Imidazo[1,2-*a*]pyridines. I. Synthesis and Inotropic Activity of New 5-Imidazo[1,2-*a*]pyridinyl-2(1*H*)-pyridinone Derivatives[1)]

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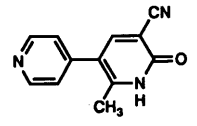
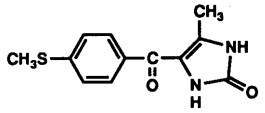
A series of 1,2-dihydro-5-imidazo[1,2-*a*]pyridinyl-2(1*H*)-pyridonones was synthesized and evaluated for positive inotropic activity. 1,2-Dihydro-5-imidazo[1,2-*a*]pyridin-6-yl-6-methyl-2-oxo-3-pyridinecarbonitrile (11a) hydrochloride monohydrate (E-1020) was found to be a potent and selective inhibitor of phosphodiesterase III and a long-acting, potent, orally active positive inotropic agent. Additional imidazo[1,2-*a*]pyridin-2-yl (3a), -3-yl (16), -7-yl (20) and -8-yl (24a) compounds were also prepared. Altering the pyridine substitution from the 2-position to the 6-position produced a 2-fold increase in the i.v. cardiotonic potency (ED_{50}) from 52 to 23 μg/kg, while substitution at the 3-, 7- or 8-position reduced potency. In the 2-positional isomers, introduction of halogen groups enhanced the activity and 3-chloro-1,2-dihydro-5-(6-fluoroimidazo[1,2-*a*]pyridin-2-yl)-6-methyl-2(1*H*)-pyridinone (3u) was the most potent (i.v. ED_{50} 11 μg/kg) in this series. E-1020 is presently under development for the treatment of congestive heart failure.

Keywords cardiotonic agent; positive inotropic activity; imidazo[1,2-*a*]pyridine; 5-imidazo[1,2-*a*]pyridinyl-2(1*H*)-pyridinone; structure–activity relationship; phosphodiesterase III inhibitor

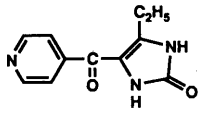
Congestive heart failure (CHF) is a major cause of death in patients with coronary artery disease. For 200 years, digitalis glycosides have been used for the treatment of CHF.[2,3)] Their use, however, is limited by their narrow therapeutic index and their propensity to cause life-threatening arrhythmias. Oral ineffectiveness and chronotropic liability prevent the use of sympathomimetic amines, dobutamine and dopamine, in chronic therapy of CHF. Therapy with vasodilators has been found to be effective in reducing the workload of the heart. There is now clinical and experimental evidence which demonstrates the advantages of combining positive inotropic stimulation with vasodilating activity to achieve maximum improvement in cardiac performance.[4,5)] Since inotropic agents increase myocardial oxygen consumption, whereas vasodilators enhance fiber shortening without changing or actually decreasing oxygen demand, these two activities may have additive effects on cardiac output.



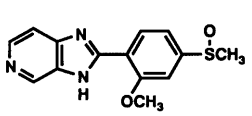
milrinone



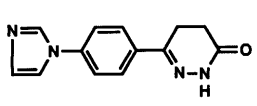
enoximone



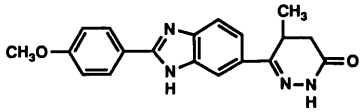
piroximone



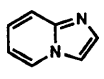
isomazole



imazodan



pimobemdan



I

Chart 1

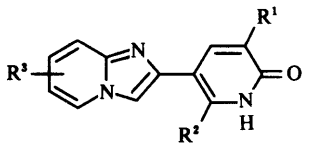
Recently several orally effective cardiotonic agents, milrinone,[6)] enoximone,[7)] piroximone,[8)] isomazole,[9)] imazodan[10)] and pimobendan,[11)] have been described as possessing these activities and some of them are at present being subjected to clinical evaluation for the treatment of CHF (Chart 1). Mechanistically, these drugs appear to drive their inotropic and vasodilator effects, at least in part, from selective inhibition of cyclic adenosine monophosphate (AMP) specific phosphodiesterase (PDE III) activity resulting in an increase in cellular cyclic AMP level.[12)] PDE I catalyzes the hydrolysis of cyclic AMP and cyclic guanosine monophosphate (GMP), but it has not been reported that selective PDE I inhibitors exert inotropic activity. Although there are a few PDE II inhibitors having cardiotonic activity, it has not been established that such activity is due to their inhibitory effects on cardiac PDE II. The nonselective "first generation" phosphodiesterase inhibitor like theophylline produces inotropic activity with a number of side effects, including tachycardia, tremor and increased rate of respiration.[13)]

The considerable therapeutic need prompted us to search for a potent, safe and orally effective agent which has these dual activities and is efficacious for a long period. Stimulated by some similarity in the structures of the agents described above, we focused our interest on imidazo[1,2-*a*]pyridine (I, Chart 1). This was thought to be a fused structure of the imidazole and the phenyl ring in imazodan holding one nitrogen in common, and the nitrogen at 1-position of I was thought to be the one derived from the pyridine in milrinone and piroximone. I also maintains a fused imidazole structure in isomazole and pimobendan. Connection of I at certain positions with the right residues of the agents in Chart 1 was expected to elicit positive inotropic activity. We report here the synthesis and inotropic activities of a novel class of 5-imidazo[1,2-*a*]pyridin-6-yl-2(1*H*)-pyridinones and their regioisomers.

Chemistry

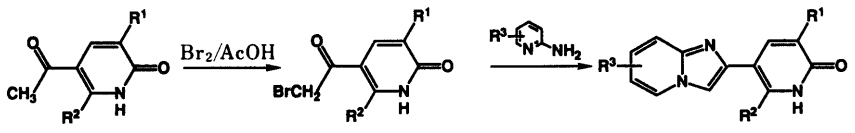
The compounds used in this study were prepared by different routes, depending on the site of 2-pyridinone ring substitution. The synthesis of 2-positional isomers,

TABLE I. 5-Imidazo[1,2-*a*]pyridinones (**3a—u**)



Compd.	R^1	R^2	R^3	mp (°C) (Solvent[a])	Yield[b] (%)	Formula	Analysis (%) Calcd (Found)		
							C	H	N
3a	CN	CH_3	H	>300 (A)	78	$C_{14}H_{10}N_4O$	67.18 (67.19)	4.04 4.00	22.39 22.57)
3b	CN	C_2H_5	H	275 (dec.) (B)	73	$C_{15}H_{12}N_4O$	68.16 (68.08)	4.59 4.49	21.20 21.19)
3c	CN	CH_3	6-CH_3	>290 (B)	71	$C_{15}H_{12}N_4C$ ·HCl	59.90 (59.74)	4.37 4.58	18.68 18.28)
3d	CN	C_2H_5	6-CH_3	278—280 (C)	65	$C_{16}H_{14}N_4O$ ·1/2H_2O	66.88 (67.28)	5.27 5.02	19.50 19.60)
3e	CN	CH_3	6-F	>300 (B)	42	$C_{14}H_9FN_4O$ ·HCl	62.68 (62.48)	3.39 3.41	20.89 20.67)
3f	CN	CH_3	8-F	>300 (B)	50	$C_{14}H_9FN_4O$ ·2/3H_2O	59.99 (59.76)	3.72 3.52	20.00 20.03)
3g	CN	CH_3	6-CN	>300 (D)	36	$C_{15}H_9N_5O$ ·2/3H_2O	62.71 (62.91)	3.52 3.52	24.38 24.47)
3h	CN	C_2H_5	6-CN	>300 (D)	59	$C_{16}H_{11}N_5O$	66.42 (66.54)	3.84 3.97	24.21 24.43)
3i	CN	CH_3	6-OCH_3	>300 (B)	42	$C_{15}H_{12}N_4O_2$ ·1.6H_2O	58.28 (58.68)	4.96 4.91	18.13 17.79)
3j	CN	CH_3	6-CF_3	>300 (B)	46	$C_{15}H_9F_3N_4O$	56.60 (56.56)	2.86 3.08	17.61 17.88)
3k	H	CH_3	H	>300 (dec.) (B′)	67	$C_{13}H_{11}N_3O$ ·HCl·1/3H_2O	58.31 (58.36)	4.79 4.66	15.70 15.86)
3l	H	CH_3	6-CH_3	>290 (E)	55	$C_{14}H_{13}N_3O$ ·HCl·2/3H_2O	58.42 (58.66)	5.36 5.12	14.60 14.87)
3m	H	CH_3	6-F	>300 (F)	24	$C_{13}H_{10}FN_3O$ ·HBr	45.63 (45.62)	3.84 3.86	12.28 12.23)
3n	Br	CH_3	H	>290 (B′)	66	$C_{13}H_{10}BrN_3O$ ·HCl	45.82 (45.57)	3.26 3.26	12.33 12.24)
3o	Br	CH_3	6-CH_3	>290 (dec.) (B)	67	$C_{14}H_{12}BrN_3O$ ·HCl	47.39 (46.99)	3.70 3.69	11.85 11.81)
3p	Br	CH_3	6-Cl	>280 (dec.) (B′)	64	$C_{13}H_9BrClN_3O$ ·HCl	41.61 (41.61)	2.69 2.80	11.20 11.02)
3q	Br	CH_3	6-F	289—290 (D)	35	$C_{13}H_9BrFN_3O$	48.45 (48.24)	2.82 2.80	13.04 12.75)
3r	Br	CH_3	6-CN	>300 (D)	41	$C_{14}H_9BrN_4O$ ·2/5H_2O	49.98 (50.31)	2.94 2.88	16.66 16.30)
3s	Br	CH_3	6-CF_3	>300 (F)	56	$C_{14}H_9BrF_3N_3O$	45.17 (45.36)	2.44 2.52	11.29 11.01)
3t	Cl	CH_3	H	296—297 (E)	51	$C_{13}H_{10}ClN_3O$	60.11 (60.03)	3.89 3.95	16.18 16.03)
3u	Cl	CH_3	6-F	305—307 (E)	26	$C_{13}H_9ClFN_3O$	56.21 (56.30)	3.27 3.38	15.13 15.13)

a) Recrystallization solvents: A, only filtration; B, DMF; B′, DMF–HCl–EtOH; C, methyl ethyl ketone–MeOH; D, DMF–H_2O; E, MeOH; F, DMF–MeCN. *b*) Not optimized.



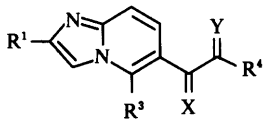
1a—e **2a—e** **3a—u**

a : R^1=CN, R^2=CH_3 **b** : R^1=CN, R^2=C_2H_5 **c** : R^1=H, R^2=CH_3 **d** : R^1=Br, R^2=CH_3 **e** : R^1=Cl, R^2=CH_3

Chart 2

5-imidazo[1,2-*a*]pyridin-2-yl-2(1*H*)-pyridinones **3a—u**[14] (Table I), was accomplished by condensation of requisite 5-bromoacetyl-1-pyridinones **2a—e**, which were obtained by bromination[15] of 5-acetyl-2-pyridinones **1a—e**, with 2-aminopyridines (Chart 2). 5-Acetyl-3-cyano-6-methyl-2-pyridinone **1a** was prepared according to the procedure in

