Cyanoamidines. II. Synthesis and Pharmacological Activity of *N*-Arylalkyl-*N'*-cyano-3-pyridinecarboxamidines[1)]

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A new series of cyanoamidines, *N*-arylalkyl-*N'*-cyano-3-pyridinecarboxamidines was synthesized and evaluated for inhibitory effects on 40 mM KCl-induced contraction and norepinephrine (NE)-induced contraction of rat aorta strips. The *N*-phenethyl cyanoamidine 4c showed potent vasodilatory action. Further *in vitro* screening program using 4c as a lead compound resulted in the discovery of highly potent *N*-[2-(2-chlorophenyl)ethyl]-*N'*-cyano-3-pyridinecarboxamidine (5j). Compound 5j induced the greatest increase in $^{86}Rb^+$ efflux among cyanoamidine series. Subsequent modification of the pyridine ring of 5j was performed with evaluation for intravenous and oral antihypertensive activities. Introduction of an amino group at the 5-position of the pyridine ring furnished the new potassium channel opener, 5-amino-*N*-[2-(2-chlorophenyl)ethyl]-*N'*-cyano-3-pyridinecarboxamidine (9e; KRN4884), which showed highly potent antihypertensive activity and a long duration of antihypertensive action after oral administration. KRN4884 is under further development as an antihypertensive agent.

Keywords cyanoamidinopyridine; vasodilation; antihypertensive agent; potassium channel opener; KRN4884

Potassium channel openers represent a novel class of smooth muscle relaxants.[2)] In the preceding paper,[1)] we reported the synthesis and vasodilating activities of *N*-substituted heteroaromatic cyanoamidines. Some of them constituted a new structural class of potassium channel openers, of which *N*-cyano-*N'*-(2-nitroxyethyl)-3-pyridinecarboxamidine (**1**) was the most potent. Its ability to increase $^{86}Rb^+$ efflux was greater than those of representative potassium channel openers, nicorandil, pinacidil, and cromakalim. The nitrate in the molecule plays a significant role not only in activating soluble guanylate cyclase but also in enhancing potassium channel opening activity, which causes vasodilation. Replacement of the nitroxyl group by a hydroxyl, an acyloxyl, or an alkoxyl group led to loss of activity.[1,3)] KRN2391, the methanesulfonate of **1**, was selected for development as an antianginal drug.

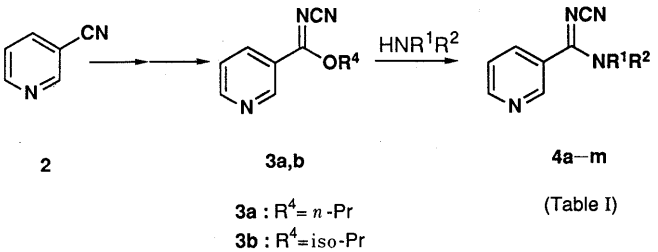
It was of major interest to find a new series of active cyanoamidines without a nitrate moiety. In this paper, we again focused our attention on the *N*-substituent and on structural modification of the pyridine ring.

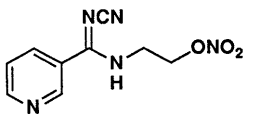
Chemistry

N-Cyano-*N'*-substituted-3-pyridinecarboxamidines **4a—m**, **5a—r** were synthesized according to the method described in the preceding paper (Chart 1).[1)] In a similar manner, *N*-[2-(2-chlorophenyl)ethyl]-*N'*-cyano-5-substituted-3-pyridinecarboxamidines **9** were prepared as outlined in Chart 2. 3-Cyano-5-substituted-pyridines **6a—c, e—j, p**[4)] were converted to imidates **7a—c, e—j, p** by acid-promoted reaction with 1-propanol, followed by alkalization. Crude imidates **7a—c, e—j, p** were then transformed to cyanoimidates **8a—c, e—j, p** by treatment with cyanamide in an aqueous phosphate buffer solution. Acetonitrile was a useful co-solvent when the imidates were poorly soluble in the reaction medium. Reaction of **8a—c, e—j, p** with 2-(2-chlorophenyl)ethylamine in methanol gave cyanoamidines **9a—c, e—j, p**. Compounds **9k—o** were synthesized by acylation or sulfonylation of the amine **9e**. The carboxylic acid **9d** was prepared by hydrolysis of the methyl ester **9p**.

Biological Activity and Discussion

The cyanoamidines **4**, **5** were evaluated for inhibition of the 40 mM KCl-induced contraction of isolated rat aorta. Selected compounds which showed $IC_{50} \leqq 10^{-5}$ M were examined for ability to relax endothelial-denuded rat aorta strips toned with norepinephrine (NE). Table I showed





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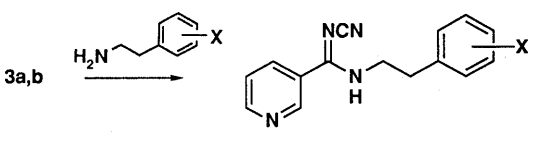
KRN2391: methanesulfonate of **1**

Fig. 1



5a—r

(Table II)

Chart 1

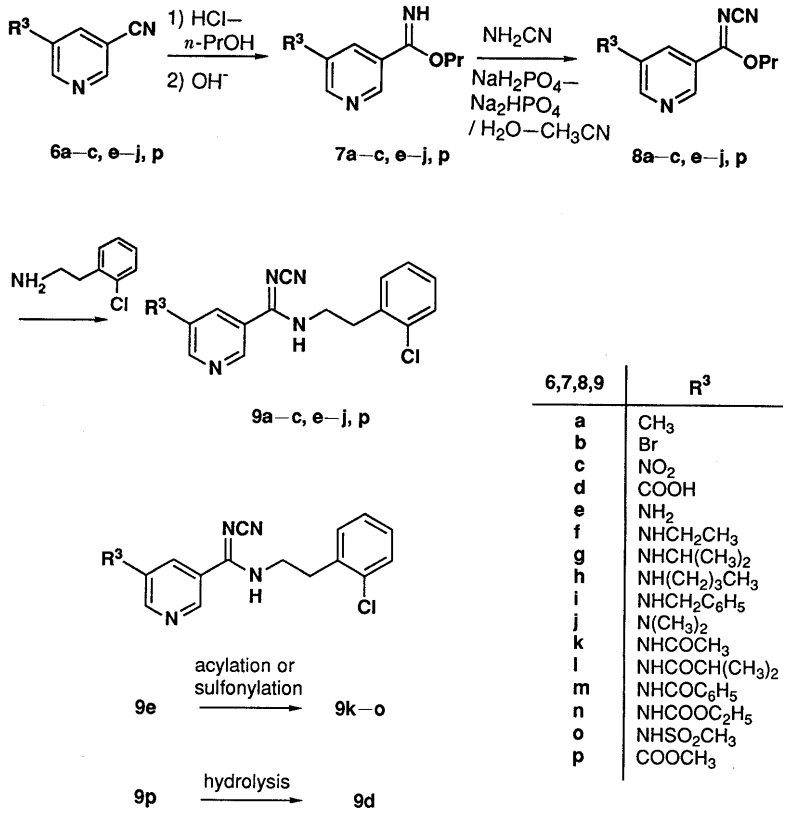
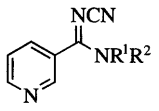


