NA	
10h	2	1.0	−13	NA	−10	5.8
3d	2	1.0	NA	+9	+10	NT
11	2	1.0	−17	NA	NA	5.9
17a	2	1.0	+13	−25	+47	NT
17b	2	1.0	NA	+32	+40	4.8
Falipamil	6	1.0	−24±3	NA	NA	5.3 (6)[h]
UL-FS49	8	0.3	−32±3	−9±1	NA	6.9 (4)[h]

a) Number of experiments. *b*) Heart rate. *c*) Mean aortic blood pressure. *d*) Contractile force: dP/dt_{max} of left ventricular pressure. *e*) Concentration that decreased the predrug value by 30%. Arithmetic mean of two determinations. *f*) Not active (HR, MAP or CF changes less than 5%). *g*) Not tested. *h*) Number of experiments.

depolarization in the sinus node, but had no effect on right ventricular papillary muscle (differing from class III antiarrhythmic agents). These results suggest that a major mechanism of bradycardic activity of these 5-imidazo[1,2-*a*]pyridin-6-ylpyridines seems to be direct action on the sinus node.

In conclusion, we successfully derived bradycardic activity from the cardiotonic agent, loprinone. The activity of *n*-propyloxy derivative **3b** was equipotent with that of falipamil, and those of *ortho* position of the phenyl ring were superior to both of them. The structural requirements were strict, differing from those of cardiotonic agents, and replacement of the imidazo[1,2-*a*]pyridine with pyridine almost abolished the activity.

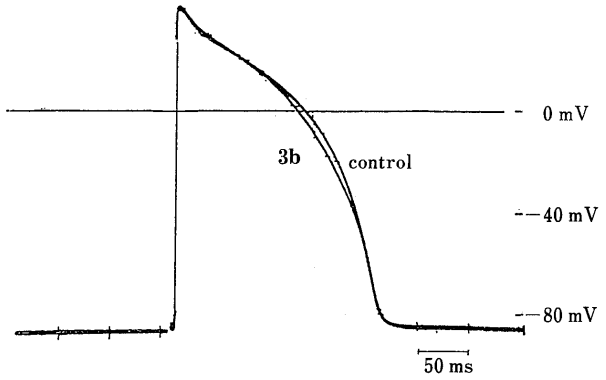


Fig. 2. Effect of Compound **3b** (10^{-4} M) on Action Potential of Isolated Guinea-Pig Right Ventricular Papillary Muscle

Experimental

Melting points were determined on a Yamato model MP 12 capillary melting point apparatus and were uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained on a Varian Unity 400, a JEOL JNM-GX 400 or a JEOL FX-90Q spectrometer with tetramethylsilane as an internal standard. ^{1}H-NMR data of all final compounds except **9a** are listed in Table III. Elemental analyses were within ±0.4% of the calculated values, the data of all final compounds except **17a, b** are listed in Tables I, II.

5-Imidazo[1,2-*a*]pyridin-6-yl-6-methyl-2-*n*-propyloxy-3-pyridinecarbonitrile (3b) and 5-Imidazo[1,2-*a*]pyridin-6-yl-6-methyl-2-oxo-1-*n*-propyl-3-pyridinecarbonitrile (4) To a mixture of **1** (1 g, 4 mmol) and K_2CO_3 (0.9 g, 6.5 mmol) in DMF (10 ml) was added a solution of *n*-propyl iodide (0.7 g, 4.1 mmol) in DMF (1 ml) and the mixture was heated at 90 °C for 2 h. After removal of the solvent *in vacuo*, CH_2Cl_2 and water 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 silica-gel column chromatography (CH_2Cl_2 : MeOH = 98 : 2) to afford 0.5 g (43%) of **3b**, mp 119—121 °C and 0.13 g (11%) of **4**. Similar treatment of **1** (1.5 g) with ethyl iodide gave 0.75 g (45%) of **3a**, mp 149—150 °C and 0.25 g (15%) of *N*-ethyl derivative, mp > 260 °C (dec.). Compound **3c** was also prepared similarly. The HCl salts of **3a, b** and some compounds mentioned later were prepared by treatment of free bases with HCl–EtOH or –AcOEt.

