Synthesis and Antiarrhythmic Activity of Disubstituted Phenylpyridine Derivative

Hiromichi SHIGYO,* Seiichi SATO, Kimiyuki SHIBUYA, Yoshio TAKAHASHI, Takashi YAMAGUCHI, Hiroyuki SONOKI, and Tomio OHTA

Tokyo Research Laboratories, Kowa Co., Ltd., 2–17–43 Noguchicho, Higashimurayama, Tokyo 189, Japan.
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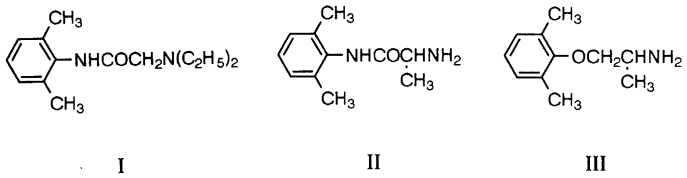
A series of disubstituted phenylpyridine derivatives was synthesized and their antiarrhythmic effects against chloroform-induced ventricular arrhythmias in mice were examined. Among them, 2- and 3-[2-(3-aminobutyramido)-4-(2,2,2-trifluoroethoxy)phenyl]pyridines (23h, 24h) and 3-[2-(3-aminobutyramido)-4-ethoxyphenyl]pyridine (24i) showed potent antiarrhythmic activity. They had approximately twice the potency of mexiletine (III). Compound 24i was selected from this series as a candidate for further development; it was found to have a class I B electrophysiological character and to show a slow kinetic rate-dependent block (RDB) of the sodium channel in cardiac muscle.

Keywords antiarrhythmic activity; phenylpyridine; class I; anilide; lidocaine; Gomberg–Bachmann–Hey reaction

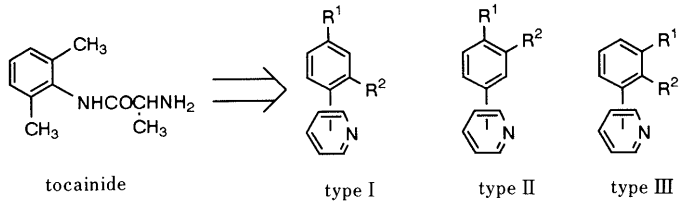
Lidocaine (I) is a well-known antiarrhythmic agent, and is widely used for the therapy of ventricular arrhythmia.[1] It is electrophysiologically classified into class I of the Vaughan Williams classification.[2] Lidocaine is highly effective in intravenous or intramuscular administration, but it is orally ineffective. Therefore, a number of investigators have been searching for new orally active antiarrhythmic agents with pharmacodynamic properties similar to those of lidocaine, and some lidocaine-like agents have been reported.[3] However, these agents with class I action have a structure associated with local anaesthetic activity and have some side effects, chiefly on the central nervous system (CNS).

Being interested in further structural modification of tocainide (II), which is one of the congeners of lidocaine, we decided to search for derivatives which would yield adequate antiarrhythmic potency for the treatment of ventricular arrhythmias after oral administration without exhibiting undesirable effects. Recently, Tenthorey and co-workers have reported that potent class I antiarrhythmic compounds can be produced by increasing lipophilicity and compounds of low CNS toxicity can be produced by increasing pK_a.[4] On the other hand, Campbell has reported that there was a statistically significant correlation between increasing molecular weight of the class I antiarrhythmic drugs and decreasing rate of onset of rate-dependent block (RDB) of the sodium channel.[5] From these points of view, in order to synthesize an antiarrhythmic agent with high efficacy and slow kinetics in RDB, we selected the pyridyl group as a substituent to replace one of the nuclear methyl groups of tocainide, because Hansch's π value[6] of a 2-pyridyl group (0.50) is nearly equal to that of a methyl group (0.56) and the molecular weight of pyridine is much larger than that of methane. This paper describes the synthesis of a series of disubstituted phenylpyridine derivatives (Fig. 2) and a comparison of their antiarrhythmic activity with that of mexiletine (III), a novel orally active class I antiarrhythmic agent.