Chart 2

TABLE I. Vasodilatory Activities of Cyanoamidines **4**



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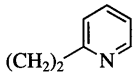
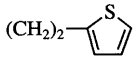
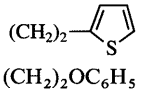
Compd.[a] No.	R^1	R^2	IC_{50} (M)[b] 40 mM K^+	IC_{50} (M)[b] NE
4a	C_6H_5	H	3.5×10^{-4}	
4b	$CH_2C_6H_5$	H	6.6×10^{-5}	5.8×10^{-4}
4c	$(CH_2)_2C_6H_5$	H	4.0×10^{-5}	2.6×10^{-6}
4d	$(CH_2)_3C_6H_5$	H	9.5×10^{-5}	1.5×10^{-5}
4e	$(CH_2)_4C_6H_5$	H	5.9×10^{-4}	
4f	$(CH_2)_2C_6H_5$	CH_3	1.6×10^{-3}	
4g	$(CH_2)_2C_6H_5$	$CH_2C_6H_5$	No effect	
4h	$(CH_2)_2C_6H_5$	$(CH_2)_2C_6H_5$	No effect	
4i		H	4.2×10^{-3}	
4j		H	2.9×10^{-3}	
4k		H	9.7×10^{-3}	
4l[c]	$(CH_2)_2OC_6H_5$	H	8.7×10^{-2}	
4m	$(CH_2)_2OCH_2C_6H_5$	H	1.7×10^{-3}	
1	$(CH_2)_2ONO_2$	H	5.1×10^{-5}	2.6×10^{-7}

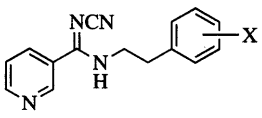
a) Structures of all compounds were confirmed by IR, NMR, and elemental analysis. *b*) Molar concentration for 50% inhibition of isolated rat aorta precontracted by 40 mM K^+ and 10^{-7} M NE. *c*) Methanesulfonate.

that activity was maximum in the *N*-phenethyl derivative **4c**. Introduction of a second alkyl group (**4f—h**) at cyanoamidine nitrogen[5] caused a marked reduction of activity. Replacement of phenyl in the *N*-substituent with pyridyl (**4i**) or thienyls (**4j, k**) and insertion of an oxygen atom into those phenylalkyl substituents (**4l, m**) each caused a substantial fall in activity. The *N*-phenethyl moiety seems to be crucial for good vasodilatory activity.

We next focused our attention upon the substituent on the benzene ring in the phenethyl group. The results are listed in Table II. Compounds **5a—c** having a methyl group showed low activity compared to **4c** and the 4-methyl compound **5c** was the least active among them. A powerful electron-withdrawing nitro substituent (**5d—f**) also diminished the activity. For fluoro substituents, the order of potency was 3-fluoro (**5h**) > 4-fluoro (**5i**) > 2-fluoro (**5g**), but **5h** was several times less active than **4c**. Chloro compounds (**5j—l**) retained good activity and the 2-chloro compound **5j** was the most active especially against the NE-induced contraction. The 2-trifluoromethyl derivative **5m** retained potency, whereas the hydroxyl compound **5n** showed weaker activity. Dihalo substituents (**5o—r**) did not increase the potency. These results indicated that the 2-(2-chlorophenyl)ethyl group might be optimum for the vasoactivity of cyanoamidines, and nitroxyethyl was not essential as an *N*-substituent for causing vasodilation.

Next, the substituent effect on the pyridine ring of cyanoamidines was studied by modification of the most vasoactive compound **5j**. The compounds were directly evaluated *in vivo* on the basis of the intravenous antihypertensive effect in spontaneously hypertensive rats

TABLE II. Physical and Biological Data for Cyanoamidines **5**



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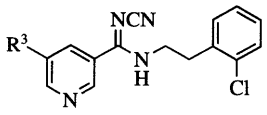
Compd.[a] No.	X	SM[b]	Yield[c] (%)	mp[d] (°C)	Formula[e]	IC_{50} (M)[f]	
						40 mM K^+	NE
4c	H	**3b**	82	149.5—150.0	$C_{15}H_{14}N_4$	4.0×10^{-5}	2.4×10^{-6}
5a	2-CH_3	**3a**	62	146	$C_{16}H_{16}N_4$	1.1×10^{-4}	
5b	3-CH_3	**3b**	73	155	$C_{16}H_{16}N_4$	2.3×10^{-4}	
5c	4-CH_3	**3b**	82	146	$C_{16}H_{16}N_4$	1.5×10^{-3}	
5d	2-NO_2	**3a**	64	120—122	$C_{15}H_{13}N_5O_2$	5.2×10^{-4}	
5e	3-NO_2	**3b**	68	163	$C_{15}H_{13}N_5O_2$	7.1×10^{-4}	
5f	4-NO_2	**3a**	60	164	$C_{15}H_{13}N_5O_2$	6.7×10^{-4}	
5g	2-F	**3b**	74	163	$C_{15}H_{13}N_4F$	7.3×10^{-4}	
5h	3-F	**3b**	80	145	$C_{15}H_{13}N_4F$	9.5×10^{-5}	6.4×10^{-6}
5i	4-F	**3b**	71	154	$C_{15}H_{13}N_4F$	2.8×10^{-4}	
5j	2-Cl	**3b**	75	138.5—140[g]	$C_{15}H_{13}N_4Cl$	3.8×10^{-5}	1.7×10^{-7}
5k	3-Cl	**3b**	82	134	$C_{15}H_{13}N_4Cl$	7.2×10^{-5}	2.0×10^{-6}
5l	4-Cl	**3a**	79	121.8—122.0	$C_{15}H_{13}N_4Cl$	4.3×10^{-5}	2.8×10^{-5}
5m	2-CF_3	**3b**	92	97	$C_{16}H_{13}N_4F_3$	3.5×10^{-5}	3.5×10^{-6}
5n	2-OH	**3b**	74	145—149	$C_{15}H_{14}N_4O$	4.1×10^{-4}	
5o	2,6-diCl	**3b**	80	135	$C_{15}H_{12}N_4Cl_2$	4.0×10^{-5}	9.3×10^{-6}
5p	2,4-diCl	**3b**	77	181—183	$C_{15}H_{12}N_4Cl_2$	1.2×10^{-4}	
5q	3,4-diCl	**3b**	65	197	$C_{15}H_{12}N_4Cl_2$	6.6×10^{-5}	3.7×10^{-5}
5r	2-Cl,3-F	**3b**	73	130	$C_{15}H_{12}N_4ClF$	4.1×10^{-5}	1.9×10^{-6}

a) Structures of all compounds were confirmed by IR, NMR, and elemental analysis. *b*) Starting material. *c*) Yield from cyanoimidate. The yield was not optimized. *d*) Recrystallized from MeOH–Et_2O, except **5j**. *e*) Analyses of C, H, and N were within 0.4% of the theoretical values for the formulae shown. *f*) Molar concentration for 50% inhibition of isolated rat aorta precontracted by 40 mM K^+ or 10^{-7} M NE. *g*) Recrystallized from MeOH–hexane.

TABLE III. Physical and Biological Data for Cyanoamidines **9**



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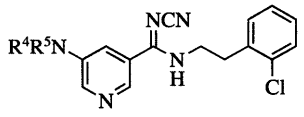
Compd.[a] No.	R^3	Yield[b] (%)	mp[c] (°C)	Formula[d]	ED_{20}[e] (μg/kg)
9a	CH_3	41	157	$C_{16}H_{15}N_4Cl$	17.1
9b	Br	63	160	$C_{15}H_{12}N_4BrCl$	52.2
9c	NO_2	89	150	$C_{15}H_{12}N_5O_2Cl$	N.E.
9d	COOH	80	177[f]	$C_{16}H_{13}N_4O_2Cl$	N.E.
9e	NH_2	68	184	$C_{12}H_{14}N_5Cl$	4.6
5j	H				13.0

a) Structures of all compounds were confirmed by IR, NMR, and elemental analysis. *b*) The yield was not optimized. Compounds **9b**, **c**, **e**: yields from cyanoimidates **8b**, **c**, **e**. Compound **9d**: yield from **8p** *via* **9p**. Compound **9a**: yield from nitrile **6a**. *c*) Recrystallized from MeOH–Et_2O. *d*) Analyses of indicated elements were within ±0.4% of the theoretical values. *e*) Dose to produce 20% reduction of the blood pressure (*i.v.*). *f*) Recrystallized from EtOH.