2-*n*-Butyl-5-imidazo[1,2-*a*]pyridin-6-yl-6-methyl-3-pyridinecarbonitrile (5) A suspension of **1** (2.0 g, 8 mmol) and K_2CO_3 (2.9 g, 21 mmol) in dioxane (100 ml) was heated under reflux for 1 h. After cooling to room temperature, trifluoromethanesulfonyl chloride (1.0 ml, 9.37 mmol) was added to the mixture and then was stirred at room temperature overnight. After water and $CHCl_3$ (50 ml) were added to the reaction mixture, the resulting precipitates (unreacted **1**) were removed by filtration and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ twice, and the combined orgaic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave crude **3e** (2.1 g), which was used in the next reaction without further purification due to its instability. ^{1}H-NMR ($CDCl_3$, 90 MHz, the purified sample by column chromatography ($CHCl_3$: MeOH = 20 : 1) in another experiment): 2.62 (3H, s, CH_3), 7.06 (1H, dd, J = 2, 10 Hz, 7-H of imidazo[1,2-*a*]pyridine (IM)), 7.64 (2H, s, 2-, 3-H of IM), 7.64 (1H, d, J = 10 Hz, 8-H of IM), 8.00 (1H, s, 4-H of pyridine (PN)), 8.18 (1H, br s, 5-H of IM). To a suspension of CuCN (1.9 g 21.2 mmol) in tetrahydrofuran (THF, 45 ml) was added dropwise below −78 °C a solution of 1.6 N *n*-BuLi in hexane (27 ml, 43.2 mmol). The resultant pale yellow solution was allowed to warm to −20 °C and then recooled to −70 °C. A solution of crude **3e** (2.1 g) in THF was added dropwise below −60 °C and the reaction mixture was allowed to warm slowly to room temperature where it was stirred overnight. The reaction was then quenched by the addition of aqueous NH_4Cl and conc. NH_4OH. After the precipitates were removed by filtration, the filtrate was extracted with $CHCl_3$ three times. The extracts were combined, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica-gel column chromatography with $CHCl_3$–MeOH (60 : 1) to give 0.38 g (16%) of **5**, mp 107—108 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.99 (3H, t, J = 7.3 Hz, CH_3), 1.48 (2H, tq, J = 7.3, 7.5 Hz, CH_2), 1.77—1.84

(2H, m, CH_2), 2.59 (3H, s, CH_3), 3.05 (2H, t, J=7.8 Hz, CH_2), 7.12 (1H, dd, J=1.8, 9.3 Hz, 7-H of IM), 7.66 (1H, dd, 0.5, 1.9 Hz, 3-H of IM), 7.71 (1H, ddd, J=0.5, 1.1, 9.3 Hz, 8-H of IM), 7.72 (1H, d, J=1.9 Hz, 2-H of IM), 7.77 (1H, s, 4-H of PN), 8.11 (1H, dd, J=1.1, 1.8 Hz, 5-H of IM).

5-(3-Bromoimidazo[1,2-*a*]pyridin-6-yl)-6-methyl-2-*n*-propyloxy-3-pyridinecarbonitrile Hydrobromide (6) To a solution of **3b** (0.45 g, 1.54 mmol) in $CHCl_3$ (20 ml) was added dropwise a solution of Br_2 (0.25 g, 1.56 mmol) in $CHCl_3$ with stirring at room temperature. After removal of the solvent, acetone was added to the residue and the resultant white crystals were collected by filtration to give 0.58 g of **6**.