I II III

Fig. 1



tocainide type I type II type III

R^1= alkoxy, alkyl, Cl, OH

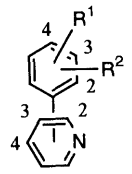
R^2= $NHCO(CH_2)_nCHNH_2$ (n= 0, 1)
CH_3

Fig. 2

Chemistry The starting nitro compounds **2**, **3** and **4** listed in Tables I and II were prepared by the synthetic routes shown in Charts 1 and 2. Thus, the (substituted nitrophenyl)pyridines **2a—d**, **f**, **3a—d**, **f**, and **4a**, **b** were obtained by the reaction of the corresponding diazotized anilines **1a—d** and **11** with pyridine (Gomberg–Bachmann–Hey reaction).[7] The starting 3-methoxy-2-nitroaniline **11**[8] was obtained in good yield by the treatment of 3-methoxy-2-nitrobenzoic acid **9** with diphenylphosphoryl azide (DPPA) in *tert*-butyl alcohol (*tert*-BuOH) followed by hydrolysis with 6 N hydrochloric acid (6 N HCl).[9] The (4-methoxy-3-nitrophenyl)pyridines **2e**, **3e** and **4e** were obtained in two steps from 4-methoxyaniline **5** *via* **6—8**, respectively, by the method reported by Coates *et al.*[10] The demethylation of the methoxy derivatives **2a**, **e**, **f**, **3a**, **f** and **4a**, **e** with 47% aqueous hydrobromic acid (47% HBr) gave (hydroxy nitrophenyl)pyridines **2g**, **n**, **p**, **3g**, **p** and **4g**, **n**, respectively, which were subsequently treated by a method analogous to that of Camps *et al.*[11] to give the [(2,2,2-trifluoroethoxy)nitrophenyl]pyridines **2h**, **o**, **q**, **3h**, **q** and **4h**, **o**, respectively. The other 4-alkoxy derivatives **2i**, **3i—m** and **4i** were prepared by the reaction of the corresponding phenols **2g**, **3g** and **4g** with appropriate alkyl halides in the presence of potassium carbonate (K_2CO_3).

The title disubstituted phenylpyridines **23—27** and **29** listed in Table IV were prepared by the synthetic route shown in Chart 3. The reduction of the nitro compounds

TABLE I. Physical Data for Phenylpyridines (**2a—f**, **3a—f**, **4a—c** and **6—8**)



Compd. No.	Position of pyridine	R^1	Position of NO_2	Starting material	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	Formula[c]
2a	2	4-OCH_3	2	**1a**	15	198—203 (dec.)	A	$C_{12}H_{10}N_2O_3 \cdot HCl$
3a	3	4-OCH_3	2	**1a**	14	97—98	B	$C_{12}H_{10}N_2O_3$
4a	4	4-OCH_3	2	**1a**	9	100—102	C	$C_{12}H_{10}N_2O_3$
2b	2	4-CH_3	2	**1b**	20	96—97	B	$C_{12}H_{10}N_2O_2$
3b	3	4-CH_3	2	**1b**	23	97—99	B	$C_{12}H_{10}N_2O_2$
4b	4	4-CH_3	2	**1b**	7	Oil	—	$C_{12}H_{10}N_2O_2$
2c	2	4-CF_3	2	**1c**	5	84—86	D	$C_{12}H_7F_3N_2O_3$
3c	3	4-CF_3	2	**1c**	5	70—71	B	$C_{12}H_7F_3N_2O_3$
2d	2	4-Cl	2	**1d**	22	104—105	E	$C_{11}H_7ClN_2O_2$
3d	3	4-Cl	2	**1d**	6	138—140	E	$C_{11}H_7ClN_2O_2$
2e	2	4-OCH_3	3	**6**	65	83—84	F	$C_{12}H_{10}N_2O_3$
3e	3	4-OCH_3	3	**7**	52	96—98	G	$C_{12}H_{10}N_2O_3$
4e	4	4-OCH_3	3	**8**	77	137—139	D	$C_{12}H_{10}N_2O_3$
2f	2	3-OCH_3	2	**11**	29	102—104	D	$C_{12}H_{10}N_2O_3$
3f	3	3-OCH_3	2	**11**	24	94—95	B	$C_{12}H_{10}N_2O_3$
6	2	4-OCH_3	—	**5**	42	55—56	D	$C_{12}H_{11}NO$
7	3	4-OCH_3	—	**5**	11	57—60	D	$C_{12}H_{11}NO$
8	4	4-OCH_3	—	**5**	17	94—96	D	$C_{12}H_{11}NO$

a) Isolated yield of chromatographically pure product. *b*) Abbreviations for the solvents used are as follows: A, MeOH–ether; B, ether–hexane; C, AcOEt–pet. ether; D, AcOEt–hexane; E, ether; F, EtOH; G, EtOH–hexane. *c*) Analysis for C, H, N were all ±0.4% of the expected values. The oily products were confirmed by HR-MS.