TABLE II. 6-Propyl and Butylimidazo[1,2-*a*]pyridines



Compd.	R^1	R^3	R^4	X	Y	mp (or bp)[a] (°C)	Yield[b] (%)	^{1}H-NMR ($CDCl_3$) δ (ppm)
8a	H	H	CH_3	H_2	CH_2	(118—122[c])	71	1.70 (3H, s, CH_3), 3.28 (2H, s, CH_2), 4.80 (1H, d, J=1 Hz, =CH), 4.90 (1H, d, J=1 Hz, =CH), 7.02 (1H, dd, J=2, 9 Hz, 7-H), 7.52 (1H, d, J=1 Hz, 3-H), 7.56 (1H, d, J=9 Hz, 8-H), 7.58 (1H, d, J=1 Hz, 2-H), 7.92 (1H, br s, 5-H)
8b	CH_3	H	CH_3	H_2	CH_2	Oil	82	1.70 (3H, s, CH_3), 2.44 (3H, s, CH_3), 3.25 (2H, s, CH_2), 4.78 (1H, s, =CH), 4.87 (1H, s, =CH), 6.97 (1H, dd, J=2, 9 Hz, 7-H), 7.28 (1H, s, 3-H), 7.44 (1H, d, J=9 Hz, 8-H), 7.84 (1H, br s, 5-H)
8c	H	CH_3	CH_3	H_2	CH_2	Oil	66	1.74 (3H, s, CH_3), 2.50 (3H, s, CH_3), 3.34 (2H, s, CH_2), 4.56 (1H, s, =CH), 4.82 (1H, s, =CH), 7.02 (1H, d, J=10 Hz, 7-H), 7.46 (1H, d, J=1 Hz, 3-H), 7.50 (1H, d, J=10 Hz, 8-H) 7.66 (1H, J=1 Hz, 2-H)
8d	CH_3OCH_2	H	CH_3	H_2	CH_2	Oil	80	1.70 (3H, s, CH_3), 3.26 (2H, s, CH_2), 3.48 (3H, s, OCH_3), 4.61 (2H, s, OCH_2), 4.76 (1H, s, =CH), 4.86 (1H, s, =CH), 6.99 (1H, dd, J=2, 9 Hz, 7-H), 7.46 (1H, d, J=9 Hz, 8-H), 7.48 (1H, s, 3-H), 7.86 (1H, br s, 5-H)
8e	ph	H	CH_3	H_2	CH_2	125—126	17	1.70 (3H, s, CH_3), 3.27 (2H, s, CH_2), 4.78 (1H, s, =CH), 4.87 (1H, s, =CH), 7.01 (1H, dd, J=2, 9 Hz, 7-H), 7.20—7.52 and 7.78—7.98 (5H, m, C_6H_5), 7.53 (1H, d, J=9 Hz, 8-H), 7.77 (1H, s, 3-H), 7.96 (1H, d, br s, 5-H)
8f	H	H	C_2H_5	H_2	CH_2	(120—124[d])	32	1.04 (3H, t, J=7 Hz, CH_3), 2.00 (2H, q, J=7 Hz, CH_2), 3.29 (2H, s, CH_2), 4.76 (1H, d, J=1 Hz, =CH), 4.88 (1H, d, J=1 Hz, =CH), 6.98 (1H, dd, J=2, 9 Hz, 7-H), 7.50 (1H, s, 3-H), 7.52 (1H, d, J=9 Hz, 8-H), 7.56 (1H, s, 2-H), 7.90 (1H, br s, 5-H)
8g	CH_3	H	C_2H_5	H_2	CH_2	Oil	39	1.02 (3H, t, J=7 Hz, CH_3), 1.99 (2H, q, J=7 Hz, CH_2), 2.38 (3H, s, CH_3), 3.25 (2H, s, CH_2), 4.71 (1H, s, =CH), 4.86 (1H, s, =CH), 6.92 (1H, dd, J=2, 9 Hz, 7-H), 7.24 (1H, s, 3-H), 7.39 (1H, d, J=9 Hz, 8-H), 7.80 (1H, br s, 5-H)
9a	H	H	CH_3	H_2	O	(155—159[e])	71	2.24 (3H, s, CH_3), 3.70 (2H, s, CH_2), 6.95 (1H, dd, J=2, 9 Hz), 7.56 (1H, s, 3-H), 7.60 (1H, d, J=9 Hz, 8-H), 7.64 (1H, s, 2-H), 8.03 (1H, br s, 5-H)
9b	CH_3	H	CH_3	H_2	O	60—61	74	2.22 (3H, s, CH_3), 2.44 (3H, s, CH_3), 3.66 (2H, s, CH_2), 6.94 (1H, dd, J=2, 9 Hz, 7-H), 7.30 (1H, s, 3-H), 7.47 (1H, d, J=9 Hz, 8-H), 7.93 (1H, br s, 5-H)
9c	H	CH_3	CH_3	H_2	O	73—75	64	2.12 (3H, s, CH_3), 2.44 (3H, s, CH_3), 3.71 (2H, s, CH_2), 6.92 (1H, d, J=9 Hz, 7-H), 7.42 (1H, d, J=1 Hz, 3-H), 7.46 (1H, d, J=9 Hz, 8-H), 7.61 (1H, d, J=1 Hz, 2-H)
9d	CH_3OCH_2	H	CH_3	H_2	O	80—81.5	38	2.24 (3H, s, CH_3), 3.48 (3H, s, OCH_3), 3.68 (2H, s, CH_2), 4.60 (2H, s, OCH_2), 6.94 (1H, dd, J=2, 9 Hz, 7-H), 7.48 (1H, d, J=9 Hz, 8-H), 7.50 (1H, s, 3-H), 7.90 (1H, br s, 5-H)
9e	ph	H	CH_3	H_2	O	144—147	74	2.24 (3H, s, CH_3), 3.68 (2H, s, CH_2), 6.96 (1H, dd, J=2, 9 Hz, 7-H), 7.24—7.55 and 7.82—8.10 (6H, m, C_6H_5 and 5-H), 7.58 (1H, d, J=9 Hz, 8-H), 7.80 (1H, s, 3-H)
9f	H	H	C_2H_5	H_2	O	Oil	40	1.06 (3H, t, J=7 Hz, CH_3), 2.52 (2H, q, J=7 Hz, CH_2), 3.64 (2H, s, CH_2), 6.94 (1H, dd, J=2, 9 Hz, 7-H), 7.50 (1H, s, 3-H), 7.53 (1H, d, J=9 Hz, 8-H), 7.56 (1H, s, 2-H), 7.98 (1H, br s, 5-H)
9g	CH_3	H	C_2H_5	H_2	O	Oil	60	0.94 (3H, t, J=7 Hz, CH_3), 2.30 (3H, s, CH_3), 2.40 (2H, q, J=7 Hz, CH_2), 3.48 (2H, s, CH_2), 6.76 (1H, dd, J=2, 9 Hz, 7-H), 7.12 (1H, s, 3-H), 7.30 (1H, d, J=9 Hz, 8-H), 7.76 (1H, br s, 5-H)
10a	H	H	CH_3	$CHN(CH_3)_2$	O	177—178	75	2.04 (3H, s, CH_3), 2.80 (6H, s, $N(CH_3)_2$), 7.03 (1H, dd, J=2, 9 Hz, 7-H), 7.55 (1H, s, 3-H), 7.57 (1H, d, J=9 Hz, 8-H), 7.63 (2H, s, 2-H and =CH), 7.94 (1H, br s, 5-H)
10b	CH_3	H	CH_3	$CHN(CH_3)_2$	O	210—219	68	2.02 (3H, s, CH_3), 2.78 (6H, s, $N(CH_3)_2$), 6.98 (1H, dd, J=2, 9 Hz, 7-H), 7.32 (1H, s, 3-H), 7.48 (1H, d, J=9 Hz, 8-H), 7.66 (1H, s, =CH), 7.87 (1H, J=2 Hz, 5-H)
10c	H	CH_3	CH_3	$CHN(CH_3)_2$	O	122—123	83	1.95 (3H, s, CH_3), 2.48 (3H, s, CH_3), 2.74 (6H, s, $N(CH_3)_2$), 7.04 (1H, d, J=10 Hz, 7-H), 7.47 (1H, s, 3-H), 7.52 (1H, d, J=10 Hz, 8-H), 7.68 (2H, s, 2-H and =CH)
10d	CH_3OCH_2	H	CH_3	$CHN(CH_3)_2$	O	163—165	62	2.03 (3H, s, CH_3), 2.78 (6H, s, $N(CH_3)_2$), 3.48 (3H, s, OCH_3), 4.60 (2H, s, OCH_2), 6.98 (1H, dd, J=2, 9 Hz, 7-H), 7.46 (1H, d, J=10 Hz, 8-H), 7.50 (1H, s, 3-H), 7.60 (1H, s, =CH), 7.86 (1H, br s, 5-H)

TABLE II. (continued)

Compd.	R^1	R^3	R^4	X	Y	mp (or bp)[a] (°C)	Yield[b] (%)	^{1}H-NMR ($CDCl_3$) δ (ppm)
10e	ph	H	CH_3	$CHN(CH_3)_2$	O	>253 (dec.)	60	2.05 (3H, s, CH_3), 2.76 (6H, s, $N(CH_3)_2$), 6.97 (1H, dd, J=2, 9 Hz, 7-H), 7.20—7.55 and 7.78—8.01 (6H, m, 8-H and C_6H_5), 7.76 (1H, s, 3-H), 8.18 (1H, s, =CH), 8.28 (1H, br s, 5-H)
10f	H	H	C_2H_5	$CHN(CH_3)_2$	O	114—115	69	1.01 (3H, t, J=7 Hz, CH_3), 2.28 (2H, q, J=7 Hz, CH_2), 2.77 (6H, s, $N(CH_3)_2$), 7.00 (1H, dd, J=2, 9 Hz, 7-H), 7.52 (1H, d, J=1 Hz, 3-H), 7.62 (1H, d, J=1 Hz, 2-H), 7.64 (1H, s, =CH), 9.92 (1H, br s, 5-H)
10g	CH_3	H	C_2H_5	$CHN(CH_3)_2$	O	130—131	52	0.92 (3H, t, J=7 Hz, CH_3), 2.21 (2H, q, J=7 Hz, CH_2), 2.36 (3H, s, CH_3), 2.70 (6H, s, $N(CH_3)_2$), 6.90 (1H, dd, J=2, 9 Hz, 7-H), 7.24 (1H, s, 3-H), 7.36 (1H, d, J=9 Hz, 8-H), 7.56 (1H, s, =CH), 7.80 (1H, br s, 5-H)

a) Purified by column chromatography on silica gel excluding **8a**, **f** and **9a**. *b*) Not optimized. *c*) Boiling point under 0.5 mmHg. *d*) Boiling point under 0.3 mmHg. *e*) Boiling point under 0.4 mmHg.

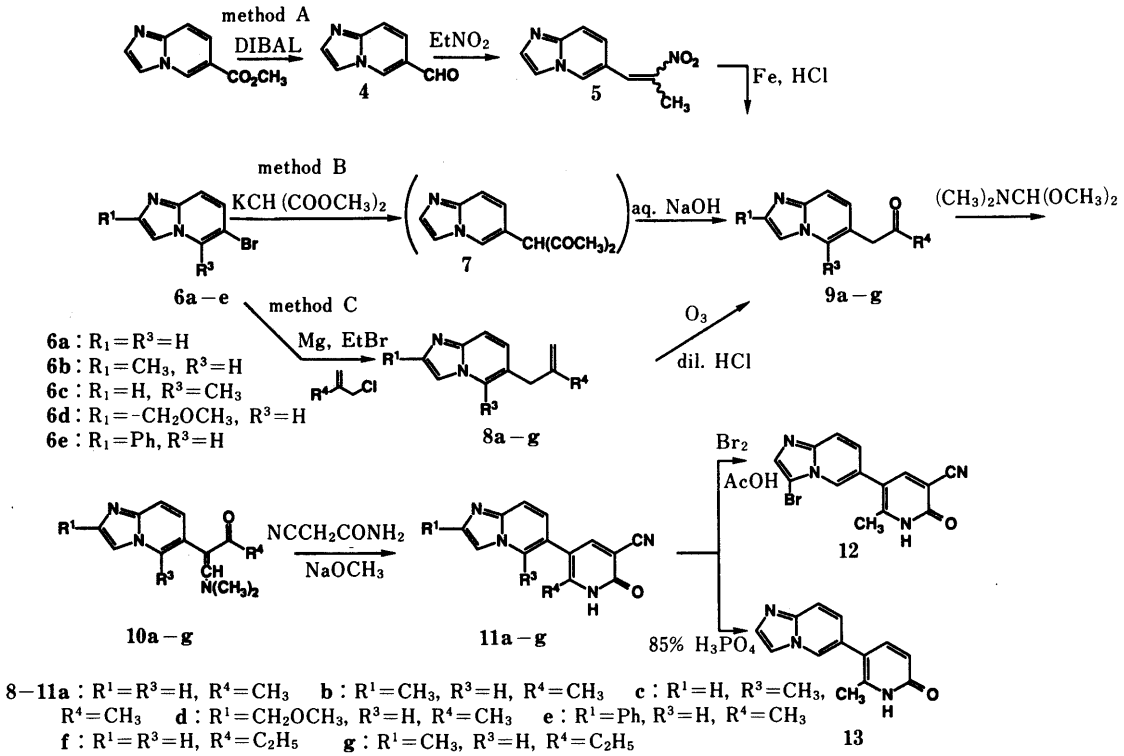


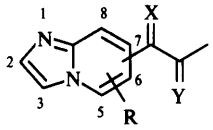
Chart 3

the literature.[16] 6-Ethyl derivative **1b** was also prepared in the same manner, but the purification of **1b** was not successful. Therefore crude **1b** was brominated without further purification to **2b**, and then purified. 5-Acetyl-2-pyridinone **1c** was obtained by treatment of **1a** with 50% H_2SO_4 followed by heating in Dowtherm A instead of using another procedure reported by Kato *et al.*[17] 5-Acetyl-3-bromo and 3-chloro-2-pyridinone **1d—e** were obtained by treatment of **1c** with 48% HBr and conc. HCl in the presence of hydrogen peroxide in 50 and 9.6% yield, respectively.