2-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]methylamino]propyl]-5-imidazo[1,2-*a*]pyridin-6-yl-6-methyl-3-pyridinecarbonitrile (7) A mixture of **1** (3.75 g, 15 mmol) and K_2CO_3 (4 g, 29 mmol) in DMF (30 ml) was heated at 60 °C for 30 min. After cooling, a solution of 1-bromo-3-chloropropane (7.1 g, 45 mmol) in DMF (5 ml) was added to the mixture and the resultant mixture was heated at 70—80 °C for 30 min. Solids were removed by filtration, and filtrate was concentrated *in vacuo*. To the residue were added $CHCl_3$ and water. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica-gel column chromatography with CH_2Cl_2–MeOH (98 : 2) to give 1.95 g (40%) of 2-(3-chloropropyloxy)-5-imidazo[1,2-*a*]pyridin-6-yl-6-methyl-3-pyridinecarbonitrile **3f** (oil). ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.31 (2H, tt, J=6.0, 6.4 Hz, CH_2), 2.49 (3H, s, CH_3), 3.79 (2H, t, J=6.4 Hz, CH_2), 4.64 (2H, t, J=6.0 Hz, OCH_2), 7.08 (1H, dd, J=1.8, 9.3 Hz, 7-H of IM), 7.65 (dd, J=0.5, 1.3 Hz, 3-H of IM), 7.70 (1H, ddd, J=0.5, 1.8, 9.3 Hz, 8-H of IM), 7.72 (1H, d, J=1.3 Hz, 2-H of IM), 8.06 (1H, dd, J=0.9, 1.8 Hz, 5-H of IM). A mixture of **3f** (1.9 g, 5.8 mmol), *N*-methyl-2-(3,4-dimethoxyphenyl)ethylamine hydroiodide (2.0 g, 6.19 mmol), potassium iodide (1.0 g, 6 mmol) and K_2CO_3 (2.4 g, 17.4 mmol) in DMF was heated at 70—75 °C for 3 h. After removal of the solvent, $CHCl_3$ and water were added to the residue. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica-gel column chromatography with $CHCl_3$–MeOH (98 : 2) to give 0.9 g (32%) of **7** (syrupy mass), which was treated with HCl–AcOEt to give the dihydrochloride.

2-*n*-Butyloxy-5-imidazo[1,2-*a*]pyridin-6-yl-6-methyl-3-pyridinecarbonitrile (9b) A solution of *n*-BuONa, prepared from Na (0.34 g, 14.8 mmol) and *n*-BuOH (40 ml), and **8** (1.3 g, 4.8 mmol) in CH_2Cl_2 (50 ml) was heated under reflux for 3 h. After removal of the solvent, $CHCl_3$ and water were added to the residue. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica-gel column chromatography with $CHCl_3$–MeOH (98 : 2) to give 1.14 g of **9b**, mp 83—85 °C. ^{1}H-NMR ($CDCl_3$, 90 MHz): 0.98 (3H, t, J=7 Hz, CH_3), 1.34—1.98 (4H, m, 2 × CH_2), 2.48 (3H, s, CH_3), 4.44 (2H, t, J=7 Hz, OCH_2), 7.04 (1H, dd, J=2, 9 Hz, 7-H of IM), 7.56—7.74 (3H, m, 2-, 3-, 8-H of IM), 8.02 (1H, br s, 5-H of IM). Compound **9c** was prepared similarly, but *n*-BuONa in CH_2Cl_2 was replaced by cyclohexylONa in cyclohexanol. The results of the HCl salt are listed in Table I.

2-*n*-Butylamino-5-imidazo[1,2-*a*]pyridin-6-yl-6-methyl-3-pyridinecarbonitrile (9d) A mixture of **8** (1.0 g, 4 mmol) and *n*-butylamine (2.7 g, 36.9 mmol) was heated under reflux for 20 h. After removal of excess amine, the residue was purified by silica-gel column chromatography with $CHCl_3$–MeOH (98 : 2) to give 0.7 g of **9d**, which was converted to HCl salt. Compounds **9e** and **f** were prepared similarly at 100 °C, replacing *n*-butylamine with cyclohexylamine and piperidine, respectively. The results are listed in Table I.