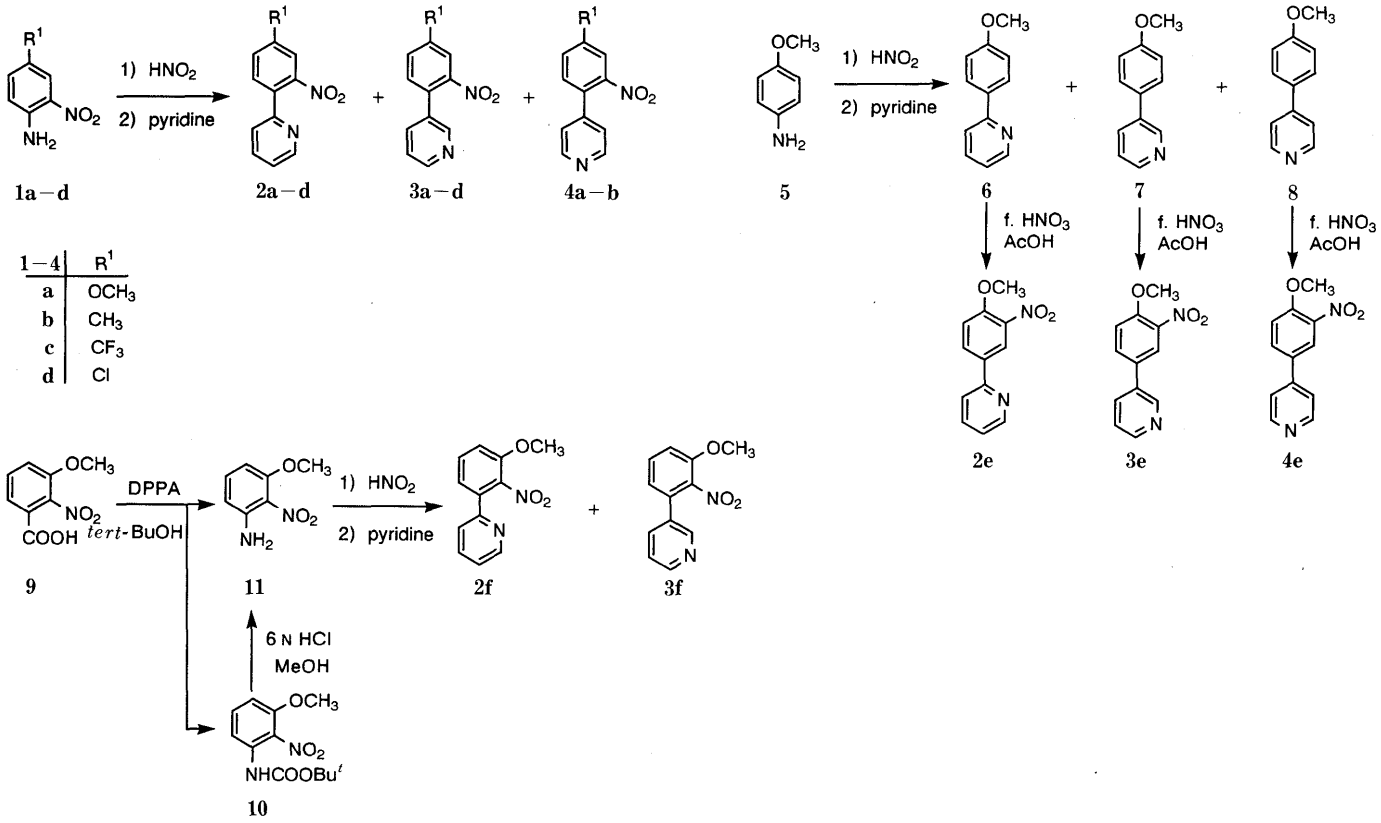
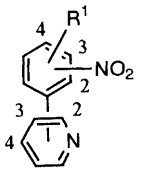