Formation of 2-pyridinone ring was carried out at the last step in the synthesis of other positional isomers; namely, 3-, 6-, 7- and 8-positional isomers (Tables IV and V) were prepared *via* the key intermediates, imidazo[1,2-*a*]pyridinyl-2-propanones.

For the synthesis of 6-positional isomers, three methods were examined (Chart 3). The first involved condensation of imidazo[1,2-*a*]pyridine-6-carboxaldehyde **4** with nitroethane and successive reduction of 6-(2-nitro-1-propenyl)-imidazo[1,2-*a*]pyridine **5** with iron powder in hydrochloric acid and EtOH (method A). The second was the reaction of 6-bromoimidazo[1,2-*a*]pyridine **6a**[18] with potassium acetoacetonate in the presence of cuprous iodide followed by treatment with aq NaOH (method B). These methods afforded imidazo[1,2-*a*]pyridin-6-yl-2-propanone **9a** in 6.1 and 37.6% yield, respectively, but were not efficient for the preparation of other 6-yl derivatives. The third method was therefore explored. After conversion of **6a** by the Grignard cross coupling reaction with 3-chloro-2-methylpropene to 6-isobutenylimidazo[1,2-*a*]pyridine **8a**, ozonolysis of **8a** under acidic conditions provided **9a** in 50% yield from **6a** (method C). Other 6-yl derivatives **9b—g** (Table II) were readily prepared according to method C. Conversion of the ketones **9a—g** to the pyridinones **11a—g** was accomplished

TABLE III. 3-, 7- and 8-Propylimidazo[1,2-*a*]pyridines



Compd.	R	Position of 	X	Y	mp (°C)[a]	Yield (%)[b]	^{1}H-NMR ($CDCl_3$) δ (ppm)
15	H	3	H_2	CH_2	64—66	41	1.72 (3H, s, CH_3), 3.56 (2H, s, CH_2), 4.64 (1H, s, =CH), 4.86 (1H, s, =CH), 6.70 (1H, ddd, J=1, 7, 8 Hz, 6-H), 7.05 (1H, ddd, J=1, 7, 9 Hz, 7-H), 7.38 (1H, s, 2-H), 7.52 (1H, dt, J=1, 2, 9 Hz, 8-H), 7.82 (1H, dt, J=1, 1, 7 Hz, 5-H)
20	H	7	H_2	CH_2	Oil	12	1.70 (3H, s, CH_3), 3.32 (2H, s, CH_2), 4.78 (1H, s, =CH), 4.86 (1H, s, =CH), 6.64 (1H, dd, J=2, 8 Hz, 6-H), 7.34 (1H, br s, 8-H), 7.48 and 7.54 (each, 1H, s, 2- and 3-H), 8.01 (1H, d, J=8 Hz, 5-H)
29	6-CH_3	8	H_2	CH_2	Oil	39	1.78 (3H, s, CH_3), 2.28 (3H, s, CH_3), 3.70 (2H, s, CH_2), 4.90 (1H, s, =CH), 4.80 (1H, s, =CH), 6.82 (1H, s, 7-H), 7.46 and 7.54 (each, 1H, d, J=1 Hz, 2- and 3-H), 7.98 (1H, s, 5-H)
16	H	3	H_2	O	83—85	69	2.18 (3H, s, CH_3), 3.94 (2H, s, CH_2), 6.74 (1H, ddd, J=1, 8, 8 Hz, 6-H), 7.12 (1H, ddd, J=1, 8, 8 Hz, 7-H), 7.50 (1H, s, 2-H), 7.56 (1H, dd, J=1, 8 Hz, 8-H), 7.84 (1H, dd, J=1, 8 Hz, 5-H)
21	H	7	H_2	O	Oil	22,[e] 75[f]	2.22 (3H, s, CH_3), 3.73 (2H, s, CH_2), 6.62 (1H, dd, J=2, 9 Hz, 6-H), 7.36 (1H, t like s, 8-H), 7.48 and 7.52 (each, 1H, d, J=1 Hz, 2- and 3-H), 8.01 (1H, dd, J=2, 9 Hz, 5-H)
30a	H	8	H_2	O	68—69	47	2.28 (3H, s, CH_3), 4.08 (2H, s, CH_2), 6.70 (1H, 1H, dd, J=8, 8 Hz, 6-H), 6.96 (1H, d, J=8 Hz, 8-H), 7.52 and 7.54 (each, 1H, s, 2- and 3-H), 8.01 (1H, d, J=8 Hz)
30b	6-CH_3	8	H_2	O	78—80	80	2.24 (3H, s, 2 × CH_3), 4.08 (2H, s, CH_2), 6.86 (1H, br s, 7-H), 7.49 and 7.54 (each, 1H, s, 2- and 3-H), 7.86 (1H, br s, 5-H)
17	H	3	$CHN(CH_3)_2$	O	142—143	60	1.82 (3H, s, CH_3), 2.2—3.0 (6H, br s, $N(CH_3)_2$), 6.86 (1H, ddd, J=1, 7, 9 Hz, 6-H), 7.22 (1H, ddd, 2, 7, 9 Hz, 7-H), 7.52 (1H, s, =CH), 7.66 (1H, dd, J=1, 9 Hz, 8-H), 7.84 (1H, dd, J=1, 9 Hz, 5-H), 8.01 (1H, s, 2-H)
22	H	7	$CHN(CH_3)_2$	O	142—144	74	2.04 (3H, s, CH_3), 2.78 (6H, s, $N(CH_3)_2$), 6.66 (1H, dd, J=2, 8 Hz, 6-H), 7.32 (1H, br s, 8-H), 7.54—7.60 (2H, m, 2, 3-H), 7.52 (1H, s, =CH), 8.04 (1H, dd, J=2, 8 Hz, 5-H)
31a	H	8	$CHN(CH_3)_2$	O	164—166	73	2.01 (3H, s, CH_3), 2.70 (6H, s, $N(CH_3)_2$), 6.88 (1H, dd, J=8 Hz, 7.01 (1H, dd, J=2, 8 Hz, 7-H), 7.60 and 7.62 (each, 1H, d, J=1 Hz, 2- and 3-H), 7.78 (1H, s, =CH), 8.10 (1H, dd, J=2, 8 Hz, 5-H)
31b	6-CH_3	8	$CHN(CH_3)_2$	O	212—214	69	2.02 (3H, s, CH_3), 2.36 (3H, s, CH_3), 2.68 (6H, s, $N(CH_3)_2$), 6.84 (1H, d, J=2 Hz, 7-H), 7.50 and 7.58 (each, 1H, d, J=1 Hz, 2- and 3-H), 7.76 (1H, s, =CH), 7.88 (1H, br s, 5-H)

a) Purified by column chromatography on silica gel. *b*) Not optimized. *c*) Reduction of the nitropropenyl derivative. *d*) Ozonolisis of the methylpropenyl derivative.

by minor modification of the general procedure of Lesher and Philino.[19] Treatment of the ketones **9a—g** with *N*,*N*-dimethylformamide dimethylacetal in dimethylformamide (DMF) or toluene provided the enamino ketones **10a—g** (Table II). The pyridinones **11a—g** were obtained by condensation of **10a—g** with cyanoacetamide in the presence of sodium methoxide in DMF or EtOH. Treatment of **11a** with bromine in AcOH gave the brominated product **12** (the position of bromine is discussed later), and with 85% H_3PO_4 provided the decyanated product **13**.

The key intermediates **16**, **21** and **30a—b** (Table III) of 3-, 7- and 8-yl regioisomers were prepared by method A or C, depending on ease of preparation of starting materials. In the case of 7-yl isomer **21**, both methods were used. The Grignard cross coupling reaction of **14**,[20] **19**[21] and **28** provided isobutenyl derivatives **15**, **20** and **29** which were converted to **16**, **21** and **30b** by ozonolysis under acidic conditions. Treatment of 7- and 8-imidazo[1,2-*a*]pyridinecarboxaldehydes **24** and **26** with nitroethane followed by reduction with iron powder also provided imidazo[1,2-*a*]pyridinyl-2-propanones **21** and **30a**. These were converted to pyridinones, **18**, **23** and **32a—b** in the same manner as mentioned above (Chart 4).

The position of bromine of **12** was presumed to be the 3-position of imidazo[1,2-*a*]pyridine (IM) in view of **14**, and confirmed by comparison of Nuclear Overhauser effects (NOE's) and coupling constants of **11a** and **12** (free base) in the proton nuclear magnetic resonance (^{1}H-NMR) (400 MHz) spectra in deuteriodimethyl sulfoxide (DMSO-d_6). Irradiation of 5-H resonance at 8.59 ppm in the spectrum of **11a** gave NOE enhancement of 11.2% and 14.7%, respectively, in two resonances at 8.16 (singlet) and 7.92 ppm (doublet of doublets), assigned to 4-H of pyridinone (PN) and 3-H of IM. On the other hand, irradiation of 5-H at 8.35 ppm in the spectrum of **12** caused only a weak enhancement of 4-H of PN at 8.19 ppm (due to near chemical shift) and no increase of intensity of the signal at 7.77 ppm. In addition, the 3-H at 7.92 ppm of **11a** had J_{2H-3H}=1.1 and J_{3H-8H}=0.8 Hz, whereas the

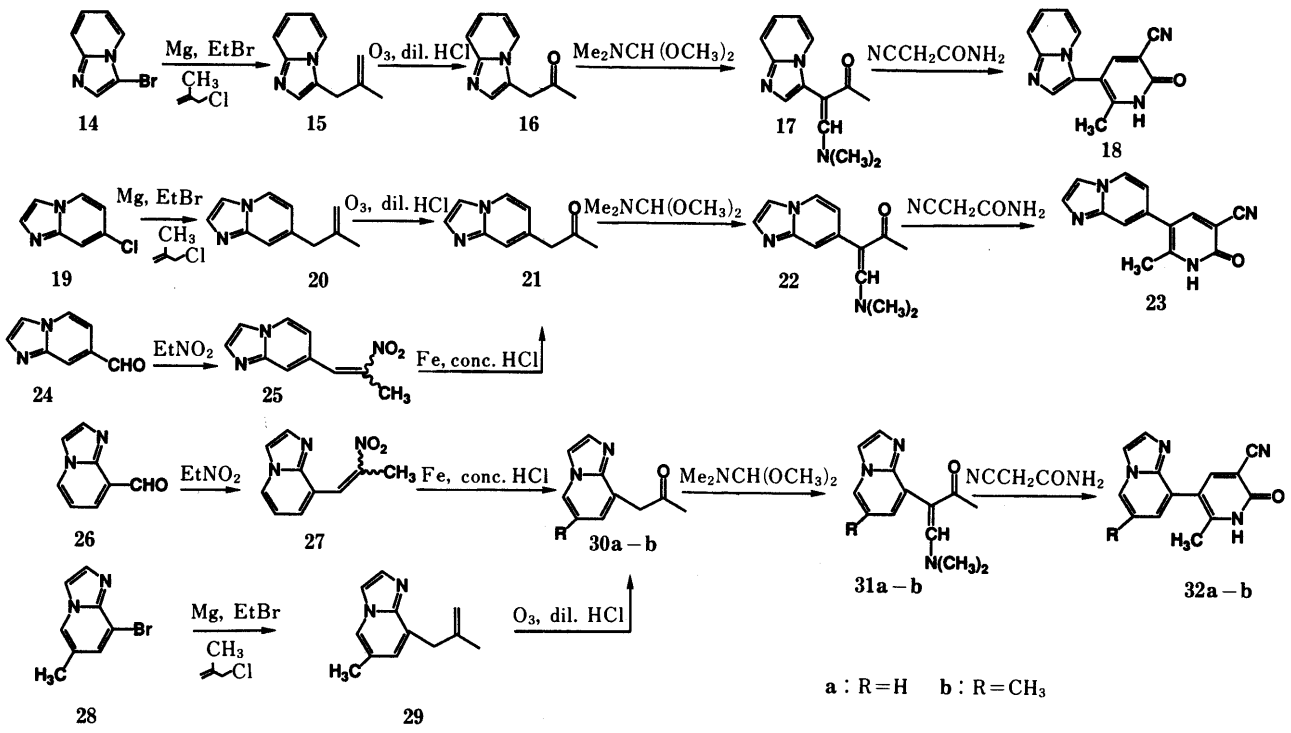
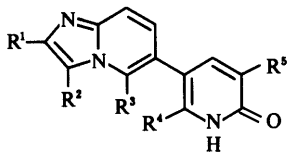