2-(2-Cyanophenyloxy)-5-imidazo[1,2-*a*]pyridin-6-yl-6-methyl-3-pyridinecarbonitrile (10b) To a mixture of 60% NaH (149 mg, 3.73 mmol) in dry dioxane (30 ml) and dry DMF (5 ml) was added portionwise 2-cyanophenol (0.45 g, 3.76 mmol) at room temperature and was stirred for a while. After the generation of H_2 ceased, **8** (0.5 g, 1.86 mmol) was added, and the mixture was heated under reflux for 3h. After removal of the solvent, aqueous 5% NaOH and $CHCl_3$ were added to the residue. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica-gel column chromatography with $CHCl_3$–MeOH (98 : 2) and recrystallized from EtOH to give 0.36 g of **10b**, mp 185—187 °C. ^{1}H-NMR ($CDCl_3$, 90 MHz): 2.36 (3H, s, CH_3), 7.02 (1H, dd, J=2, 9 Hz, 7-H of IM), 7.1—7.7 (7H, m, C_6H_4, 2-, 3-, 8-H of IM), 7.84 (1H, s, 4-H of IM), 8.02 (1H, br s, 5-H of IM).

Compounds **10a**, **c**—**h** and **11** were prepared similarly, replacing 2-cyanophenol with requisite phenols or 2-hydroxypyridine. These results are listed in Table II.

2-(2-Cyanophenyloxy)-5-imidazo[1,2-*a*]pyridin-6-yl-6-methyl-pyridine (3d) A mixture of **2** (0.44 g, 2 mmol) and 55% NaH (90 mg, 2.1 mmol) in dry DMF (20 ml) was stirred for a while. After the generation of H_2 ceased, 2-fluorobenzonitrile (0.35 g, 2.9 mmol) was added, and the mixture was heated at 100 °C for 50 h. After removal of the solvent, the residue was purified by silica-gel chromatography with $CHCl_3$–MeOH (96 : 4) to give 0.2 g of **3d**.

5-Imidazo[1,2-*a*]pyridin-6-yl-6-methyl-2-*n*-propylthio-3-pyridinecarbonitrile (14c) A mixture of 4-dimethylamino-3-(6-imidazo[1,2-*a*]pyridinyl)-3-buten-2-one **12** (1.0 g, 4.36 mmol), 2-cyanothioacetamide (0.48 g, 4.8 mmol) and NaOMe (0.52 g, 9.6 mmol) in EtOH (30 ml) was heated under reflux for 13 h. Then, 2-cyanothioacetamide (0.48 g, 4.8 mmol) was added again and refluxed further for 4 h. After removal of the solvent, water was added to the residue, and the pH of the mixture was adjusted to 6.5 with AcOH. The precipitates were collected by filtration, treated with charcoal in MeOH and recrystallized from MeOH to give 0.5 g (43%) of 1,2-dihydro-5-imidazo[1,2-*a*]pyridin-6-yl-6-methyl-2-thioxo-3-pyridinecarbonitrile (**13**), mp >300 °C. *Anal.* Calcd for $C_{14}H_{10}NS \cdot 1/4H_2O$: C, 62.08; H, 3.91; N, 20.69. Found: C, 62.22; H, 3.80; N, 20.60. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.40 (3H, s, CH_3), 7.26 (1H, dd, J=1.8, 9.3 Hz, 7-H of IM), 7.62 (1H, d, J=1.1 Hz, 2-H of IM), 7.62 (1H, ddd, J=0.5, 1.1, 9.3 Hz, 8-H of IM), 7.94 (1H, dd, J=0.5, 1.1 Hz, 3-H of IM), 8.11 (1H, s, 4-H of PN), 8.63 (1H, dd, J=1.1, 1.8 Hz, 5-H of IM). A mixture of **13** (1.87 g, 7 mmol), *n*-propyl iodide (1.43 g, 8.4 mmol) and K_2CO_3 (0.97 g, 7 mmol) in DMF (20 ml) was stirred at 50 °C for 20 min. After removal of the solvent, the residue was purified by silica-gel chromatography with $CHCl_3$–MeOH (98 : 2) to give 1.0 g of **14c**, mp 115—116 °C. ^{1}H-NMR ($CDCl_3$, 90 MHz): 1.08 (3H, t, J=7 Hz, CH_3), 1.80 (2H, tq, J=7, 7 Hz, CH_2), 2.56 (3H, s, CH_3), 3.30 (2H, t, J=7 Hz, CH_2), 7.10 (dd, J=2, 9 Hz, 7-H of IM), 7.66—7.74 (4H, m, 2-, 3-, 8-H of IM, 4-H or PN), 7.12 (1H, br s, 5-H of IM). Compounds **14a**, **b**, and **c** were prepared similarly, but replacing *n*-propyl iodide with requisite alkyl iodides. These results are listed in Table I.