TABLE IV. Physical and Biological Data for Cyanoamidines **9**



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Compd.[a] No.	R^4	R^5	Yield[b] (%)	mp[c] (°C)	Formula[d]	ED_{20}[e] (μg/kg)
9f	CH_3CH_2	H	80	168	$C_{17}H_{18}N_5Cl$	7.9
9g	$CH(CH_3)_2$	H	80	62	$C_{18}H_{20}N_5Cl$	36.5
9h	$(CH_2)_3CH_3$	H	67	122	$C_{19}H_{22}N_5Cl$	N.E.
9i	$CH_2C_6H_5$	H	85	146	$C_{22}H_{20}N_5Cl$	N.E.
9j	CH_3	CH_3	70	158	$C_{17}H_{18}N_5Cl$	N.E.
9k	$COCH_3$	H	75	230	$C_{17}H_{16}N_5OCl$	12.3
9l	$COCH(CH_3)_2$	H	96	202	$C_{19}H_{20}N_5OCl$	N.E.
9m	COC_6H_5	H	29	220	$C_{19}H_{18}N_5OCl$	N.E.
9n	$COOC_2H_5$	H	94	186	$C_{18}H_{18}N_5O_2Cl$	N.E.
9o	SO_2CH_3	H	32	205	$C_{16}H_{16}N_5O_2SCl$	N.E.
9e	H	H				4.6

a) Structures of all compounds were confirmed by IR, NMR, and elemental analysis. *b*) The yield was not optimized. Compounds **9f**—**i**: yields from cyanoimidates **8f**—**i**. Compounds **9k**—**o**: yields from **9e**. Compound **9j**: yield from nitrile **6j**. *c*) Recrystallized from MeOH–Et_2O. *d*) Analyses of indicated elements were within ±0.4% of the theoretical values. *e*) Dose to produce 20% reduction of the blood pressure (*i.v.*).

(SHRs) (Table III). Substitution of the 5-position on the pyridine ring with methyl (**9a**) and bromo (**9b**) resulted in retention of the activity, while the nitro (**9c**) and carboxyl (**9d**) compounds were less active than **5j**. The strongest activity was found in the case of the 5-amino derivative **9e**, which was about 3-fold more potent than **5j**. Intravenous antihypertensive activity of substituted-amino derivatives **9f**—**o** was also investigated (Table IV). Alkylation, acylation, and sulfonylation generally resulted in loss of activity. In particular, substitution with bulky alkyl or acyl groups resulted in complete loss of activity. Dimethylation also eliminated the activity.

Potassium channel opening ability of the potent vasorelaxants **4c**, **5j** and **9e**, as well as **1**, was investigated by studying the increase in basal efflux rate of $^{86}Rb^+$ as a K^+ marker in rat aorta (Table V).[6] All these compounds

TABLE V. Effect of Selected Cyanoamidines on $^{86}Rb^+$ Efflux

Compound No.[a]	Increase in $^{86}Rb^+$ efflux over basal rate (%)[b]
4c	159
5j	525
9e	248
1	420

a) 1×10^{-5} M. *b*) Percentage change in $^{86}Rb^+$ efflux from background control.

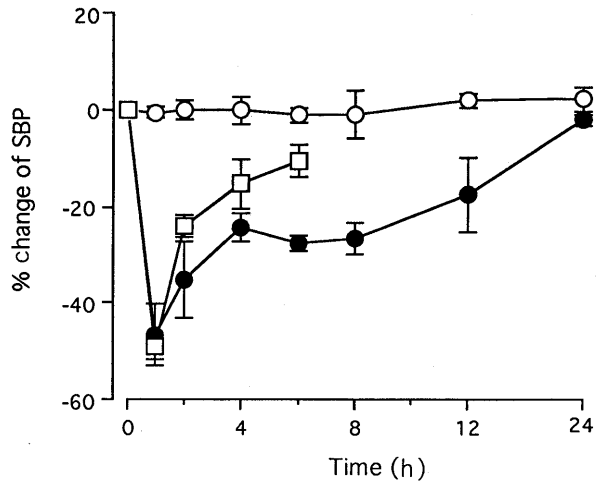

Fig. 2. Effect of Single Oral Administration on Systolic Blood Pressure (SBP) in Conscious SHRs

○, vehicle; □, **5j**; ●, **9e**. The dose of drugs was 3.0 mg/kg, and the vehicle was PEG_{200} : saline = 1 : 1. Each point was the mean ± S.E. derived from 4 or 5 rats.

greatly stimulated the $^{86}Rb^+$ efflux. Thus, they are expected to have potassium channel opening action. The *N*-[2-(2-chlorophenyl)ethyl] substituent could enhance the potassium channel opening activity as well as the vasodilating potency. But potassium channel opening activity and antihypertensive potency did not correlate well to each other (**5j** *vs.* **9e**). The reason for this is not obvious, but it might reflect the intrinsic pharmacokinetic features of the amino-substituted compound **9e**.

Finally, intravenously active cyanoamidines **5j**, **9a**, **b**, **e**, **f**, **g** were evaluated for oral antihypertensive activity using conscious SHRs. Cyanoamidines **9e**, **f** showed prolonged action. The time-course of the effect of the most active and long-lasting compound **9e** was compared with that for **5j** (Fig. 2). Maximal falls in blood pressure were observed at 1 h after administration of compounds and the effects of the two compounds were approximately equal. But the antihypertensive action of **9e** lasted for longer than 12 h, whereas that of **5j** disappeared within 6 h. It was found in our laboratory[7] that the recovery of the 25 mM K^+-induced contraction in isolated rat aorta was inhibited by **9e** even after repeated washings, whereas the action of **5j** was completely abolished after a single washing. Therefore, strong affinity of **9e** for the vascular bed might account for the prolonged duration of antihypertensive action.

In summary, an optimization study of the vasorelaxant activity of cyanoamidines without a nitrate moiety was conducted. Introduction of a 2-(2-chlorophenyl)ethyl group at the cyanoamidine nitrogen led to the most potent vasodilating activity and potassium channel opening activity. It was found that a nitroxyalkyl group was not a crucial *N*-substituent for inducing vasorelaxation. *N*-[2-(2-chlorophenyl)ethyl]-*N'*-cyano-3-pyridinecarboxamidine (**5j**) was the most active compound found in the *in vitro* screening program. Further modification of the pyridine ring and subsequent *in vivo* screening furnished 5-amino-*N*-[2-(2-chlorophenyl)ethyl]-*N'*-cyano-3-pyridinecarboxamidine (**9e**) as the compound showing the most potent and long-lasting activity after oral administration. The new potassium channel opener **9e**, which was designated as KRN4884, has been selected for development as an antihypertensive agent.

TABLE VI. Physical Properties of Cyanoamidines **4**

Compd. No.	Starting material	Yield[a] (%)	Recryst. solvent	mp (°C)	Formula[b]
4a	**3b**	59	MeOH–Et_2O	218	$C_{13}H_{10}N_4$
4b	**3b**	74	MeOH–Et_2O	104.0—104.5	$C_{14}H_{12}N_4$
4c	**3a**	82	MeOH–Et_2O	149.5—150.0	$C_{15}H_{14}N_4$
4d	**3b**	80	MeOH–Et_2O	98.5—99.1	$C_{16}H_{16}N_4$
4e	**3b**	80	MeOH–Et_2O	91	$C_{17}H_{18}N_4$
4f	**3a**	92	Et_2O	68.0	$C_{16}H_{16}N_4$
4g	**3a**	62	MeOH–Et_2O	100.0	$C_{22}H_{20}N_4$
4h	**3b**	36	[c]	Oil	$C_{23}H_{22}N_4$
4i	**3a**	54	MeOH–Et_2O	143.5—144.0	$C_{14}H_{13}N_5$
4j	**3b**	74	MeOH–Et_2O	125	$C_{13}H_{12}N_4S$
4k	**3a**	69	MeOH–Et_2O	134.5	$C_{13}H_{12}N_4S$
4l[d]	**3a**	54[e]	MeOH–Et_2O	163.0	$C_{15}H_{14}N_4O \cdot CH_4O_3S$
4m	**3a**	71	MeOH–Et_2O	69.0—70.0	$C_{16}H_{16}N_4O$

a) Yield from cyanoimidates. The yield was not optimized. *b*) Analysis of indicated elements was within ± 0.4% of the theoretical values. *c*) Purified by chromatography (analytically pure). *d*) Methanesulfonate. *e*) Yield of methanesulfonate.