Chart 4

TABLE IV. 5-Imidazo[1,2-*a*]pyridin-6-yl-2(1*H*)-pyridinones (**11a—g, 12, 13**)



Compd.	R^1	R^2	R^3	R^4	R^5	mp (°C) (Solvent[a])	Yield[b] (%)	Formula	Analysis (%) Calcd (Found)		
									C	H	N
11a	H	H	H	CH_3	CN	>300 (B)	51	$C_{14}H_{10}N_4O \cdot HCl \cdot H_2O$	55.16 (55.26	4.30 4.40	18.39 18.44)
11b	CH_3	H	H	CH_3	CN	>260 (dec.) (E)	45	$C_{15}H_{12}N_4O \cdot HCl \cdot 1/6H_2O$	59.30 (59.28	4.42 4.58	18.44 18.56)
11c	H	H	CH_3	CH_3	CN	>300 (E)	15	$C_{15}H_{12}N_4O \cdot 1/6H_2O$	67.39 (67.49	4.65 4.70	20.96 20.90)
11d	CH_3OCH_2	H	H	CH_3	CN	>270 (dec.) (E)	35	$C_{16}H_{14}N_4O_2 \cdot H_2O$	61.52 (61.68	5.17 5.23	17.94 17.68)
11e	C_6H_5	H	H	CH_3	CN	>300 (B)	43	$C_{20}H_{14}N_4O \cdot 1/2H_2O$	71.62 (71.63	4.51 4.51	16.70 16.58)
11f	H	H	H	C_2H_5	CN	250—252 (E)	37	$C_{15}H_{12}N_4O \cdot HCl \cdot 3/5H_2O$	57.82 (57.93	4.60 4.58	17.99 17.63)
11g	CH_3	H	H	C_2H_5	CN	276—278 (E)	35	$C_{16}H_{14}N_4O$	69.05 (69.28	5.07 5.35	20.13 20.26)
12	H	Br	H	CH_3	CN	>300 (E)	55	$C_{14}H_{19}BrN_4O \cdot HBr \cdot 2/3H_2O$	39.83 (39.59	2.70 2.95	13.27 12.88)
13	H	H	H	CH_3	H	290—292 (G)	50	$C_{13}H_{11}N_3O$	69.31 (69.57	4.93 5.11	18.66 18.67)

a) Recrystallization solvent: see the footnote of Table I. G, EtOH–ether. *b*) Not optimized.

resonance at 7.77 ppm of **12** was a singlet and showed no correlation with 8-H. These results supported that the position of bromine was the 3-position of IM.

Biological Results and Discussion

The pyridinones in Tables I, IV and V were evaluated for inotropic activity intravenously in an acutely instrumented anesthetized dog model and orally in a chronically instrumented conscious dog model. Brief description of the method is included in the experimental section. Heart rate, myocardial contractility (derived by measuring dP/dt max of left ventricular pressure), and

TABLE V. 5-Imidazo[1,2-*a*]pyridin-3-,7- and 8-yl-2(1*H*)-pyridinones (**18**, **23**, **32a** and **32b**)

Compd.	mp (°C) (Solvent[a])	Yield[b] (%)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
18	>300 (B)	54	$C_{14}H_{10}N_4O \cdot HCl \cdot 4/5H_2O$	55.83 (55.86	4.23 4.36	18.60 18.51)
23	>290 (E)	33	$C_{14}H_{10}N_4O \cdot 1/6H_2O$	66.39 (66.67	4.12 4.42	22.13 21.83)
32a	276—278 (E)	23	$C_{14}H_{10}N_4O \cdot 5/4H_2O$	61.63 (61.84	4.55 4.57	20.54 20.63)
32b	>300 (E)	35	$C_{15}H_{12}N_4O \cdot HCl \cdot 0.03H_2O$	59.78 (59.48	4.38 4.55	18.60 19.00)

a, *b*) See footnote in Table I.

TABLE VI. Cardiovascular Profile of 5-Imidazo[1,2-*a*]pyridinyl-2(1*H*)-pyridinones in Anesthetized Dogs after i.v. Administration

Compd.	*n*[a]	Dose (mg/kg)	% change			ED_{50}[e] (μg/kg)
			$LVdP/dt_{max}$[b]	HR[c]	MAP[d]	
3a	5	0.100	75	18	−17	52±10
3b	2	0.300	15	4	−5	>300
3c	2	0.100	22	11	−15	>300
3d	2	0.300	19	3	−12	>300
3e	3	0.100	97	27	−27	31±14
3f	3	0.100	60	36	−15	58±11
3g	2	0.100	86	9	−12	32
3h	2	0.300	26	−1	−10	>300
3i	2	0.300	47	6	−8	>300
3j	2	0.300	16	4	−3	>300
3k	2	0.300	84	26	−9	123
3l	2	0.300	12	9	−6	>300
3m	2	0.300	43	18	−18	195
3n	3	0.100	82	30	−27	33±6
3o	2	0.100	31	19	−8	177
3p	2	0.300	57	23	−30	193
3q	2	0.300	62	22	−40	27
3r	2	0.300	25	8	−10	>300
3s	2	0.300	17	11	−7	>300
3t	2	0.100	47	21	−32	91
3u	2	0.030	86	32	−31	11
11a	6	0.100	99	28	−9	23±2
11b	2	0.100	131	40	−21	18
11c	2	0.300	30	10	−10	>300
11d	2	0.300	57	14	−7	218
11e	2	1.000	30	9	−8	>1000
11f	2	0.100	89	17	−9	52
11g	2	0.100	24	13	−21	197
12	2	0.300	76	12	−13	172
13	2	0.100	52	12	−21	87
18	2	1.000	43	8	1	>1000
23	2	1.000	25	11	−11	>1000
32a	2	0.300	5	8	7	>300
32b	2	1.000	6	3	1	>1000
Milrinone	6	0.100	98	33	−18	25±6

a) Number of experiments. *b*) Maximum rate of rise in left ventricular pressure. *c*) Heart rate. *d*) Mean arterial pressure. *e*) Values are doses that produced 50% increase in $LVdP/dt_{max}$ and are expressed as the mean ± S.E.M. When two determinations were made, the values shown is the arithmetic mean.

systolic and diastolic blood pressure were recorded. Dose response curves were determined with at least three doses of each compound.

Cardiovascular data in anesthetized dogs after intravenous administration are summarized in Table VI.

TABLE VII. Guinea Pig. Right Ventricular Papillary Muscle Contractility

Compound	*n*[a]	% change from control		
		1×10^{-6}	1×10^{-5}	1×10^{-4}[b]
3a	5	37±5.3	64± 5.6	84± 7.4
11a	8	35±6.1	83±11.1	120±18.3
18	3		5± 2.9	91± 2.5
23	4		12± 4.8	67±15
Milrinone	9	33±7.5	83± 8.8	129±12

a) The number of experiments. *b*) Concentration of compounds (M).

TABLE VIII. Effect of Cardiotonic Agents on Myocardial Contractility in Conscious Dogs Following Oral Administration

Compd.	*n*[a]	mg/kg	% increase[b]		Duration[c] (h)
			$LVdP/dt_{max}$	HR	
11a	3	0.3	27±3[d]	6±4	3
	4	1.0	37±4[d]	6±3	6
	3	3.0	69±9[d]	14±7	8
Milrinone	3	0.3	30±7[d]	21±4[d]	2
	3	1.0	59±17[d]	57±17[d]	4

a) Number of experiments. *b*) Values are maximum response from control average ± S.E.M. *c*) Values are maximum numbers of hours after administration that the inotropic response was significant at $p<0.05$ compared to control. *d*) Significant difference from control, $p<0.05$.

TABLE IX. IC_{50} Values of Guinea Pig. Phosphodiesterase

Compound	IC_{50} (M)		
	PDE I	PDE II	PDE III
11a	1.8×10^{-4}	1.0×10^{-4}	6.3×10^{-7}
Milrinone	1.5×10^{-4}	1.1×10^{-4}	7.6×10^{-7}

Among a series of 2-positional isomers, **3a** produced substantial inotropic responses ($ED_{50}=52\,\mu g/kg$) when administered intravenously to anesthetized dogs. Introduction of a fluorine or cyano group into the 6-position of imidazo[1,2-*a*]pyridine enhanced this activity (ED_{50} of **3e** and **3g** were 31 and 32 μg/kg, respectively), while that of methoxy, methyl and trifluoromethyl groups reduced it ($ED_{50}>300\,\mu g/kg$). Replacement of the cyano group in the pyridinone rings of **3a**, **3c**, **3e** and **3g** with bromine led to an increase in activity for **3n** and **3o** ($ED_{50}=33$ and 177 μg/kg) and retention of activity for **3q** ($ED_{50}=27$ μg/kg), but diminished potency for **3r** ($ED_{50}>300\,\mu g/kg$). The most striking effect of fluorine substitution and replacement of the cyano group was shown in **3u** ($ED_{50}=11\,\mu g/kg$), which had a fluorine in the 6-position of the imidazo[1,2-*a*]pyridine, and a chlorine in the 3-position of pyridinone. Replacement of methyl with ethyl or cyano group with hydrogen in the pyridinone ring resulted in decreased potency. The inotropic response of those compounds which had halogen groups in the pyridinone ring was of shorter duration than that of compounds having a cyano group (data not shown).

Among a series of 6-positional isomers, **11a** produced dose related increases in myocardial contractility ($ED_{50}=23\,\mu g/kg$), and was 2 times more potent than **3a**. Methyl substitution in the 2-position of imidazo[1,2-*a*]pyridine

TABLE X. ^{1}H-NMR (90 MHz) Spectra of **3b—u**, **11a—g**, **18**, **23** and **32a—b**