Chart 1

2—4 gave (substituted aminophenyl)pyridines **12—14**, respectively (Table III). Compounds **23a—f**, **h**, **o**, **q**, **24a—e**, **g**, **h**, **q** and **25a**, **b**, **e**, **h**, **o** were prepared by the condensation of the corresponding anilines **12a—f**, **h**, **o**, **q**, **13a—e**, **g**, **h**, **q** and **14a**, **b**, **e**, **h**, **o** with *N*-(Boc)-3-aminobutanoic acid **15** (Boc = *tert*-butoxycarbonyl) by use of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (WSC), followed by acid-catalyzed hydrolysis. Compounds **23i**,

TABLE II. Physical Data for (Alkoxy Nitrophenyl)pyridines (**2h, i, o, q, 3h—m, q** and **4h, i, o**)



Compd. No.	Position of pyridine	R^1	Position of NO_2	Starting material	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	Formula[c]
2h	2	4-OCH_2CF_3	2	**2g**	95	Oil	—	$C_{13}H_9F_3N_2O_3$
2i	2	4-OCH_2CH_3	2	**2g**	53	Oil	—	$C_{13}H_{12}N_2O_3$
2o	2	4-OCH_2CF_3	3	**2n**	82	132—136	A	$C_{13}H_9F_3N_2O_3$
2q	2	3-OCH_2CF_3	2	**2p**	92	Oil	—	$C_{13}H_9F_3N_2O_3$
3h	3	4-OCH_2CF_3	2	**3g**	85	Oil	—	$C_{13}H_9F_3N_2O_3$
3i	3	4-OCH_2CH_3	2	**3g**	81	61—63	A	$C_{13}H_{12}N_2O_3$
3j	3	4-$O(CH_2)_2CH_3$	2	**3g**	85	Oil	—	$C_{14}H_{14}N_2O_3$
3k	3	4-$OCH(CH_3)_2$	2	**3g**	100	Oil	—	$C_{14}H_{14}N_2O_3$
3l	3	4-OCH_2–$CH=CH_2$	2	**3g**	73	79—81	A	$C_{14}H_{12}N_2O_3$
3m	3	4-$O(CH_2)_7CH_3$	2	**3g**	100	173—176	B	$C_{19}H_{24}N_2O_3 \cdot HCl$
3q	3	3-OCH_2CF_3	2	**3p**	84	92—94	A	$C_{13}H_9F_3N_2O_3$
4h	4	4-OCH_2CF_3	2	**4g**	77	Oil	—	$C_{13}H_9F_3N_2O_3$
4i	4	4-OCH_2CH_3	2	**4g**	51	79—81	A	$C_{13}H_{12}N_2O_3$
4o	4	4-OCH_2CF_3	3	**4n**	72	88—91	C	$C_{13}H_9F_3N_2O_3$

a) Isolated yield of chromatographically pure product. *b*) Abbreviations for the solvents used are as follows: A, AcOEt–hexane; B, AcOEt–EtOH–ether; C, ether. *c*) Analysis for C, H, N were all ±0.4% of the expected values. The oily products were confirmed by HR-MS.