Experimental

Melting points were determined using a Yanagimoto micro melting-point apparatus and are uncorrected. IR spectra were run on a Jasco A-3 spectrophotometer. ^1H-NMR spectra were recorded at 500 MHz with a JEOL GX-500 spectrometer and at 90 MHz with a JEOL EX-90 spectrometer using tetramethylsilane as the internal standard and chemical shifts are given in ppm. Microanalyses were performed on a Perkin-Elmer Model 240c elemental analyzer.

Synthesis The following examples are representative of the experimental procedures for synthesizing cyanoamidines. Physical properties of cyanoimidates **8** and cyanoamidines **4**, **5**, **9** are presented in Tables II—IV, VI, and VII. Spectral data are given in Tables VII and VIII.

***N*-Cyano-*N'*-phenethyl-3-pyridinecarboxamidine (4c)** Phenethylamine (1.6 g, 13.2 mmol) was added to a solution of **3b**[1] (1.8 g, 9.52 mmol) in MeOH (5 ml). The mixture was stirred at room temperature for 1.5 h and diluted with Et_2O (30 ml). The resulting precipitate was collected by filtration and rinsed several times with Et_2O. Recrystallization of the precipitate from MeOH–Et_2O gave **4c** (1.94 g, 82%) as a colorless crystalline solid, mp 149.5—150.0 °C. *Anal.* Calcd for $C_{15}H_{14}N_4$: C, 71.98; H, 5.64; N, 22.38. Found: C, 71.70; H, 5.68; N, 22.30.

Cyanoamidines **4a**, **b**, **d**—**k**, **m** were prepared similarly.

***N*-Cyano-*N'*-(2-phenoxyethyl)-3-pyridinecarboxamidine Methanesulfonate (4l)** 2-Phenoxyethylamine (0.40 g, 2.9 mmol) was added to a solution of **3a**[1] (0.50 g, 2.6 mmol) in MeOH (10 ml) and the mixture was stirred at room temperature for 1 h. After evaporation of the solvent, the residue was purified by column chromatography (silica gel, $CHCl_3$–MeOH (50 : 1)) to afford *N*-cyano-*N'*-(2-phenoxyethyl)-3-pyridine-carboxamidine (0.46 g, y.65%) as a syrup. MsOH (0.17 g, 1.8 mmol) was added to a solution of the syrup in MeOH (5 ml). After removal of the solvent *in vacuo*, the residue was crystallized from MeOH–Et_2O to give **4l** (0.5 g, 54%) as crystals, mp 163.0 °C. *Anal.* Calcd

TABLE VII. Physical Properties and Spectral Data of Cyanoimidates **8**

Compd.[a] No.	Yield[b] (%)	mp (°C)	IR[c] ν_{max} (cm^{-1})	^{1}H-NMR: δ (ppm)[d]
8b	71	Oil	2960, 2200, 1610, 1440, 1330	9.17 (1H, d, J=2.4 Hz), 8.90 (1H, d, J=2.4 Hz), 8.51 (1H, dd, J=2.4, 2.4 Hz), 4.44 (2H, t, J=6.4 Hz), 1.89 (2H, m), 1.07 (3H, t, J=7.3 Hz)
8c	44	Oil	2970, 2200, 1620, 1535, 1355, 750	9.64 (1H, d, J=2.4 Hz), 9.57 (1H, d, J=2.0 Hz), 9.11 (1H, dd, J=2.4, 2.0 Hz), 4.54 (2H, t, J=6.6 Hz), 1.94 (2H, m), 1.09 (3H, t, J=7.0 Hz)
8e	54	99	3195, 2190, 1595, 1560, 1320[e]	8.26 (1H, d, J=2.4 Hz), 8.16 (1H, d, J=2.4 Hz), 7.39 (1H, dd, J=2.4, 2.4 Hz), 5.84 (2H, br s), 4.35 (2H, t, J=6.4 Hz), 1.78 (2H, m), 0.98 (3H, t, J=7.6 Hz)[f]
8f	54	Oil	2960, 2200, 1600, 1460, 1330	8.41 (1H, d, J=2.0 Hz), 8.18 (1H, d, J=2.9 Hz), 7.61 (1H, dd, J=2.9, 2.0 Hz), 4.39 (2H, t, J=6.5 Hz), 3.95 (1H, br s), 3.22 (2H, m), 1.82 (2H, m), 1.31 (3H, t, J=7.1 Hz), 1.06 (3H, t, J=6.8 Hz)
8g	44	Oil	2950, 2180, 1580, 1445, 1310	8.38 (1H, d, J=1.8 Hz), 8.16 (1H, d, J=3.1 Hz), 7.58 (1H, dd, J=1.8, 3.1 Hz), 4.38 (2H, t, J=6.4 Hz), 4.09 (1H, br s), 3.66 (1H, m), 1.86 (2H, m), 1.26 (6H, d, J=6.1 Hz), 1.05 (3H, t, J=7.3 Hz)
8h	66	Oil	2950, 2170, 1590, 1460, 1320	8.40 (1H, d, J=2.0 Hz), 8.19 (1H, d, J=2.9 Hz), 7.57 (1H, dd, J=2.0, 2.9 Hz), 4.39 (2H, t, J=6.6 Hz), 3.16 (2H, m), 2.0—1.2 (6H, m), 1.1—0.8 (6H, m)
8i	57	Oil	2955, 2190, 1600, 1450, 1325	8.46 (1H, d, J=2.0 Hz), 8.22 (1H, d, J=2.9 Hz), 7.63 (1H, dd, J=2.9, 2.0 Hz), 7.35 (5H, m), 4.6—4.2 (5H), 1.82 (2H, m), 1.03 (3H, t, J=7.0 Hz)
8p	76	Oil	2960, 2180, 1730, 1610, 1280	9.41 (1H, d, J=1.8 Hz), 9.39 (1H, d, J=1.8 Hz), 8.94 (1H, t, J=1.8 Hz), 4.48 (2H, t, J=6.4 Hz), 4.01 (3H, s), 1.91 (2H, m), 1.08 (3H, t, J=7.6 Hz)

a) Cyanoimidates **8a, j** were not isolated. *b*) Overall yield from nitrile. The yield was not optimized. *c*) Neat except **8e**. *d*) Measured in $CDCl_3$; 90 MHz except **8e**. *e*) KBr. *f*) Measured in DMSO-d_6; 500 MHz.