Compound	δ (ppm) in DMSO-d_6
3b	1.22 (3H, t, J=7 Hz, CH_3), 2.99 (2H, q, J=7 Hz, CH_2), 6.93 (1H, ddd, J=1, 7, 7 Hz, 6-H), 7.27 (1H, ddd, J=1, 7, 8 Hz, 7-H), 7.57 (1H, dd, J=1, 8 Hz, 8-H), 8.18 (1H, s, 3-H), 8.47 (1H, s, 4-H of PN), 8.55 (1H, dd, J=1, 7 Hz, 5-H), 12.84 (1H, brs, NH)
3c	2.52 (3H, s, CH_3), 7.77 (1H, dd, J=2, 9 Hz, 7-H), 7.86 (1H, d, J=9 Hz, 8-H), 8.35 (1H, s, 3-H), 8.44 (1H, s, 4-H of PN), 8.62 (1H, brs, 5-H), 12.96 (1H, brs, NH)
3d	1.21 (3H, t, J=7 Hz, CH_3), 2.28 (3H, s, CH_3), 3.00 (2H, q, J=7 Hz, CH_2), 7.13 (1H, dd, J=1, 9 Hz, 7H), 7.49 (1H, d, J=9 Hz, 8-H), 8.08 (1H, s, 3-H), 8.34 (1H, d, J=1 Hz, 5-H), 8.45 (1H, s, 4-H of PN)
3e	(400 MHz) 2.56 (3H, s, CH_3), 7.85 (1H, ddd, J=2.4, 9.1, 9.9 Hz, 7-H), 7.94 (1H, dd, J=4.8, 9.9 Hz, 8-H), 8.39 (1H, s, 3-H), 8.47 (1H, s, 4-H of PN), 9.10 (1H, t like s, 5-H), 13.05 (1H, brs, NH)
3f	2.61 (3H, s, CH_3), 6.88 (1H, ddd, J=5, 7, 8 Hz, 6-H), 7.16 (1H, ddd, J=2, 8, 11 Hz, 7-H), 8.29 (1H, d, J=3 Hz, 3-H), 8.39 (1H, dd, J=2, 7 Hz, 5-H), 8.54 (1H, s, 4-H or PN), 12.82 (1H, brs, NH)
3g	2.61 (3H, s, CH_3), 7.52 (1H, dd, J=2, 9 Hz, 7-H), 7.75 (1H, d, J=9 Hz, 8-H), 8.28 (1H, s, 3-H), 8.55 (1H, s, 4-H of PN), 9.35, 1H, d, J=2 Hz, 5-H), 12.70 (1H, brs, NH)
3h	1.21 (3H, t, J=7 Hz, CH_3), 2.97 (2H, q, J=7 Hz, CH_2), 7.51 (1H, dd, J=2, 9 Hz, 7-H), 7.74 (1H, d, J=9 Hz, 8-H), 8.28 (1H, s, 3-H), 8.49 (1H, s, 4-H of PN), 9.35 (1H, d, J=2 Hz, 5-H), 12.72 (1H, brs, NH)
3i	2.52 (3H, s, CH_3), 3.26 (3H, s, OCH_3), 7.02 (1H, dd, J=2, 10 Hz, 7-H), 7.50 (1H, d, J=10 Hz, 8-H), 8.07 (1H, s, 3-H), 8.22 (1H, d, J=2 Hz, 5-H), 8.50 (1H, s, 4-H of PN), 12.78 (1H, brs, NH)
3j	2.62 (3H, s, CH_3), 7.52 (1H, dd, J=2, 10 Hz, 7-H), 7.78 (1H, d, J=10 Hz, 8-H), 8.28 (1H, s, 3-H), 8.55 (1H, s, 4-H of PN), 12.81 (1H, brs, NH)
3k	2.45 (3H, s, CH_3), 6.36 (1H, d, J=9 Hz, 3-H of PN), 7.30—7.50 (1H, m, 6-H), 7.74 (1H, d, J=9 Hz, 4-H of PN), 7.84—7.92 (2H, m, 7- and 8-H), 8.36 (1H, s, 3-H), 8.83 (1H, dt, J=1, 7 Hz, 5-H), 12.92 (1H, brs, NH)
3l	2.44 (3H, s, CH_3), 6.34 (1H, d, J=10 Hz, 3-H of PN), 7.66 (1H, dd, J=2, 9 Hz, 7-H), 7.70 (1H, d, J=10 Hz, 4-H of PN), 7.80 (1H, d, J=9 Hz, 8-H), 8.23 (1H, s, 3-H), 8.62 (1H, brs, 5-H), 12.64 (1H, brs, NH)
3m	2.42 (3H, s, CH_3), 6.39 (1H, d, J=10 Hz, 3-H of PN), 7.70 (1H, d, J=10 Hz, 4-H of PN), 7.84—8.00 (1H, m, 7-H), 7.90—8.08 (1H, m, 8-H), 8.36 (1H, s, 3-H), 9.04—9.20 (1H, m, 5-H), 12.90 (1H, brs, NH)
3n	2.46 (3H, s, CH_3), 7.36—7.54 (1H, m, 6-H), 7.78—8.02 (2H, m, 7 and 8-H), 8.28 (1H, s, 4-H of PN), 8.44 (1H, s, 3-H), 8.86 (1H, dt, J=1, 1, 7 Hz, 5-H), 12.60 (1H, brs, NH)
3o	2.44 (6H, s, 2 × CH_3), 7.74 (1H, dd, J=1, 9 Hz, 7-H), 7.88 (1H, d, J=9 Hz, 8-H), 8.22 (1H, s, 4-H of PN), 8.34 (1H, s, 3-H), 8.66 (1H, brs, 5-H), 12.60 (1H, brs, NH)
3p	2.44 (3H, s, CH_3), 7.70 (1H, dd, J=2, 9 Hz, 7-H), 7.86 (1H, d, J=9 Hz, 8-H), 8.27 (1H, s, 4-H of PN), 9.03 (1H, t like s, 5-H), 12.50 (1H, brs, NH)
3q	2.48 (3H, s, CH_3), 7.18—7.48 (1H, m, 7-H), 7.63 (1H, dd, J=5, 9 Hz, 8-H), 8.13 (1H, s, 3-H), 8.38 (1H, s, 4-H of PN), 8.63—8.78 (1H, m, 5-H), 12.56 (1H, brs, NH)
3r	2.50 (3H, s, CH_3), 7.50 (1H, dd, J=2, 9 Hz, 7-H), 7.73 (1H, d, J=9 Hz, 8-H), 8.22 (1H, s, 3-H), 8.40 (1H, s, 4-H of PN), 9.30 (1H, d, J=2 Hz, 5-H), 12.40 (1H, brs, NH)
3s	2.50 (3H, s, CH_3), 7.50 (1H, dd, J=2, 10 Hz, 7-H), 7.77 (1H, d, J=10 Hz, 8-H), 8.24 (1H, s, 4-H of PN), 8.40 (1H, s, 3-H), 9.19 (1H, brs, 5-H), 12.37 (1H, brs, NH)
3t	2.52 (3H, s, CH_3), 6.91 (1H, ddd, J=1, 7, 7 Hz, 6-H), 7.26 (1H, ddd, J=1, 7, 9 Hz, 7-H), 7.56 (1H, d, J=9 Hz, 8-H), 8.13 (1H, s, 3-H), 8.23 (1H, s, 4-H of PN), 8.51 (1H, dt, J=1, 1, 7 Hz, 5-H), 12.28 (1H, brs, NH)
3u	2.46 (3H, s, CH_3), 7.34 (1H, ddd, J=2, 8, 10 Hz, 7-H), 7.62 (1H, dd, J=6, 10 Hz, 8-H), 8.13 (1H, s, 3-H), 8.20 (1H, s, 4-H of PN), 8.70 (1H, m, 5-H), 12.21 (1H, brs, NH)
11a	(HCl salt) 2.34 (3H, s, CH_3), 7.94 (1H, d, J=9 Hz, 7-H), 8.06 (1H, d, J=9 Hz, 8-H), 8.20 (1H, s, 4-H of PN), 8.25 and 8.37 (each, 1H, d, J=2 Hz, 2- and 3-H), 9.02 (1H, brs, 5-H), 12.94 (1H, brs, NH)
11b	2.30 (3H, s, CH_3), 2.50 (3H, s, CH_3), 7.88 (1H, dd, J=2, 9 Hz, 7-H), 7.93 (1H, d, J=9 Hz, 8-H), 8.05 (1H, s, 3H), 8.20 (1H, s, 4-H of PN), 8.90 (1H, brs, 5-H), 12.90 (1H, brs, NH)
11c	2.10 (3H, s, CH_3), 2.42 (3H, s, CH_3), 7.08 (1H, d, J=10 Hz, 7-H), 7.50 (1H, d, J=10 Hz, 8-H), 7.66 and 7.88 (each, 1H, d, J=1 Hz, 2- and 3-H), 8.02 (1H, s, 4-H of PN), 12.68 (1H, brs, NH)
11d	2.28 (3H, s, CH_3), 3.32 (3H, s, OCH_3), 4.49 (2H, s, OCH_2), 7.18 (1H, dd, J=2, 9 Hz, 7-H), 7.52 (1H, d, J=9 Hz, 8-H), 7.82 (1H, s, 3-H), 8.14 (1H, s, 4-H of PN), 8.56 (1H, brs, 5-H), 12.70 (1H, brs, NH)
11e	2.32 (3H, s, CH_3), 7.23 (1H, dd, J=2, 10 Hz, 7-H), 7.20—7.58 and 7.86—8.08 (5H, m, C_6H_5), 7.62 (1H, d, J=10 Hz, 8-H), 8.17 (1H, s, 4H of PN), 8.37 (1H, s, 3-H), 8.55 (1H, brs, 5-H), 12.80 (1H, brs, NH)
11f	1.11 (3H, t, J=8 Hz, CH_3), 2.53 (2H, q, J=8 Hz, CH_2), 7.91 (1H, bd, J=9 Hz, 7-H), 8.04 (1H, d, J=9.2 Hz, 8-H), 8.18 (1H, s, 4-H of PN), 8.24 and 8.36 (each, 1H, d, J=2 Hz, 2- and 3-H), 8.96 (1H, brs, 5-H), 12.90 (1H, brs, NH)
11g	1.09 (3H, t, J=7 Hz, CH_3), 2.33 (3H, s, CH_3), 2.52 (2H, q, J=7 Hz, CH_2), 7.08 (1H, dd, J=2, 9 Hz, 7-H), 7.45 (1H, d, J=9 Hz), 7.65 (1H, s, 3-H), 8.10 (1H, s, 4-H of PN), 8.44 (1H, brs, 5-H), 12.68 (1H, brs, NH)
18	2.20 (3H, s, CH_3), 7.42—7.60 (1H, m, 6-H), 7.88—8.12 (2H, m, 7- and 8-H), 8.24 (1H, s, 4-H of PN), 8.28 (1H, s, 2-H), 8.66 (1H, d, J=7 Hz, 5-H), 12.80 (1H, brs, NH)
23	2.32 (3H, s, CH_3), 6.92 (1H, dd, J=2, 8 Hz, 6-H), 7.56 and 7.96 (each, 1H, s, 2- and 3-H), 7.62 (1H, d, J=2 Hz, 8-H), 8.16 (1H, s, 4-H of PN), 8.56 (1H, d, J=8 Hz, 5-H), 12.64 (1H, brs, NH)
32a	2.20 (3H, s, CH_3), 6.92 (1H, t, J=7, 8 Hz, 6-H), 7.16 (1H, dd, J=2, 8 Hz, 7-H), 7.52 and 7.92 (each, 1H, d, J=1 Hz, 2- and 3-H), 8.14 (1H, s, 4-H of PN), 8.54 (1H, dd, J=2, 7 Hz, 5-H), 12.80 (1H, brs, NH)
32b	2.16 (3H, s, CH_3), 2.43 (3H, s, CH_3), 7.74 (1H, brs, 8-H), 8.13 and 8.33 (each, 1H, br d, 2- and 3-H), 8.15 (1H, s, 4-H of PN), 8.75 (1H, brs, 5-H), 12.74 (1H, brs, NH)

PN: Pyridinone ring.

(**11b**) retained the activity of **11a**, whereas substitution in other positions or with other substituents did not offer any advantage over **11a** and only resulted in decreased potency.

Regioisomers at the positions 3, 7 and 8 of the imidazo[1,2-*a*]pyridine moiety, **18**, **23** and **32a**, were less potent than **3a** and **11a**. The weak activities of these isomers were also shown in guinea pig papillary muscles (Table VII). The drastic decreases in the activity of 7-yl isomer

23 in comparison with that of 6-yl isomer **11a** shows the orientation of nitrogen which may function as a hydrogen-bond-acceptor appears to be a critical determinant of inotropic potency.

The selected compounds, **3e** and **11a** (**3n** and **3u** were not chosen due to their short duration) were further examined for oral activity in conscious dogs. Table VIII shows comparative data obtained from **11a** and milrinone. The inotropic response of **11a** at a dose of 1 mg/kg (maximum response: a 37% increase) lasted in excess of 6 h without a significant increase in heart rate. The same dose of milrinone produced a 60% increase in contractility, but the effect was of relatively short duration and the effect on heart rate was greater than that of **11a**. According to electrophysiological studies, the positive chronotropic effect of **11a** in isolated guinea pig sinus nodes was lower than that of milrinone. The reason was the magnitude of the increase in the slope of slow diastolic depolarization, and the shortening of the action potential duration caused by **11a** was less than that caused by milrinone.[22] The mechanism of inotropic action of milrinone and related compounds appears to involve, at least at part, the selective inhibition of the low-K_m, cyclic AMP specific phosphodiesterase (PDE III) that is present in myocardial cells as mentioned above. **11a** was consequently investigated for its ability to inhibit cardiac PDE III, and demonstrated a potent inhibitory effect. The inhibitory effects for PDE I and PDE II were significantly less (Table IX).