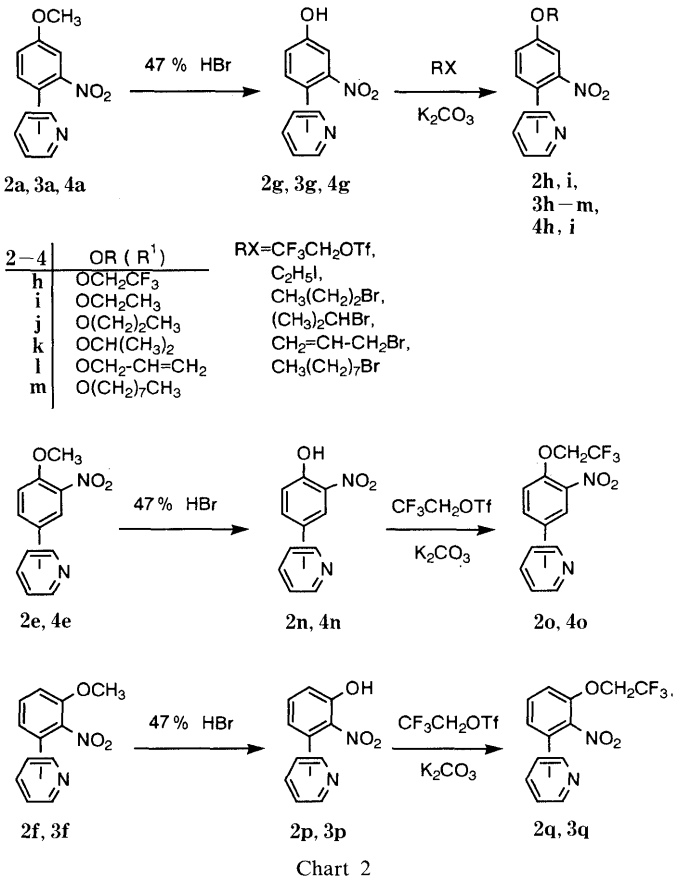


Chart 2

24i—m and **25i** were prepared by the condensation of the corresponding anilines **12i**, **13i—m** and **14i** with *N*-(TFA)-3-aminobutyryl chloride **16** (TFA = trifluoroacetyl) in the presence of triethylamine (Et_3N), followed by alkali-catalyzed hydrolysis. Compounds **26** and **27** were prepared by the condensation of the corresponding anilines **12h** and **13h** with *N*-Boc-3-aminopropionic acid **17** by use of WSC, followed by hydrolysis. The pyridine *N*-oxide **29** was also prepared by the reaction of the *N*-Boc amido compound **19b** with *m*-chloroperbenzoic acid (*m*-CPBA), followed by hydrolysis.

Since compound **24i** possessed the most favorable combination of desired activity and low side effects, optically active **24i** was prepared to examine the activity of the stereoisomers. The optically active compounds *S*(+)-**24i** and *R*(−)-**24i** were obtained by the condensation of the aniline **13i** with optically active *N*-TFA-3-aminobutyryl chlorides *S*-**16** and *R*-**16**, respectively, in the presence of triethylamine (Et_3N), followed by alkali-catalyzed hydrolysis. The optically active *N*-TFA-3-aminobutyryl chlorides *S*-**16** and *R*-**16** were derived from *S*(+)- and *R*(−)-3-aminobutanoic acid, respectively, by *N*-protection with ethyl trifluoroacetate and Et_3N in MeOH, followed by treatment with oxalyl chloride in the presence of *N*,*N*-dimethylformamide (DMF) in benzene. The two samples were identified by comparing their retention times on high-performance liquid chromatography (HPLC) with that of the racemic compound **24i**.

Biological Tests The compounds were all tested for ability to prevent chloroform-induced ventricular fibrillation in mice.[12] During the period between treatment and exposure to chloroform vapor, the animals were checked for overt signs of CNS toxicity.

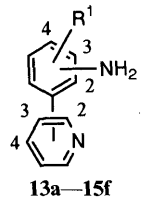
The electrophysiological properties in isolated guinea-pig papillary muscle were examined using a standard microelectrode technique.

Results and Discussion

The antiarrhythmic effects and symptoms of the new disubstituted phenylpyridines (**23—27**, **29**) are shown in Table V.

Compounds **23**, **24** and **25** were examined to evaluate

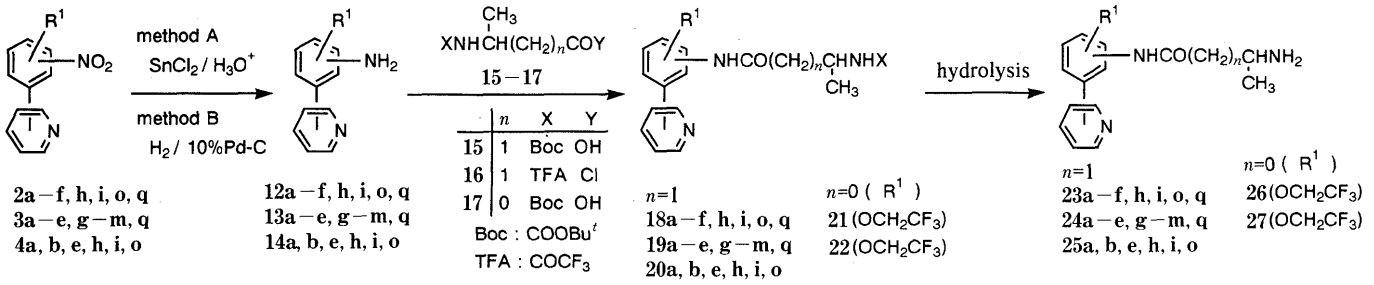
TABLE III. Physical Data for (Substituted Aminophenyl)pyridines (**13**—**15**)[a]