TABLE VIII. Spectral Data for Cyanoamidines **4, 5, 9**

Compd. No.	IR (KBr) ν_{max} (cm^{-1})	Solvent	^{1}H-NMR: δ (ppm)[a]
4a	3080, 2200, 1605, 1590, 1550, 1495, 760, 715	90 MHz DMSO-d_6	11.00 (1H, s), 8.92 (1H, d, J=1.8 Hz), 8.82 (1H, dd, J=4.8, 1.5 Hz), 8.18 (1H, ddd, J=8.1, 1.8, 1.5 Hz), 7.8—7.2 (6H, m)
4b	3230, 3100, 2170, 1580, 1550, 710	90 MHz $CDCl_3$–CD_3OD	8.7—8.6 (2H, m), 8.08 (1H, dt, J=7.9, 2.9 Hz), 7.50 (1H, dd, J=7.9, 4.8 Hz), 7.36 (5H, m), 4.65 (1H, d, J=3.4 Hz), 4.59 (1H, d, J=3.4 Hz)
4c	3220, 3120, 2180, 1590, 1550, 710	90 MHz $CDCl_3$–CD_3OD	8.70 (1H, dd, J=5.1, 2.4 Hz), 8.61 (1H, dd, J=2.0, 1.0 Hz), 8.00 (1H, ddd, J=8.2, 2.4, 2.0 Hz), 7.50 (1H, ddd, J=8.2, 5.1, 1.0 Hz), 7.26 (5H, m), 3.74 (2H, t, J=7.8 Hz), 2.98 (2H, t, J=7.8 Hz)
4d	3240, 2180, 1590, 1550, 1440, 710	90 MHz $CDCl_3$	8.7—8.4 (2H, m), 7.80 (1H, d, J=7.4 Hz), 7.4—7.0 (7H, m), 3.49 (2H, dt, J=7.4, 7.4 Hz), 2.70 (2H, t, J=7.4 Hz), 1.98 (2H, m)
4e	3240, 2190, 1595, 1550, 1440, 710	90 MHz DMSO-d_6	9.29 (1H, br s), 8.8—8.7 (2H, m), 8.01 (1H, ddd, J=7.9, 2.4, 1.8 Hz), 7.58 (1H, ddd, J=7.9, 4.8, 0.9 Hz), 7.23 (5H, m), 3.39 (2H, t, J=5.5 Hz), 2.62 (2H, t, J=7.0 Hz), 1.63 (4H, m)
4f	2200, 1590, 1420, 760, 710	500 MHz $CDCl_3$	8.72 (1H, d, J=4.9 Hz), 8.31 (1H, br s), 7.64 (1H, br d, J=7.9 Hz), 7.41 (1H, dd, J=7.9, 4.9 Hz), 7.3—7.2 (5H, m), 3.81 (2H, t, J=6.6 Hz), 3.06 (3H, s), 3.01 (2H, t, J=6.6 Hz)
4g	2200, 1580, 1560, 1440, 760, 710	500 MHz $CDCl_3$	8.75 (1H, d, J=4.9 Hz), 8.41 (1H, br s), 7.64 (1H, br d, J=7.9 Hz), 7.5—7.1 (11H, m), 4.98 (2H, br s), 3.91 (2H, t, J=5.9 Hz), 3.24 (2H, t, J=5.9 Hz)
4h	2200, 1550, 760, 710[b]	90 MHz $CDCl_3$	8.68 (1H, d, J=4.9 Hz), 8.11 (1H, br s), 7.4—7.0 (12H, m), 4.1—3.7 (4H, m), 3.2—2.8 (4H, m)
4i	2170, 1590, 1550, 710	90 MHz DMSO-d_6	9.38 (1H, br s), 8.76 (1H, dd, J=4.8, 1.8 Hz), 8.69 (1H, dd, J=2.3, 0.9 Hz), 8.53 (1H, ddd, J=4.6, 1.8, 0.9 Hz), 7.98 (1H, ddd, J=7.9, 2.3, 1.8 Hz), 7.75 (1H, ddd, J=7.7, 7.5, 1.8 Hz), 7.58 (1H, ddd, J=7.9, 4.8, 0.9 Hz), 7.4—7.1 (2H, m), 3.75 (2H, t, J=7.1 Hz), 3.07 (2H, t, J=7.1 Hz)
4j	2190, 1590, 1550, 1380	90 MHz $CDCl_3$	8.7—8.5 (2H, m), 7.96 (1H, d, J=7.9 Hz), 7.40 (1H, dd, J=7.9, 4.7 Hz), 7.3—6.7 (3H, m), 3.79 (2H, m), 3.21 (2H, t, J=6.6 Hz)
4k	2200, 1590, 1550, 1380, 710	90 MHz $CDCl_3$	8.81 (1H, d, J=5.1 Hz), 8.70 (1H, s), 7.97 (1H, d, J=7.5 Hz), 7.52—7.23 (2H, m), 7.1—6.9 (2H, m), 3.81 (2H, m), 3.04 (2H, t, J=7.0 Hz)
4l[c]	2200, 1600, 1220, 1050, 760	90 MHz DMSO-d_6	9.62 (1H, t, J=5.3 Hz), 9.0—8.8 (2H, m), 8.15 (1H, ddd, J=8.6, 2.4, 1.8 Hz), 7.79 (1H, dd, J=8.6, 5.7 Hz), 7.5—7.2 (2H, m), 7.1—6.8 (3H, m), 4.21 (2H, t, J=5.3 Hz), 3.79 (2H, q, J=5.3 Hz), 2.48 (3H, s)
4m	2200, 1600, 1560, 1410, 720	500 MHz $CDCl_3$	8.78 (1H, d, J=4.9 Hz), 8.73 (1H, br s), 8.01 (1H, br d, J=7.9 Hz), 7.45 (1H, dd, J=7.9, 4.9 Hz), 6.42 (1H, br s), 4.55 (2H, s), 3.74—3.70 (4H, m)
5a	2170, 1580, 1545	90 MHz DMSO-d_6	9.42 (1H, br s), 8.8—8.6 (2H, m), 7.99 (1H, ddd, J=7.9, 2.2, 1.8 Hz), 7.59 (1H, ddd, J=7.9, 4.6, 0.7 Hz), 7.2—7.0 (4H, m), 3.58 (2H, t, J=7.4 Hz), 2.91 (2H, t, J=7.4 Hz), 2.33 (3H, s)
5b	2170, 1590, 1575, 1540	90 MHz DMSO-d_6	9.37 (1H, br s), 8.77 (1H, dd, J=4.6, 1.8 Hz), 8.67 (1H, d, J=2.2 Hz), 7.97 (1H, ddd, J=7.9, 2.2, 1.8 Hz), 7.59 (1H, dd, J=7.9, 4.6 Hz), 7.3—7.0 (4H, m), 3.60 (2H, t, J=7.1 Hz), 2.87 (2H, t, J=7.1 Hz), 2.30 (3H, s)
5c	2160, 1640, 1545, 1510	90 MHz DMSO-d_6	9.36 (1H, t, J=5.9 Hz), 8.76 (1H, dd, J=4.8, 1.5 Hz), 8.66 (1H, dd, J=2.2, 0.7 Hz), 7.97 (1H, ddd, J=7.9, 2.2, 1.5 Hz), 7.59 (1H, ddd, J=7.9, 4.8, 0.7 Hz), 3.58 (2H, dt, J=7.3, 5.9 Hz), 2.86 (2H, t, J=7.3 Hz), 2.28 (3H, s)

TABLE VIII. (continued)