6-Methyl-2-*n*-propyloxy-5-pyridin-4-yl-3-pyridinecarbonitrile (17a) A suspension of milrinone (**15**)[15] (5.0 g, 23.7 mmol) and DMF (0.3 ml) in $POCl_3$ (50 ml) was refluxed for 3 h. After removal of excess $POCl_3$ *in vacuo*, a 20% aqeous NaOH was added to the residue under ice cooling untill the pH of the solution was adjusted to 6. Then, the solution was adjusted to pH 8 with saturated aqeuous K_2CO_3 and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica-gel column chromatography with $CHCl_3$–MeOH (98 : 2) to give 3.6 g (66%) of 2-chloro-6-methyl-5-pyridin-4-yl-3-pyridinecarbonitrile (**16**), mp 151—152 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.57 (3H, s, CH_3), 7.25 (2H, dd, J=1.6, 4.4 Hz, 3-, 5-H of 4-PN (pyridine substituted at 4-position)), 7.82 (1H, s, 4-H of PN), 8.76 (2H, dd, J=1.6, 4.4 Hz, 2-, 6-H of 4-PN). A mixture of **16** (1.2 g, 5.2 mmol) and PrONa (Na: 0.36 g, 15.6 mmol; PrOH: 30 ml) in CH_2Cl_2 (30 ml) was heated under reflux for 3 h. After removal of the solvent, CH_2Cl_2 and water were added to the residue. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica-gel chromatography with $CHCl_3$–MeOH (98 : 2) and recrystallized from benzene–hexane to give 1.1 g (84%) of **17a**, mp 111—113 °C. Treatment of **17a** with HCl–EtOH to give the HCl salt, mp 236—240 °C (dec.). *Anal.* Calcd for $C_{15}H_{15}N_5O \cdot HCl \cdot H_2O$: C, 58.53; H, 5.91; N, 13.65. Found: C, 58.73; H, 5.66; N, 13.80.

2-(2-Cyanophenyloxy)-6-methyl-5-pyridin-4-yl-3-pyridinecarbonitrile (17b) To a mixture of 60% NaH (0.35 g, 8.75 mmol) in dry DMF (30 ml) was added portionwise 2-cyanophenol (1.05 g, 8.76 mmol) at room temperature, stirring for a while. After the generation of H_2 ceased, **16** (1.0 g, 4.35 mmol) was added to the mixture, and stirred at 80 °C for 2 h. After removal of the solvent, the residue was purified by silica-gel chromatography with $CHCl_3$–MeOH (98 : 2) and recrystallized from AcOEt to give 0.74 g (55%) of **17b**, mp 161—163 °C. *Anal.* Calcd for $C_{19}H_{12}N_4O$: C, 73.07; H, 3.87; N, 17.94. Found C, 73.21; H, 4.01; N, 17.97.