In conclusion, a series of 5-imidazo[1,2-*a*]pyridinyl-2(1*H*)-pyridinone possessing potent cardiotonic properties has been discovered. These new agents also retain potent inhibitory activity of cardiac PDE III. On the basis of extensive pharmacological and toxicological evaluations, **11a** hydrochloride monohydrate (E-1020)[23] was selected for development for the management of congestive heart failure.

Experimental

Melting points were determined on a Yamato Model MP 12 capillary melting point apparatus and are uncorrected. ^{1}H-NMR spectra (90 MHz and 400 MHz) were obtained on a JEOL FX-90Q or a JEOL JNM-GX400 spectrometer. Chemical shifts are expressed in values (ppm) with tetramethylsilane as an internal standard. Elemental analyses were within ±0.4% of the calculated values, except where noted otherwise. The reported yields for the procedures obtained were not optimized.

5-Acetyl-6-methyl-2(1*H*)-pyridinone (1c) A mixture of **1a**[16] (12.8 g, 72.6 mmol) in 50% H_2SO_4 (100 ml) was refluxed for 7.5 h. After cooling, the reaction mixture was adjusted to pH 2 with 20% NaOH solution. The precipitates were collected by filtration, washed with water and dried to give 6.9 g (49%) of 5-acetyl-1,2-dihydro-6-methyl-2-oxo-3-pyridinecarboxylic acid, mp 236—238 °C. *Anal.* Calcd for $C_9H_9NO_4$: C, 55.38; H, 4.66; N, 7.17. Found: C, 55.41; H, 4.62; N, 7.19. A mixture of the acid (30.5 g) in Dowtherm A (100 ml) was refluxed for 3 h. After cooling, the precipitates were collected by filtration and recrystallized from EtOH to afford 18.4 g (78%) of **1c**, mp 196—198 °C. ^{1}H-NMR ($CDCl_3$): 2.47 (2H, s, $COCH_3$), 2.70 (3H, s, CH_3), 6.48 (1H, d, J=11 Hz, 3-H), 7.90 (1H, d, J=11 Hz, 4-H), 12.32 (1H, br s, NH).

5-Acetyl-3-bromo-6-methyl-2(1*H*)-pyridinone (1d) To a stirred mixture of **1c** (5.4 g, 35.7 mmol) in 4.5 ml of 48% HBr, 7 ml (72 mmol) of 35% H_2O_2 was added dropwise at 40—60 °C, then the mixture was stirred at 60 °C for 1 h. After cooling, the solid materials were collected by filtration and were recrystallized from MeOH to afford 4.12 g (50%) of **1d**, mp 216—217 °C. *Anal.* Calcd for $C_8H_8BrNO_2$: C, 41.76; H, 3.51; N, 6.09. Found: C, 41.93; H, 3.46; N, 6.08. ^{1}H-NMR ($CDCl_3$): 2.48 (3H, s, $COCH_3$), 2.70 (3H, s, CH_3), 8.24 (1H, s, 4-H), 12.90 (1H, br s, NH).

5-Acetyl-3-chloro-6-methyl-2(1*H*)-pyridinone (1e) To a stirred mixture of **1c** (13.5 g, 89.3 mmol) in 35 ml of conc. HCl, 17.4 ml (179 mmol) of 35% H_2O_2 was added dropwise at 40—60 °C, and the mixture was stirred at 60 °C for 1 h. After cooling, the reaction mixture was neutralized with K_2CO_3 solution and extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was twice chromatographed on silica gel with AcOEt–hexane (7 : 3), and recrystallized from EtOH to give 1.6 g (9.6%) of **1e**, mp 182—183 °C. *Anal.* Calcd for $C_8H_8ClNO_2$: C, 51.76; H, 4.35; N, 7.55. Found: C, 51.60; H, 4.24; N, 7.56. ^{1}H-NMR ($CDCl_3$): 2.46 (3H, s, $COCH_3$), 2.70 (3H, s, CH_3), 7.98 (1H, s, 4-H), 13.0 (1H, br s, NH).

5-Bromoacetyl-1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile (2a) To a suspension of **1a** (19.3 g, 109.7 mmol) in 30% HBr–AcOH (3 ml) and AcOH (160 ml) was added dropwise Br_2 (5.79 ml, 109.7 mmol), and the mixture was heated at 50—60 °C with stirring until the red color of bromine disappeared (for about 1 h). The precipitates were collected by filtration, washed with ether and recrystallized from DMF–MeOH to afford 20.3 g (73%) of **2a**, 210—212 °C. ^{1}H-NMR (DMSO-d_6): 2.54 (3H, s, CH_3), 4.72 (2H, s, CH_2), 8.68 (1H, s, 4-H), 12.44 (1H, br s, NH). **2c**—**e** were prepared similarly. **2c**: Yield 54%, mp 204—206 °C. ^{1}H-NMR ($CDCl_3$): 2.74 (3H, s, CH_3), 4.23 (2H, s, CH_2), 6.48 (1H, d, J=10 Hz, 3-H), 7.88 (1H, d, J=10 Hz, 4-H), 12.40 (1H, br s, NH). **2d**: Yield 70% (purified by chromatography with AcOEt–hexane = 8 : 2), mp 192—194 °C. ^{1}H-NMR ($CDCl_3$): 2.72 (3H, s, CH_3), 4.22 (2H, s, CH_2), 8.22 (1H, s, 4-H), 12.42 (1H, br s, NH). **2e**: Yield 10% (purified by chromatography with AcOEt : hexane = 8 : 2), mp 179—181 °C. ^{1}H-NMR ($CDCl_3$): 2.76 (3H, s, CH_3), 4.22 (2H, s, CH_2), 8.04 (1H, s, 4-H), 12.22 (1H, br s, NH).

5-Bromoacetyl-6-ethyl-1,2-dihydro-2-oxo-3-pyridinecarbonitrile (2b) **1b** was obtained as a mixture with 1,2-dihydro-6-methyl-2-oxo-5-(*n*-propanoyl)-3-pyridinecarbonitrile (the ratio estimated by ^{1}H-NMR was 2 : 3) in accordance with the method for **1a** but replacing acetylacetone with 2,4-hexanedione. The mixture (7.0 g) was brominated similarly and recrystallized three times from AcOEt–hexane to give 0.9 g of **2b** (23%), mp 183—185 °C. ^{1}H-NMR (DMSO-d_6): 1.16 (3H, t, J=7 Hz, CH_3), 2.86 (2H, q, J=7 Hz, CH_2), 4.76 (2H, s, CH_2), 8.72 (1H, s, 4-H), 12.23 (1H, br s, NH).

1,2-Dihydro-5-imidazo[1,2-*a*]pyridin-2-yl-6-methyl-2-oxo-3-pyridinecarbonitrile (3a) (General Procedure) 2-Aminopyridine (2.4 g, 25.5 mol) was added portionwise to a boiling clean solution of **2a** (2 g, 8.4 mmol) in CH_3CN (250 ml). After refluxing for 1.5 h, the precipitates were collected by filtration while hot and washed with CH_3CN, acetone and EtOH to yield 1.54 g (77.8%) of pure **3a** (Table I). ^{1}H-NMR (CF_3COOD): 2.4 (3H, s, CH_3), 7.56 (1H, ddd, J=2, 5, 9 Hz, 6-H of imidazo[1,2-*a*]pyridine (IM)), 7.9—8.16 (1H, m, 7-H of IM), 8.0 (1H, s, 8-H of IM), 8.06 (1H, s, 3-H of IM), 8.27 (1H, s, 4-H of pyridinone (PN)), 8.64 (1H, d, J=9 Hz, 5-H of IM). Compounds **3b**—**u** were prepared similarly and the results are listed in Table I. HCl salts of some compounds were prepared by treatment of hot solutions of free bases in DMF with HCl–EtOH.

Methyl 6-Imidazo[1,2-*a*]pyridinecarboxylate After a mixture of bromoacetaldehyde diethyl acetal (11.38 g, 57.5 mmol), H_2O (40 ml) and conc. HCl (1.15 ml, 11.3 mmol) was stirred vigorously at room temperature for 2.5 h, it was heated in an 80 °C oil bath for 40 min to give a clear solution. The cold solution was treated with portions of $NaHCO_3$ (6.28 g, 74.8 mmol) and methyl 2-amino-5-pyridinecarboxylate[24] (7 g, 46 mmol). The mixture was stirred overnight at room temperature. The precipitates were collected by filtration, washed with a small volume of water and dried over P_2O_5 to give 7.5 g (99%) of methyl 6-imidazo[1,2-*a*]pyridinecarboxylate, mp 145—146 °C, which was used in the next reaction without futher purification. ^{1}H-NMR ($CDCl_3$): 3.94 (3H, s, CH_3), 7.62—7.74 (4H, m, 2-, 3-, 7- and 8-H), 8.92 (1H, t like s, 5-H). Methyl 7-imidazo-[1,2-*a*]pyridinecarboxylate was similarly prepared in 89% yield from methyl 2-amino-4-pyridinecarboxylate,[25] mp 143—144 °C. ^{1}H-NMR ($CDCl_3$): 3.97 (3H, s, CH_3), 7.40 (1H, dd, J=2, 7 Hz, 6-H), 7.70 (1H, d, J=1 Hz, 2-H), 7.80 (1H, d, J=1 Hz, 3-H), 8.19 (1H, dd, J=1, 7 Hz, 5-H), 8.37 (1H, br s, 8-H).

Methyl 8-Imidazo[1,2-*a*]pyridinecarboxylate A solution of 2-amino-3-pyridinecarbonitrile[26] (9.5 g, 79.7 mmol) and bromoacetaldehyde diethylacetal (50 g, 253.7 mmol) in *n*-butanol (100 ml) was refluxed overnight. The precipitates were collected by filtration and dissolved in H_2O (200 ml). The solution was adjusted to pH 8 with sat. $NaHCO_3$ solution, extracted with $CHCl_3$, washed with brine and dried over $MgSO_4$. Removal of solvent *in vacuo* gave 8.2 g (72%) of 8-imidazo[1,2-*a*]pyridinecarbonitrile, mp 167—169 °C, which was used in the next reaction without further purification. ^{1}H-NMR ($CDCl_3$): 6.90 (1H, dd, J=7, 7 Hz, 6-H), 7.79 (1H, d, J=1 Hz, 2-H), 8.36 (1H, dd, J=1, 7 Hz, 5-H). A solution of 8-imidazo[1,2-*a*]pyridinecarbonitrile (9 g, 62.9 mmol) in MeOH and conc. H_2SO_4 (25 g) was refluxed for 2 d. After solvent was removed *in*

vacuo, ice was added to the residue. Then the solution was adjusted to pH 8 with 20% NaOH and sat. $NaHCO_3$ solution, and extracted with $CHCl_3$. The organic layer was washed with brine and dried over $MgSO_4$. After removal of solvent, the residue was chromatographed on silica gel with AcOEt–MeOH (95:5) to give 3.9 g (38%) of methyl 8-imidazo[1,2-*a*]pyridinecarboxylate, mp 70—72 °C. ^{1}H-NMR ($CDCl_3$): 4.00 (3H, s, CH_3), 6.82 (1H, dd, J=8, 8 Hz, 6-H), 7.66 (1H, d, J=1 Hz, 3-H), 7.72 (1H, d, J=1 Hz, 2-H), 7.94 (1H, dd, J=2, 8 Hz, 5-H), 8.30 (1H, dd, J=2, 8 Hz, 7-H).

The following compounds were prepared according to the method of Hand and Paudler[27] like methyl 6-imidazo[1,2-*a*]pyridinecarboxylate.

6-Bromoimidazo[1,2-*a*]pyridine (**6a**): Yield 71%, bp 123—125 °C (1.5 mmHg), mp 76—78 °C (lit.[18] mp 53—55 °C). ^{1}H-NMR ($CDCl_3$): 7.21 (1H, dd, J=2, 10 Hz, 7-H), 7.48 (1H, d, J=10 Hz, 8-H), 7.58 (1H, d, J=1 Hz, 2-H), 7.64 (1H, d, J=1 Hz, 3-H), 8.30 (1H, dd, J=1, 2 Hz, 5-H).