Compd. No.	IR (KBr) ν_{max} (cm^{-1})	Solvent	^{1}H-NMR: δ (ppm)[a]
5d	2180, 1580, 1550, 1530, 1430, 1350	90 MHz DMSO-d_6	9.40 (1H, br s), 8.76 (1H, dd, J=4.8, 1.8 Hz), 8.67 (1H, d, J=1.5 Hz), 8.1–7.9 (2H, m), 7.8—7.5 (4H, m), 3.72 (2H, t, J=6.9 Hz), 3.19 (2H, t, J=6.9 Hz)
5e	2180, 1590, 1550, 1520, 1350	90 MHz DMSO-d_6	9.49 (1H, br s), 8.76 (1H, dd, J=4.8, 1.8 Hz), 8.66 (1H, dd, J=2.2, 0.9 Hz), 8.3—7.5 (6H, m), 3.69 (2H, t, J=6.8 Hz), 3.08 (2H, t, J=6.8 Hz)
5f	2180, 1580, 1540, 1530, 1355	90 MHz DMSO-d_6	9.40 (1H, br s), 8.77 (1H, dd, J=4.8, 1.5 Hz), 8.68 (1H, dd, J=2.4, 0.9 Hz), 8.20 (2H, dd, J=6.8, 2.0 Hz), 7.97 (1H, ddd, J=7.9, 2.4, 1.5 Hz), 7.7—7.5 (3H, m), 3.68 (2H, t, J=6.9 Hz), 3.07 (2H, t, J=6.9 Hz)
5g	2170, 1590, 1550	90 MHz DMSO-d_6	9.43 (1H, br s), 8.77 (1H, dd, J=4.8, 1.5 Hz), 8.67 (1H, dd, J=2.4, 0.9 Hz), 7.96 (1H, ddd, J=8.6, 1.5, 0.9 Hz), 7.7—7.1 (5H, m), 3.62 (2H, t, J=7.3 Hz), 2.97 (2H, t, J=7.3 Hz)
5h	2170, 1590, 1550	90 MHz DMSO-d_6	9.38 (1H, br s), 8.76 (1H, dd, J=4.8, 1.8 Hz), 8.66 (1H, dd, J=2.2, 0.9 Hz), 7.96 (1H, ddd, J=8.6, 2.2, 1.8 Hz), 7.58 (1H, ddd, J=8.6, 4.8, 0.9 Hz), 7.4—7.0 (4H, m), 3.63 (2H, t, J=7.0 Hz), 2.94 (2H, t, J=7.0 Hz)
5i	2190, 1590, 1550	90 MHz DMSO-d_6	9.40 (1H, br s), 8.76 (1H, dd, J=4.8, 1.5 Hz), 8.67 (1H, dd, J=2.2, 0.7 Hz), 7.96 (1H, ddd, J=7.9, 2.2, 1.5 Hz), 7.58 (1H, ddd, J=7.9, 4.8, 0.7 Hz), 7.7—7.2 (4H, m), 3.60 (2H, t, J=6.8 Hz), 2.90 (2H, t, J=6.8 Hz)
5j	2180, 1590, 1550	90 MHz $CDCl_3$–CD_3OD	8.77 (1H, dd, J=4.8, 1.7 Hz), 8.68 (1H, d, J=2.0 Hz), 8.12 (1H, m), 7.6—7.2 (5H, m), 3.76 (2H, J=7.6 Hz), 3.14 (2H, t, J=7.6 Hz)
5k	2170, 1590, 1545	90 MHz DMSO-d_6	9.30 (1H, br s), 8.77 (1H, dd, J=4.8, 1.5 Hz), 8.66 (1H, dd, J=2.2, 0.9 Hz), 7.96 (1H, ddd, J=7.9, 2.2, 1.5 Hz), 7.58 (1H, ddd, J=7.9, 4.8, 0.9 Hz), 7.4—7.2 (4H, m), 3.63 (2H, t, J=7.1 Hz), 2.93 (2H, t, J=7.1 Hz)
5l	2180, 1590, 1550	90 MHz $CDCl_3$	8.8—8.5 (2H, m), 7.97 (1H, d, J=7.9 Hz), 7.5—7.1 (5H), 6.70 (1H, t, J=6.8 Hz), 3.78 (2H, dt, J=6.8, 6.8 Hz), 2.99 (2H, t, J=6.8 Hz)
5m	2180, 1580, 1560, 1315	90 MHz DMSO-d_6	9.48 (1H, br s), 8.9—8.6 (2H, m), 8.01 (1H, ddd, J=7.9, 2.4, 1.8 Hz), 7.8—7.4 (5H, m), 3.65 (2H, t, J=7.7 Hz), 3.10 (2H, t, J=7.7 Hz)
5n	2185, 1590, 1555	90 MHz DMSO-d_6	9.41 (1H, br s), 8.8—8.6 (2H, m), 7.98 (1H, dd, J=7.6, 1.5 Hz), 7.58 (1H, ddd, J=7.6, 5.5, 0.4 Hz), 7.35 (1H, br s), 7.2—7.0 (2H, m), 6.9—6.7 (2H, m), 3.58 (2H, t, J=7.0 Hz), 2.86 (2H, J=7.0 Hz)
5o	2185, 1590, 1550	90 MHz DMSO-d_6	9.52 (1H, br s), 8.9—8.7 (2H, m), 8.01 (1H, ddd, J=8.4, 2.2, 1.8 Hz), 7.7—7.2 (4H, m), 3.66 (2H, t, J=6.6 Hz), 3.32 (2H, t, J=6.6 Hz)
5p	2170, 1590, 1550	90 MHz DMSO-d_6	9.41 (1H, br s), 8.77 (1H, dd, J=4.8, 1.8 Hz), 8.69 (1H, d, J=2.3 Hz), 7.98 (1H, ddd, J=7.9, 2.3, 1.8 Hz), 7.7—7.4 (4H, m), 3.63 (2H, t, J=6.7 Hz), 3.04 (2H, t, J=6.7 Hz)
5q	2170, 1590, 1550	90 MHz DMSO-d_6	9.32 (1H, t, J=6.6 Hz), 8.76 (1H, dd, J=4.8, 1.8 Hz), 8.66 (1H, dd, J=2.2, 0.7 Hz), 7.94 (1H, ddd, J=7.9, 2.2, 1.8 Hz), 7.7—7.5 (3H, m), 7.27 (1H, dd, J=7.8, 1.8 Hz), 3.61 (2H, q, J=6.6 Hz), 2.92 (2H, t, J=6.6 Hz)
5r	2180, 1580, 1555	90 MHz DMSO-d_6	9.47 (1H, br s), 8.77 (1H, dd, J=4.8, 1.5 Hz), 8.68 (1H, dd, J=2.4, 0.9 Hz), 7.97 (1H, ddd, J=7.9, 2.4, 1.5 Hz), 7.64 (1H, dd, J=4.6, 0.7 Hz), 7.4—7.1 (3H), 3.61 (2H, t, J=7.0 Hz), 3.10 (2H, t, J=7.0 Hz)
9a	2160, 1580, 1540, 1440, 1210, 740, 720	90 MHz $CDCl_3$	8.98 (1H, d, J=2.7 Hz), 8.67 (1H, d, J=1.8 Hz), 8.27 (1H, m), 7.4—7.2 (4H, m), 3.82 (2H, dd, J=6.7, 12.8 Hz), 3.12 (2H, t, J=6.7 Hz), 2.47 (3H, s)
9b	3220, 2185, 1580, 1540, 1430	500 MHz DMSO-d_6	9.50 (1H, br s), 8.93 (1H, d, J=2.4 Hz), 8.71 (1H, d, J=1.8 Hz), 8.26 (1H, dd, J=2.4, 1.8 Hz), 7.5—7.4 (2H, m), 7.4—7.2 (2H, m), 3.63 (2H, t, J=7.0 Hz), 3.05 (2H, t, J=7.0 Hz)
9c	3230, 2175, 1610, 1585, 1565, 1540, 1350	500 MHz DMSO-d_6	9.67 (1H, br s), 9.56 (1H, d, J=2.4 Hz), 9.14 (1H, d, J=1.8 Hz), 8.80 (1H, dd, J=2.4, 1.8 Hz), 7.5—7.4 (2H, m), 7.4—7.2 (2H, m), 3.67 (2H, t, J=7.2 Hz), 3.09 (2H, t, J=7.2 Hz)
9d	3225, 2175, 1725, 1590, 1560	90 MHz DMSO-d_6	9.53 (1H, br s), 9.16 (1H, d, J=2.0 Hz), 8.78 (1H, d, J=2.2 Hz), 8.33 (1H, dd, J=2.2, 2.0 Hz), 7.5—7.2 (4H, m), 3.64 (2H, m), 3.07 (2H, t, J=7.0 Hz)
9e	3200, 2170, 1570	90 MHz CD_3OD	8.08 (1H, d, J=2.6 Hz), 7.83 (1H, br s), 7.5—7.2 (5H, m), 3.73 (2H, t, J=7.3 Hz), 3.13 (2H, t, J=7.3 Hz)
9f	3230, 2170, 1560, 1445, 750	90 MHz $CDCl_3$	7.95 (1H, d, J=2.6 Hz), 7.79 (1H, d, J=1.8 Hz), 7.4—7.0 (5H, m), 4.35 (1H, br s), 3.76 (2H, m), 3.3—2.9 (4H, m), 2.88 (1H, br s), 1.26 (3H, t, J=7.1 Hz)
9g	2960, 2160, 1555, 1440	90 MHz $CDCl_3$	7.98 (1H, d, J=2.6 Hz), 7.78 (1H, d, J=1.8 Hz), 7.5—7.2 (4H, m), 7.12 (1H, dd, J=1.8, 2.6 Hz), 6.62 (1H, m), 4.11 (1H, br s), 3.76 (2H, m), 3.46 (1H, m), 3.14 (2H, t, J=6.6 Hz), 1.24 (6H, d, J=6.4 Hz)
9h	2950, 2160, 1560, 1460, 750	90 MHz $CDCl_3$	7.92 (1H, d, J=2.6 Hz), 7.77 (1H, d, J=1.8 Hz), 7.5—7.1 (4H, m), 7.07 (1H, dd, J=1.8, 2.6 Hz), 4.46 (1H, m), 3.75 (2H, m), 3.2—2.8 (2H, m), 1.7—1.2 (4H, m), 0.95 (3H, t, J=6.8 Hz)
9i	2180, 1560, 1445, 750	90 MHz $CDCl_3$	7.94 (1H, d, J=2.6 Hz), 7.82 (1H, d, J=1.8 Hz), 7.4—7.0 (10H, m), 4.29 (2H, d, J=5.5 Hz), 3.8—3.6 (3H, m), 3.09 (2H, t, J=606 Hz)
9j	3400, 2160, 1575, 1430	90 MHz DMSO-d_6	9.25 (1H, br s), 8.26 (1H, d, J=2.9 Hz), 7.95 (1H, d, J=1.8 Hz), 7.5—7.2 (4H, m), 7.11 (1H, dd, J=1.8, 2.9 Hz), 3.63 (2H, m), 3.5 (2H, t, J=7.0 Hz), 2.98 (6H, s)
9k	3230, 2160, 1700, 1580, 720	90 MHz DMSO-d_6	10.43 (1H, br s), 9.41 (1H, br s), 8.87 (1H, d, J=2.4 Hz), 8.33 (1H, d, J=2.0 Hz), 8.24 (1H, dd, J=2.0, 2.4 Hz), 7.5—7.3 (4H, m), 3.63 (2H, m), 3.08 (2H, t, J=3.2 Hz), 2.12 (3H, s)
9l	3255, 2175, 1675, 1600, 1565, 1540, 1430	90 MHz DMSO-d_6	10.31 (1H, br s), 9.41 (1H, br s), 8.90 (1H, d, J=2.2 Hz), 8.33 (2H, m), 7.5—7.2 (4H, m), 3.64 (2H, m), 3.05 (2H, t, J=6.8 Hz)
9m	3260, 2160, 1655, 1550, 1430	90 MHz DMSO-d_6	10.71 (1H, br s), 9.46 (1H, br s), 9.11 (1H, d, J=2.2 Hz), 8.5—8.3 (2H, m), 8.1—7.3 (9H, m), 3.63 (2H, m), 3.08 (2H, t, J=7.2 Hz)