Pharmacological Methods 1. Bradycardic Tests: Male guinea pigs of Hartley strain, weighing 300—500 g, were stunned with a blow on the head and exsanguinated. The heart was excised, and the right atrium was rapidly isolated. The tissues were mounted in organ baths of 6 ml capacity which were filled with a modified Krebs solution of the following composition (mM): NaCl (118.4), KCl (4.7), $CaCl_2$ (2.5), $MgSO_4$ (1.3), KH_2PO_4 (1.2), $NaHCO_3$ (25.0) and glucose (11.0), and pH was 7.4. The solution was maintained at 37 °C and equilibrated with a mixture of 95% O_2 and 5% CO_2. The spontaneous beating rate of the atria was counted with a heart rate tachometer (AT-601G; Nihon Koden) which was triggered by tension signals. An equilibration time of at least 60 min preceded the com-

mencement of each experiment. Drugs were directly applied to the bathing solution.

2. Electrophysiological Studies: Male Hartley guinea pigs were used in the experiment. After the same treatment as mentioned above, the heart was quickly dissected out and placed in a Tyrode solution oxygenated with a 95% O_2–5% CO_2 gas mixture at room temperature. The composition (mM) of the Tyrode solution was NaCl (123.8), KCl (5.0), $CaCl_2$ (2.0), $MgSO_4$ (1.2), NaH_2PO_4 (1.2), $NaHCO_3$ (25.0) and glucose (11.0), and pH was 7.4. A small specimen of the sinus node (2 mm × 2 mm) or papillary muscles were excised from the right atrium or the right ventricle, respectively. The preparation was fixed with pins in an organ bath of 1.2 ml volume and superfused with Tyrode solution aerated with the oxygen gas mixture at 36±0.5 °C, flowing at the rate of 5 ml/min. In the case of right ventricular papillary muscles, the preparation was driven electrically by 1 ms rectangular pulses at a voltage slightly above the threshold voltage applied through platinum electrodes. Action potentials were recorded with a glass micro-electrode with 10—20 M resistance filled with 3 M KCl. The microelectrode was connected through an Ag–AgCl junction to a high-input impedance preamplifier with capacitance neutralization (ME 3241, M. E. Commercial Co., Tokyo). The action potential upstroke was electronically differentiated with a differentiator (IMD-10, Fukuda Denshi Co.) to give the maximum rate of rise (V_{max}). Action protentials and V_{max} were displayed on a dual-beam oscilloscope (VC-10, Nihon Koden Co.) and photographed by a camera (RLG-610, Nihon Koden Co.).

The experiment was started after the action potential configuration became stable. In order to examine the effect of drugs, the perfusion solution was replaced with solutions containing drugs.

3. Anesthetized Dog Studies: Mongrel dogs of either sex, weighing 8—15 kg, were used. Anesthesia was initiated with ketamine hydrochloride 15 mg/kg i.m. After orotracheal incubation, respiration was controlled by an anesthesia ventilator. Halothane (0.5—1.0%) was delivered from a calibrated vaporizer in a mixture of oxygen and nitrus oxide (1 : 2). Mean aotic pressure was measured by introducing a Millar microtip catheter pressure transducer (MPC-500, 5F Millar instruments) into the femoral artery and positioning it in the thoracic aorta. Left ventricular pressure (LVP) was measured by introducing a Millar microtip catheter pressure transducer (PC-360, 6F) into the carotid artery of vein and positioning it in the left ventricle. Maximum rate of rise of LVP (LVd P/d t_{max}) was derived using an analog differentiator (EQ-601G, Nihon Koden). LVd P/d t_{max} was obtained as an index of cardiac contractile force (CF). Heart rate (HR) was measured by a cardiotachometer triggered by LVP. After completion of surgery the dogs were allowed equibration for a minimum of 30 min. Compounds were dissolved in saline or in diluted HCl and were administered in cannula inserted in the femoral vein.

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