13a—**15f**

Compd. No.	Position of pyridine	R^1	Position of NH_2	Starting material	Method[b]	Yield[c] (%)	mp (°C)	Recrystn. solvent[d]	Formula[e]
13a	2	4-OCH_3	2	**2a**	A	72	Oil	—	$C_{12}H_{12}N_2O$
13b	2	4-CH_3	2	**2b**	A	82	200—205	C	$C_{12}H_{12}N_2 \cdot HCl$
13c	2	4-CF_3	2	**2c**	A	100	74—76	D	$C_{12}H_9F_3N_2$
13d	2	4-Cl	2	**2d**	A	59	68—70	E	$C_{11}H_9ClN_2$
13e	2	4-OCH_3	3	**2e**	A	94	97—99	B	$C_{12}H_{12}N_2O$
13f	2	3-OCH_3	2	**2f**	B	89	Oil	—	$C_{12}H_{12}N_2O$
13g	2	4-OCH_2CF_3	2	**2h**	A	93	81—83	G	$C_{13}H_{11}F_3N_2O$
13h	2	4-OCH_2CH_3	2	**2i**	A	72	98—99	E	$C_{13}H_{14}N_2O$
13i	2	4-OCH_2CF_3	3	**2o**	A	77	89—90	B	$C_{13}H_{11}F_3N_2O$
13j	2	3-OCH_2CF_3	2	**2q**	A	97	Oil	—	$C_{13}H_{11}F_3N_2O$
14a	3	4-OCH_3	2	**3a**	A	85	93—95	A	$C_{12}H_{12}N_2O$
14b	3	4-CH_3	2	**3b**	A	88	Oil	—	$C_{12}H_{12}N_2$
14c	3	4-CF_3	2	**3c**	A	82	99—101	E	$C_{12}H_9F_3N_2$
14d	3	4-Cl	2	**3d**	A	63	205—210 (dec.)	C	$C_{11}H_9ClN_2 \cdot HCl \cdot 0.1H_2O$
14e	3	4-OCH_3	3	**3e**	B	64	109—111	B	$C_{12}H_{12}N_2O$
14f	3	4-OH	2	**3g**	A	70	120—121	F	$C_{11}H_{10}N_2O \cdot 0.1C_4H_8O$
14g	3	4-OCH_2CF_3	2	**3h**	B	98	80—82	H	$C_{13}H_{11}F_3N_2O$
14h	3	4-OCH_2CH_3	2	**3i**	A	88	121—123	G	$C_{13}H_{14}N_2O$
14i	3	4-$OCH_2CH_2CH_3$	2	**3j**	A	98	74—76	E	$C_{14}H_{16}N_2O$
14j	3	4-$OCH(CH_3)_2$	2	**3k**	A	95	99—100	H	$C_{14}H_{16}N_2O$
14k	3	4-OCH_2–$CH=CH_2$	2	**3l**	A	100	73—75	E	$C_{14}H_{14}N_2O$
14l	3	4-$O(CH_2)_7CH_3$	2	**3m**	A	73	177—182	I	$C_{19}H_{26}N_2O \cdot 2HCl$
14m	3	3-OCH_2CF_3	2	**3q**	A	99	Oil	—	$C_{13}H_{11}F_3N_2O$
15a	4	4-OCH_3	2	**4a**	A	64	143—145	B	$C_{12}H_{12}N_2O$
15b	4	4-CH_3	2	**4b**	A	63	117—118	B	$C_{12}H_{12}N_2$
15c	4	4-OCH_3	3	**4f**	B	81	171—172	J	$C_{12}H_{12}N_2O \cdot HCl$
15d	4	4-OCH_2CF_3	2	**4h**	B	90	120—122	E	$C_{13}H_{11}F_3N_2O$
15e	4	4-OCH_2CH_3	2	**4i**	A	66	139—140	B	$C_{13}H_{14}N_2O$
15f	4	4-OCH_2CF_3	3	**4o**	A	90	127—129	H	$C_{13}H_{11}F_3N_2O$