TABLE VIII. (continued)

Compd. No.	IR (KBr) ν_{max} (cm^{-1})	Solvent	^{1}H-NMR: δ (ppm)[a]
9n	3230, 2175, 1735, 1570, 1550, 1440, 1225	90 MHz DMSO-d_6	10.16 (1H, br s), 9.41 (1H, br s), 8.78 (1H, d, J=2.4 Hz), 8.29 (1H, d, J=2.0 Hz), 8.09 (1H, dd, J=2.4, 2.0 Hz), 7.4—7.2 (4H, m), 4.19 (2H, q, J=5.3 Hz), 3.63 (2H, m), 3.05 (3H, t, J=6.8 Hz), 1.27 (3H, t, J=5.3 Hz)
9o	3400, 2150, 1590, 1555, 1150	90 MHz DMSO-d_6	10.42 (1H, br s), 9.46 (1H, br s), 8.87 (1H, d, J=2.4 Hz), 8.39 (1H, d, J=2.0 Hz), 7.76 (1H, dd, J=2.0, 2.4 Hz), 7.5—7.3 (4H, m), 3.6—3.5 (5H, m), 3.16 (2H, t, J=5.2 Hz)
9p	3220, 2160, 1590, 1435, 1380, 750	90 MHz DMSO-d_6	9.62 (1H, m), 9.16 (1H, d, J=1.8 Hz), 8.75 (1H, d, J=2.2 Hz), 7.40 (1H, dd, J=1.8, 2.2 Hz), 7.2—7.0 (4H, m), 3.70 (2H, m), 3.07 (2H, t, J=6.8 Hz)

a) br s: broad singlet; br d: broad doublet. *b*) Film. *c*) Methanesulfonate.

for $C_{16}H_{18}N_4O_4S$: C, 53.03; H, 5.01; N, 15.46. Found: C, 52.90; H, 5.03; N, 15.48.

***N*-[2-(2-Chlorophenyl)ethyl]-*N'*-cyano-3-pyridinecarboxamidine (5j)** 2-(2-Chlorophenyl)ethylamine (0.45 g, 2.9 mmol) was added to a solution of **3b**[1] (0.50 g, 2.6 mmol) in MeOH (10 ml) and the mixture was stirred at room temperature for 7 h. After evaporation, the residue was purified by column chromatography (silica gel, $CHCl_3$–MeOH (100 : 1)) to afford **5j**. Recrystallization from MeOH–hexane yielded **5j** (0.56 g, 75%) as crystals, mp 138.5—140.0 °C. *Anal.* Calcd for $C_{15}H_{13}ClN_4$: C, 63.27; H, 4.60; N, 19.68. Found: C, 63.17; H, 4.64; N, 19.45.

Cyanoamidines **5a—i, k—r** were prepared similarly.

5-Amino-*N*-[2-(2-chlorophenyl)ethyl]-*N'*-cyano-3-pyridinecarboxamidine (9e) Dry HCl was passed into a solution of 5-amino-3-cyanopyridine (**6e**)[4] (9.18 g, 77.1 mmol) in 1-PrOH (500 ml) at 0 °C for 1 h. The reactor was stoppered and the mixture was allowed to warm to room temperature and stirred for 22 h. After evaporation, the residual solid was added to saturated aqueous $NaHCO_3$ (350 ml). The mixture was immediately extracted with $CHCl_3$ (200 ml × 2), and the combined extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give crude **7e** (13.9 g). Crude **7e** was added to a vigorously stirred solution of NH_2CN (6.50 g, 155 mmol), $NaH_2PO_4 \cdot 2H_2O$ (41.8 g, 308 mol) and Na_2HPO_4 (21.9 g, 154 mmol) in water (500 ml). After stirring at room temperature overnight, the reaction mixture was extracted with $CHCl_3$ (300 ml × 3). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, Et_2O) to afford propyl 5-amino-*N*-cyano-3-pyridinecarboximidate (**8e**) (11.0 g, 70%) as a yellow solid. 2-(2-Chlorophenyl)ethylamine (1.8 g, 11.6 mmol) was added to a solution of **8e** (2.0 g, 9.8 mmol) in MeOH (10 ml) and the mixture was stirred at room temperature overnight. After evaporation, the residue was purified by column chromatography (silica gel, $CHCl_3$–MeOH (30 : 1)) and subsequent recrystallization from MeOH–Et_2O yielded **9e** (2.0 g, 68%) as crystals, mp 184 °C. *Anal.* Calcd for $C_{15}H_{14}ClN_5$: C, 60.10; H, 4.71; N, 23.36. Found: C, 59.94; H, 4.67; N, 23.32.