6-Bromo-5-methylimidazo[1,2-*a*]pyridine (**6c**) (from 2-Amino-5-bromo-6-methylpyridine)[28]: Yield 76%, mp 122—124 °C (recrystallized from cyclohexane). ^{1}H-NMR ($CDCl_3$): 2.74 (3H, s, CH_3), 7.26 (1H, d, J=9 Hz, 7-H), 7.42 (1H, d, J=9 Hz, 8-H), 7.46 (1H, s, 3-H), 7.64 (1H, s, 2-H).

8-Bromo-6-methylimidazo[1,2-*a*]pyridine (**28**) (from 2-Amino-3-bromo-5-methylpyridine)[29]: Yield 71%, mp 70.5—71.5 °C (recrystallized from cyclohexane). ^{1}H-NMR ($CDCl_3$): 2.28 (3H, s, CH_3), 7.28 (1H, d, J=2 Hz, 7-H), 7.56 (1H, d, J=1 Hz, 3-H), 7.62 (1H, d, J=1 Hz, 2-H), 7.88 (1H, d, J=2 Hz, 5-H).

6-Bromo-2-methylimidazo[1,2-*a*]pyridine (**6b**) and 6-Bromo-2-phenylimidazo[1,2-*a*]pyridine (**6e**) were obtained by the procedure of Godovikova and Gol'dfab.[30]

6-Bromo-2-methoxymethylimidazo[1,2-*a*]pyridine (6d) A solution of 2-amino-5-bromopyridine (19.9 g, 114 mmol) and ethyl bromopyruvate (25.8 g, 132.3 mmol) in dimethoxyethane was stirred at room temperature for 2 h. The precipitates were collected by filtration and refluxed in EtOH (700 ml) for 3 h. After removing solvent, the residue was dissolved in H_2O. The solution was adjusted to pH 8 with sat. $NaHCO_3$ solution and extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated to afford 22.2 g (72%) of ethyl 6-bromoimidazo[1,2-*a*]pyridine-2-carboxylate, mp 126—128 °C, which was used without further purification. ^{1}H-NMR ($CDCl_3$): 1.44 (3H, t, J=7 Hz, CH_3), 4.44 (2H, q, J=7 Hz, CH_2), 7.28 (1H, s, dd, J=2, 10 Hz, 7-H), 7.58 (1H, d, J=10 Hz, 8-H), 8.12 (1H, s, 3-H), 8.28 (1H, d, J=2 Hz, 5-H). To a stirred solution of ethyl 6-bromoimidazo[1,2-*a*]pyridinyl-2-carboxylate (12 g, 44.6 mmol) in CH_2Cl_2 (150 ml). 1 M solution of diisobutylaluminum hydride (DIBAL) in CH_2Cl_2 (100 ml) was added dropwise at −5—0 °C under N_2. The mixture was stirred for 3 h at 0—10 °C, then 3.5 ml of MeOH was added at −40 °C and 4.5 ml of H_2O was added at 0 °C with stirring. After dissolving solids by adding 6 N HCl, the solution was alkalized with 20% NaOH solution and extracted three times with $CHCl_3$ (300 ml). The combined organic extracts were washed with brine and dried and evaporated to solid. Chromatography on silica gel, eluting with $CHCl_3$–MeOH (98:2), gave 6.8 g (66.3%) of 6-bromo-2-hydroxymethylimidazo[1,2-*a*]pyridine, mp 137 °C. ^{1}H-NMR ($CDCl_3$): 3.2—4.2 (1H, br s, OH), 4.82 (2H, s, CH_2), 7.18 (1H, dd, J=2, 9 Hz, 7-H), 7.48 (1H, d, J=9 Hz, 8-H), 7.50 (1H, s, 3-H), 8.20 (1H, m, 5-H). To a solution of 6-bromo-2-hydroxymethylimidazo[1,2-*a*]pyridine (2.85 g, 12.3 mmol) in CH_2Cl_2 (200 ml) was added thionyl chloride (1.6 g, 13.4 mmol) at 5 °C, and the mixture was stirred at room temperature for 2 h. After ice and sat. aq. $NaHCO_3$ solution (50 ml) were added, the organic layer was separated, washed with brine and evaporated to give crude 6-bromo-2-chloromethylimidazo[1,2-*a*]pyridine (3.08 g) which was used without further purification. The mixture of 6-bromo-2-chloromethylimidazo-[1,2-*a*]pyridine (3.0 g) and 1.3 g (24 mmol) of NaOMe in MeOH (50 ml) was refluxed for 3 h. After solvent was evaporated, the residue was dissolved in $CHCl_3$. The solution was washed with brine and dried over $MgSO_4$. Solvent was removed *in vacuo*, and the residue was chromatographed on silica gel with $CHCl_3$–MeOH (98:2) to give 2.8 g (95.4%) of **6d**, mp 104—106 °C. ^{1}H-NMR ($CDCl_3$): 3.46 (3H, s, OCH_3), 4.73 (2H, s, CH_2), 7.20 (1H, dd, J=2, 9 Hz, 7-H), 7.46 (1H, d, J=9 Hz, 8-H), 7.56 (1H, s, 3-H), 8.20 (1H, br s, 5-H).

1-Imidazo[1,2-*a*]pyridin-6-yl-2-propanone (9a) (General Procedure) Method A To a solution of methyl 6-imidazo[1,2-*a*]pyridinecarboxylate (49 g, 298.5 mmol) in CH_2Cl_2 (500 ml), 1.0 M solution of DIBAL in CH_2Cl_2 (400 ml, 1.34 mmol) was added dropwise at −60 °C under N_2 over a 3 h period. The excess DIBAL was decomposed with MeOH and then water. The solids were removed by filtration and washed with MeOH. After removal of solvent *in vacuo*, the crude product was chromatographed on silica gel with $CHCl_3$–MeOH (98:2) to afford 7.5 g (17.2%) of pure 6-imidazo[1,2-*a*]pyridinecarboxaldehyde **4**, mp 146—148 °C. ^{1}H-NMR ($CDCl_3$): 7.64—7.80 (4H, m, 2-, 3-, 7- and 8-H), 8.70 (1H, m, 5-H), 9.96 (1H, s, CHO). 7- and 8-imidazo[1,2-*a*]pyridinecarboxaldehydes, **24** and **26**, were similarly prepared. **24**: Yield 23%, mp 143—144 °C. ^{1}H-NMR ($CDCl_3$): 7.34 (1H, dd, J=2, 7 Hz, 6-H), 7.76 (1H, s, 2-H), 7.86 (1H, d, J=1H, 3-H), 8.13 (1H, dd, J=1, 2 Hz, 8-H), 8.22 (1H, d, J=7 Hz, 5-H), 10.00 (1H, s, CHO). **26**: Yield 57%, mp 103—104 °C. ^{1}H-NMR ($CDCl_3$): 6.90 (1H, dd, J=7, 7 Hz, 6-H), 7.66 (1H, d, J=1 Hz, 3-H), 7.72 (1H, d, J=1 Hz, 2-H), 7.76 (1H, dd, J=2, 7 Hz, 7-H), 8.30 (1H, dd, J=2, 7 Hz, 5-H). A mixture of **4** (6.9 g, 47.2 mmol), nitroethane (10.6 g, 141.2 mmol), *n*-butylamine (30 drops) in EtOH (40 ml) was refluxed for 14 h, then some of ethylamine was added, and the mixture was refluxed for an additional 18 h. The solids were removed by filtration while hot EtOH (50 ml) and Et_2O (150 ml) were added and the solids were removed by filtration again. After removal of solvent *in vacuo*, the residue was purified twice by recrystallization from EtOH to give 1.14 g (11.9%) of 6-(2-nitro-1-propenyl)imidazo[1,2-*a*]pyridine **5**, mp 190—192 °C (dec.). ^{1}H-NMR ($CDCl_3$): 2.52 (3H, d, J=1 Hz, CH_3), 7.26 (1H, dd, J=2, 9 Hz, 7-H), 7.66 (1H, d, J=1 Hz, 3-H), 7.70 (1H, d, J=9 Hz, 8-H), 7.73 (1H, d, J=1 Hz, 2-H), 8.04 (1H, d, J=1 Hz, =CH), 8.30 (1H, d, J=2 Hz, 5-H). 7- and 8-(2-Nitro-1-propenyl)imidazo[1,2-*a*]pyridine, **25** and **27**, were prepared similarly. **25**: Yield 48%, mp 135—137 °C. ^{1}H-NMR ($CDCl_3$): 2.53 (3H, d, J=1 Hz, CH_3), 6.86 (1H, dd, J=2, 7 Hz, 6-H), 7.68 (1H, dd, J=1, 2 Hz, 8-H), 7.76 (2H, br s, 2- and 3-H), 8.05 (1H, br s, =CH), 8.20 (1H, dd, J=1, 7 Hz, 5-H). **27**: Yield 25% mp 158—160 °C. ^{1}H-NMR ($CDCl_3$): 2.46 (3H, d, J=1 Hz, CH_3), 6.85 (1H, dd, J=8, 8 Hz, 6-H), 7.22 (1H, d, J=8 Hz, 7-H), 7.63 (2H, s, 2- and 3-H), 8.16 (1H, d, J=8 Hz, 5-H), 8.48 (1H, d, br s, =CH). A vigorously stirred mixture of 1.14 g (5.6 mmol) of **5**, Fe powder (2.35 g), $FeCl_2 \cdot (H_2O)_x$ (0.1 g) in EtOH (25 ml)–H_2O (25 ml) was heated at 80 °C and treated dropwise with 2.5 ml of conc. HCl. Upon refluxing for an additional 1 h, the hot reaction mixture was filtered. After removal of solvent *in vacuo*, the residue was made basic with $NaHCO_3$ solution and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with brine, dried over $MgSO_4$, and evaporated to give an oil, which was purified by chromatography on silica gel with $CHCl_3$–MeOH (99:1) to afford 0.5 g (51.2%) of **9a** (bp is shown at method C). ^{1}H-NMR ($CDCl_3$): 2.24 (3H, s, CH_3), 3.70 (2H, s, CH_2), 6.95 (1H, dd, J=2, 9 Hz, 7-H), 7.56 (1H, br s, 3-H), 7.60 (1H, d, J=9 Hz, 8-H), 7.64 (1H, s, 2-H), 8.03 (1H, m, 5-H). **21** and **30a** were prepared similarly and the results are listed in Table III.

Method B A mixture of **6a** (1.97 g, 10 mmol), potassium acetoacetonate (6.91 g, 50 mmol), dried potassium iodide (1.66 g, 10 mmol), and cuprous iodide (0.1 g, 0.5 mmol) in DMF was stirred at 100 °C for 15 h under N_2. To the cooled reaction mixture 20% solution of NaOH (30 ml) was added and the mixture was stirred at room temperature for 3 h. Then, the mixture was adjusted to pH 1 with conc. HCl, and washed with $CHCl_3$ (3 × 100 ml). The aqueous layer was made basic with excess $NaHCO_3$, saturated with NaCl and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with brine, dried over $MgSO_4$, and evaporated to give a dark brown oil, which was purified by silica gel chromatography ($CHCl_3$: MeOH = 99 : 1) to afford 655 mg (37.6%) of **9a**.

Method C A solution of ethylbromide (8.25 g, 76 mmol) in THF (14 ml) was added dropwise to magnesium turning (24.5 g, 1 mol) under N_2, and to the resulting mixture a solution of **6a** (49.25 g, 0.25 mol) and ethylbromide (74.25 g, 0.68 mol) in tetrahydrofuran (THF) (300 ml) was added dropwise over a 40 min-period maintaining the temperature at 50 to 60 °C. After completion of the addition, the reaction mixture was refluxed for 1 h. To the stirred reaction mixture, a solution of 3-chloro-2-methylpropene (97.5 g, 1.08 mol) in THF (200 ml) was added dropwise at 0 to 10 °C, and the mixture was then refluxed for 2 h. After cooling, a solution of ammonium chloride (50 g) in water (500 ml) was added dropwise to the mixture, and then toluene (250 ml), hexane (200 ml) and water (200 ml) were added. The organic layer was separated, washed twice with brine, and dried over $MgSO_4$. After removal of solvent *in vacuo*, the product was purified by distillation under reduced pressure to give 30.5 g (70.9%) of 6-isobutenylimidazo[1,2-*a*]pyridine **8a**, boiling at 118—122 °C/0.5 mmHg. ^{1}H-NMR ($CDCl_3$): 1.70 (3H, s, CH_3), 3.28 (2H, s, CH_2), 4.80 (1H, d, J=1 Hz, H of $=CH_2$), 4.90 (1H, d, J=1 Hz, H of $=CH_2$), 7.02 (1H, dd, J=2, 9 Hz, 7-H), 7.52 (1H, d, J=1 Hz, 3-H), 7.56 (1H, d, J=9 Hz, 8-H), 7.72 (1H, d, J=1 Hz, 2-H), 7.92 (1H, br s, 5-H). **8b—e**, **15**, **20** and **29** were prepared similarly and the results are listed in Tables II and III. Ozone produced by an ozone generator (Nihon Ozone 0-10-3) was introduced to a solution of **8a** (20 g, 116.1 mmol) in conc. HCl (12.3 g), water (45 ml) and MeOH (45 ml) at −5 to 0 °C. The endpoint of the reaction was confirmed by thin layer chromatography (TLC). After

completion of reaction, a solution of sodium sulfite (30.6 g) in water (160 ml) was added dropwise under cooling at a rate that did not exceed 20 °C. Then, $NaHCO_3$ (22 g) and an appropriate amount of NaCl were added as solid and the mixture was extracted with $CHCl_3$. The organic layer was washed twice with brine and dried over $MgSO_4$. After removal of solvent *in vacuo*, the product was purified by distillation under reduced pressure to provide 14.2 g (70.5%) of **9a** boiling at 155—159 °C/0.4 mmHg. **9b—e**, **16**, **21** and **30b** were prepared similarly. *Via* method C but replacing 3-chloro-2-methylpropene with 3-chloro-2-ethylpropene, 1-imidazo-[1,2-*a*]pyridin-6-yl-2-butanones, **9f** and **9g**, were obtained. These results are listed in Tables II and III.

4-Dimethylamino-3-(6-imidazo[1,2-*a*]pyridinyl)-3-buten-2-one (10a) (General Procedure) A mixture of **9a** (33.17 g, 0.19 mol) and *N*,*N*-dimethylformamide dimethylacetal (45.4 g, 0.38 mol) in DMF (200 ml) was stirred at 80 °C for 1 h. The solution was concentrated under reduced pressure and the residue was purified by silica gel chromatography with $CHCl_3$–MeOH (97 : 3) to afford 32.46 g (74.5%) of **10a**, mp 176—178 °C. *Anal.* Calcd for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 67.91; H, 6.67; N, 18.34. ^{1}H-NMR ($CDCl_3$): 2.04 (3H, s, CH_3), 2.80 (6H, s, $N(CH_3)_2$), 7.03 (1H, dd, J=2, 9 Hz, 7-H), 7.55 (1H, s, 3-H), 7.57 (1H, d, J=9 Hz, 8-H), 7.63 (2H, s, 2-H and =CH), 7.90 (1H, br s, 5-H). **10b—g**, **17**, **22** and **31a**, **b** were prepared similarly and the results are listed in Tables II and III.

1,2-Dihydro-5-imidazo[1,2-*a*]pyridin-6-yl-6-methyl-2-oxo-3-pyridinecarbonitrile (11a) Hydrochloride Monohydrate (General Procedure) To a solution of **10a** (23.5 g, 0.102 mol) in DMF (230 ml) was added 2-cyanoacetamide (9.48 g, 0.113 mol) and $NaOCH_3$ (12.2 g, 0.226 mol) and the mixture was heated at 80—90 °C for 12 h. DMF was evaporated under reduced pressure, and the residue was dissolved in water and washed with $CHCl_3$. After the pH of the aqueous layer was adjusted to 6.5 with AcOH (5 ml), the precipitated crystals were collected by filtration and washed with water. The crystals were dissolved in 2.5% NaOH solution (200 ml) and treated with chacol. PH of the solution was adjusted to 6.5 with AcOH (7 ml) and the precipitates were collected by filtration and washed with water, CH_3CN and ether. This was recrystallized from DMF to give **11a** (13 g, 50.9%), mp >300 °C. *Anal.* Calcd for $C_{14}H_{10}N_4O$: C, 67.18; H, 4.04; N, 22.39. Found: C, 67.17; H, 4.02; N, 22.56. ^{1}H-NMR (400 MHz, DMSO-d_6): 2.29 (3H, s, CH_3), 7.23 (1H, dd, J=1.8, 9.5 Hz, 7-H of IM), 7.60 (1H, ddd, J=0.8, 1.1, 9.5 Hz, 8-H of IM), 7.61 (1H, d, J=1.1 Hz, 2-H of IM), 7.92 (1H, dd, J=0.8, 1.1 Hz, 3-H of IM), 8.16 (1H, s, 4-H of PN), 8.58 (1H, dd, J=1.1, 1.8 Hz, 5-H of IM), 12.76 (1H, br s, NH). To a hot solution of **11a** (12.1 g) in DMF (180 ml) was added HCl–EtOH to give hydrochloride (13.5 g) of **11a**, mp >300 °C. *Anal.* Calcd for $C_{14}H_{10}N_4O \cdot HCl \cdot H_2O$: C, 55.16; H, 4.30; N, 18.39. Found: C, 55.26; H, 4.40; N, 18.44. Compounds **11b—g**, **18**, **23** and **32a—b** were prepared similarly and the results are listed in Tables IV and V.

5-(3-Bromoimidazo[1,2-*a*]pyridin-6-yl)-1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile Hydrobromic Acid (12) To a solution of **11a** (0.3 g, 1.2 mmol) in AcOH (10 ml) was added bromine (0.2 g, 1.25 mmol) in AcOH (1 ml) and the mixture was warmed at 30 °C for 30 min. The precipitates were collected by filtration, washed with ether and recrystallized twice from MeOH to give 0.3 g (55%) of **12**, mp >300 °C. ^{1}H-NMR (DMSO-d_6): 2.30 (3H, s, CH_3), 7.81 (1H, dd, J=2, 9 Hz, 7-H of IM), 7.99 (1H, d, J=9 Hz, 8-H of IM), 8.24 (1H, s, 4-H of PN), 8.32 (1H, s, 2-H of IM), 8.68 (1H, d, J=2 Hz, 5-H of IM), 12.98 (1H, br s, NH). A suspension of **12** (0.15 g) in water (30 ml) was adjusted to pH 8 with 28% NH_4OH with stirring. The precipitates were collected by filtration, washed with water and MeOH, and recrystallized from MeOH to give 70 mg of free base of **12**, mp 274—276 °C (dec.). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.28 (3H, s, CH_3), 7.35 (1H, dd, J=1.8, 9.5 Hz, 7-H of IM), 7.69 (1H, dd, J=0.75, 9.5 Hz, 8-H of IM), 7.77 (1H, s, 2-H of IM), 8.19 (1H, s, 4-H of PN), 8.35 (1H, dd, J=0.7, 1.8 Hz, 5-H of IM), 12.76 (1H, br s, NH).

5-Imidazo[1,2-*a*]pyridin-6-yl-6-methyl-2(1*H*)-pyridinone (13) A solution of **11a** (1 g, 4 mmol) in 85% (v/v) phosphoric acid (10 ml) was refluxed for 18 h. After cooling, water (50 ml) was added and the solution was adjusted to pH 8 with 28% NH_4OH. The precipitates were extracted with $CHCl_3$ and the extract was washed with brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was recrystallized from EtOH–ether to give 0.4 g (50%) of **13**, mp 290—292 °C. ^{1}H-NMR ($CDCl_3$): 2.38 (3H, s, CH_3), 6.52 (1H, d, J=9 Hz, 4-H of PN), 7.06 (1H, dd, J=2, 10 Hz, 7-H of IM), 7.40 (1H, d, J=9 Hz, 3-H of PN), 7.52—7.70 (3H, m, 2-, 3- and 8-H of IM), 8.00 (1H, d, J=2 Hz, 5-H of IM), 12.62 (1H, br s, NH).

Pharmacological Methods and Materials 1. Anesthetized Dog Studies: Using mongrel dogs of either sex (10—15 kg) under artificial respiration and anesthetization with halothane-nitrous oxide, the cardiotonic effect of compounds was evaluated. Aortic pressure was recorded with a catheter inserted into the aorta and connected to a pressure transducer. The left ventricular pressure was recorded with a micro tip pressure transducer (Millar PC-360) inserted into the left ventricle. The heart rate was monitored by means of a tachograph triggered by the left ventricular pressure pulse. As an index of cardiac contractility, LV dP/dt_{max}, was recorded. Depending on solubility of the agent, compounds were dissolved in saline, diluted hydrochronic acid or polyethylene glycol, and were administered intravenously.

2. Conscious Dog Studies: Male beagle dogs (10—13 kg) were chronically instrumented to monitor left ventricular pressure and heart rate. Under halothane-nitrous oxide anesthesia, a precalibrated Konigsberg P6.5 pressure transducer was implanted into the left ventricle through a stab wound at the apex. After recovery from surgery, a period of about 1 week was allowed to train the dogs to lie quietly. This conditioning was necessary to obtain stable, reproducible results from day to day. As an index of cardiac contractility, LV dP/dt_{max} was recorded. Drugs were administered orally in gelatin capsules.

3. Isolated Heart Muscle Preparations: 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 and thin papillary muscles (diameter: 0.5—1 mm) from the right ventricle were 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 (mmol/l): 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. The solution was maintained at 37 °C and equilibrated with a mixture of 95% O_2 and 5% CO_2 to make the pH 7.4. Two platinum electrodes were attached close to the base of the papillary muscle to stimulate the muscle with rectangular pulses of 3 ms duration and voltage 20% above the threshold. The basic stimulation frequency was 1 Hz. Contractile force was recorded isometrically by means of a force transducer (TB-611T; Nihon-Koden, Tokyo, Japan) connected to a pen recorder. The resting tension applied to papillary muscles and right atria was adjusted to produce the maximum developed tension. 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 commencement of each experiment. Drugs were directly applied to the bathing solution.

4. Measurement of Phosphodiesterase Activity: Fractions of phosphodiesterase (PDE) were prepared using elution chromatography according to a method similar to that reported by Thompson *et al.*[31] Hearts from guinea pigs were homogenized and sonicated at 4 °C in 5 volumes of 10 mmol/Tris–HCl buffer (pH 7.5) containing 2 mmol/l $MgCl_2$ and 1 mmol/l dithiothreitol. The homogenate was centrifuged at 9300 × *g* for 20 min and the supernatant was again centrifuged at 30000 × *g* for 20 min. The supernatant fraction thus obtained was applied to a column (DEAE-Toyopearl 650S; Toso, Tokyo, Japan). Three fractions of PDE activity (fractions I, II and III) were eluted with an acetate gradient. Each fraction was concentrated by ultrafiltration with PM-10 membrane (Amicon, Danvers, MA, U.S.A.), diluted with 65% ethyleneglycol and stored at −20 °C. PDE activity was determined basically according to the method reported by Thompson *et al.* Briefly, an appropriate dilution of each of the three fractions of the enzyme was incubated at 30 °C in 0.2 ml of medium containing 40 mmol/Tris–HCl, 10 mmol/$MgCl_2$, 3.75 mmol/l 2-mercaptoethanol, 25 μg bovine serum albumin, 1 μmol/l [^{3}H] cyclic AMP and a test compound. After incubation for 5 min, the reaction was terminated by boiling the medium and then cooling in an ice bath. The reaction mixture was incubated for an additional 10 min with 0.05 ml of 1 mg/ml snake venom. This reaction was terminated by the addition of 0.5 ml of a slurry consisting of 1 part resin AG-X2 (Bio-Rad Laboratories, Richmond, CA, U.S.A.) and 3 parts water. The tube containing the mixture was allowed to stand at 4 °C for at least 10 min and centrifuged at 6800 × *g* for 90 s. An aliquot (0.45 ml) of the supernatant was transferred to a vial containing ACS scintillator (Amersham, Buckinghamshire, England) and the radioactivity was determined by a liquid scintillation counter (LSC753; Aloka, Tokyo, Japan).

References and Notes

1) This work was presented in part at the 194th National Meeting of the American Chemical Society, New Orleans, Louisiana, Aug 1987, Abstracts of Papers, MEDI 58.
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14) Some of the 3-pyridinecarbonitriles were disclosed in Japan, patent, J 86-10557, by Jurszky *et al.* after we finished synthesizing them, but no *in vivo* data were shown there.
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