Cyanoamidines **9a—c, f—j, p** were prepared from the requisite nitriles **6a—c, f—j, p**[4] *via* the imidates **7a—c, f—j, p** in a similar manner. For the reaction of imidates **7c, f, h, i, j, p** with cyanamide in phosphate buffer solution, acetonitrile (10—20% v/v) was used as a co-solvent.

5-Acetamido-*N*-[2-(2-chlorophenyl)ethyl]-*N'*-cyano-3-pyridinecarboxamidine (9k) To a solution of **9e** (100 mg, 0.33 mmol) in pyridine (1 ml), Ac_2O (20 mg, 0.34 mmol) was added at 0 °C. The mixture was stirred at room temperature for 3 h and diluted with cold water. The precipitate was collected by filtration and washed with water (2 ml × 2). The filter cake was purified by crystallization from MeOH–Et_2O to give **9k** (86 mg, 75%) as crystals, mp 230 °C. *Anal.* Calcd for $C_{17}H_{16}ClN_5O$: C, 59.74; H, 4.72; N, 20.49. Found: C, 59.68; H, 4.78; N, 20.53.

Compounds **9l—o** were prepared by acylation or sulfonylation of **9e** in the same manner as above.

5-Carboxy-*N*-[2-(2-chlorophenyl)ethyl]-*N'*-cyano-3-pyridinecarboxamidine (9d) To a solution of **9p** (500 mg, 1.46 mmol) in MeOH (30 ml), 40% aqueous NaOH (150 mg, 1.50 mmol) was added and the mixture was stirred at room temperature for 10 h. Dowex-50 resin (H^+ form, 350 mg, 1.58 meq) was added to the solution with stirring. After removal of the resin, the solution was evaporated *in vacuo*. The residue was crystallized from EtOH to give **9d** (422 mg, 88%) as crystals, mp 177 °C. *Anal.* Calcd for $C_{16}H_{13}ClN_4O_2$: C, 56.23; H, 3.54; N, 20.49. Found: C, 55.91; H, 3.77; N, 20.19.

Biological Determinations. *In Vitro* Studies All tissues used in these experiments were obtained from male Wistar rats.

Tissue Bath Studies Tissue bath studies were performed according to the method in the preceding paper.[1] The results are shown in Tables I and II. Thoracic aorta were removed from surrounding connective tissue and cut into ring segments each about 3 mm long. The endothelium was removed mechanically by rubbing the intimal surface with a wooden stick. Each preparation was mounted in a tissue bath filled with 10 ml Krebs–Ringer solution of the following composition (mM): NaCl 112, KCl 4.7, $CaCl_2$ 2.2, $NaHCO_3$ 25, $MgCl_2$ 1.2, KH_2PO_4 1.2 and glucose 14. This was maintained at 37 °C and gassed with 95% O_2 and 5% CO_2. The tension of each segment was measured isometrically with a force-displacement transducer and preparations were loaded at 1 g tension then allowed to equilibrate for 120 min before acute experiments were started. After the equilibration period, preparations were contracted by changing the solution in the bath to one containing 40 mM KCl. Contraction of the preparations was also induced by the addition of NE to the bath to give a final concentration of 10^{-7} M. The ability of a test compound to relax established contractions due to high K^+ or NE was determined using a cumulative protocol. The response was expressed as percentage inhibition of each contraction and the mean IC_{50} value (with 95% confidence limits) was calculated.

$^{86}Rb^+$ Efflux[6] This study was performed according to the method described in the preceding paper.[1] The aorta was cut into two rings and each ring was opened into a flat sheet by cutting it longitudinally. Each segment was hooked onto a bent pin then inserted into a tube containing 2 ml Krebs–Ringer solution at 37 °C bubbled with 95% O_2 and 5% CO_2. After a 30 min-equilibration period, the preparation was loaded with $^{86}Rb^+$ (0.74 MBq/ml) for 180 min. $^{86}Rb^+$ was then allowed to leave the tissues using 2 min collection periods and after nine such periods (18 min efflux) the ability of the compounds **1**, **4c**, **5j**, **9e** to enhance efflux was tested by exposing the tissue to the compounds under test between minutes 18—26 of the efflux period. At the end of the efflux period, the radioactivity in the tubes and that remaining in the tissues was measured. The rate coefficients were calculated from $^{86}Rb^+$ released during each 2 min period and expressed as a percentage of the mean tissue $^{86}Rb^+$ remaining during that period. The mean rate coefficient over minutes 13—18 of the efflux period was taken as the basal rate. Stimulation of the efflux rate by a compound was calculated as the maximum rate observed over minutes 18—26 of the efflux period divided by the basal rate and was expressed as a percentage. The results are shown in Table V.

***In Vivo* Studies. Intravenous Administration** SHRs (18 weeks old) were divided into two groups. Animals were anesthetized with urethane (1 g/kg, i.p.) and α-chloralose (25 mg/kg, i.p.). Systemic blood pressure was measured in the carotid artery using a pressure transducer (TP-400T, Nihon Kohden) connected to a carrier amplifier (AP-641G, Nihon Kohden). The results are shown in Tables III and IV.

Statistical Analysis Results are expressed as mean values ± S.E. mean. The ED_{20} values (the doses which lowered the blood pressure by 20%) were obtained from a linear regression of the effects change after intravenous administration *vs.* log dose.

Oral Administration SHRs (18—22 weeks old) were used after 18 h fasting. Systolic blood pressure (SBP) were measured by the tail-cuff method (PS-100, Riken Kaihatsu) in prewarmed rats (40 °C, 10 min). Measurements were made before and at 1, 2, 4, 6, 8, 12, and 24 h after oral administration of test drugs. The results for **5j** and **9e** are presented in Fig. 2.

References and Notes

1) T. Nakajima, T. Izawa, T. Kashiwabara, S. Nakajima, Y. Munezuka, *Chem. Pharm. Bull.*, **42**, 2475 (1994).
2) Reference cited in the preceding paper.[1)]
3) For example, T. Yanagisawa, Y. Okada, *Cardiovasc. Drugs Rev.*, **11**, 94 (1993); T. Ishibashi, M. Hamaguchi, S. Imai, *Kekkann*, **16**, 61 (1993); Y. Jinno, H. Kasai, H. Ohta, K. Nishikiori, H. Fukushima, N. Ogawa, *Br. J. Pharmacol.*, **106**, 906 (1992); T. Ishibashi, M. Hamaguchi, S. Imai, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **346**, 94 (1992).
4) 3-Cyano-5-methylpyridine (**6a**),[4a)] 3-cyano-5-nitropyridine (**6c**),[4b)] and 5-amino-3-cyanopyridine (**6e**)[4c)] were prepared according to the cited methods. 5-Bromo-3-cyanopyridine (**6b**) was synthesized from 5-bromonicotinic acid. 5-Alkylamino-3-cyanopyridines (**6f**—**i**) were prepared by reductive alkylation[4d)] of 5-amino-3-cyanopyridine (**6e**), and 3-cyano-5-dimethylaminopyridine (**6j**) was synthesized by alkylation of **6e** with methyl iodide; *a*) J. Okada, S. Morita, Y. Miwa, *Chem. Pharm. Bull.*, **22**, 2402 (1974); *b*) M. Nakadate, Y. Takano, T. Hirayama, S. Sakaizawa, T. Hirano, K. Okamato, K. Hirao, T. Kawamura, M. Kimura, *ibid.*, **13**, 113 (1965); *c*) G. F. Holland, J. N. Pereira, *J. Med. Chem.*, **10**, 149 (1967); *d*) C. F. Lana, *Synthesis*, **1975**, 135.
5) In our experiments, compounds **4f**—**h** were synthesized from cyanoimidate and secondary amines.
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7) The results will be reported elsewhere.