a) NMR and IR spectra consistent with the assigned structures were obtained in all cases. *b*) Method A: $SnCl_2$ $2H_2O$/conc. HCl/EtOH, 100 °C, 2 h. Method B: H_2/10% Pd–C/AcOEt, room temperature, 2—4 h. *c*) Isolated yield of chromatographically pure product. *d*) Abbreviations for the solvents used are as follows: A, ethyl ether; B, AcOEt–hexane; C, MeOH–ether; D, pet. ether; E, ether–hexane; F, AcOEt; G, $CHCl_3$–hexane; H, ether–pet. ether; I, EtOH–acetone–hexane; J, MeOH–AcOEt. *e*) Analysis for C, H, N were all ±0.4% of the expected values. The oily products were confirmed by HR-MS.



	type	R^1
a	I	4 - OCH_3
b	I	4 - CH_3
c	I	4 - CF_3
d	I	4 - Cl
e	II	4 - OCH_3
f	III	3 - OCH_3
g	I	4 - OH
h	I	4 - OCH_2CF_3
i	I	4 - OCH_2CH_3
j	I	4 - $O(CH_2)_2CH_3$
k	I	4 - $OCH(CH_3)_2$
l	I	4 - OCH_2-$CH=CH_2$
m	I	4 - $O(CH_2)_7CH_3$
o	II	4 - OCH_2CF_3
q	II	3 - OCH_2CF_3

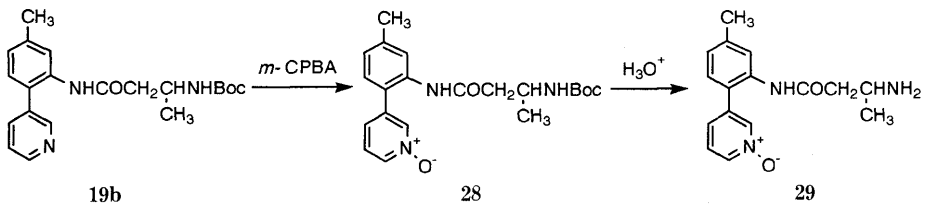
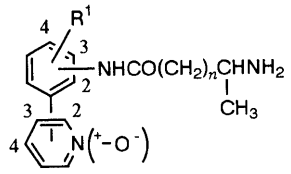


Chart 3

TABLE IV. Physical Data for (Substituted Aminoalkylamidophenyl)pyridines (**23**—**27** and **29**)



23a—**29**

Compd. No.	Position of pyridine	R^1	$NHCO(CH_2)_nCHNH_2$ CH_3 Position	n	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
23a	2	4-OCH_3	2	1	89	185—188	A	$C_{16}H_{19}N_3O_2 \cdot HCl$	59.72	6.26	13.06	59.56	6.17	13.10
23b	2	4-CH_3	2	1	78	Oil	—	$C_{16}H_{19}N_3O$	269.1528			269.1524[d]		
23c	2	4-CF_3	2	1	100	245—246	B	$C_{16}H_{16}F_3N_3O \cdot HCl$	53.42	4.76	11.68	53.59	4.79	11.82
23d	2	4-Cl	2	1	83	223—224 (dec.)	C	$C_{15}H_{16}ClN_3O \cdot HCl$	55.23	5.25	12.88	55.09	5.34	12.64
23e	2	4-OCH_3	3	1	62	174—176	A	$C_{16}H_{19}N_3O_2 \cdot HCl \cdot 0.2H_2O$	59.06	6.32	12.91	59.18	6.18	12.93
23f	2	3-OCH_3	2	1	81	125—127	C	$C_{16}H_{19}N_3O_2$	67.35	6.71	14.73	67.23	6.58	14.98
23h	2	4-OCH_2CF_3	2	1	91	184—186	E	$C_{17}H_{18}F_3N_3O_2 \cdot HCl$	52.38	4.91	10.78	52.51	4.83	10.86
23i	2	4-OCH_2CH_3	2	1	82	Oil	—	$C_{17}H_{21}N_3O_2$	299.1634			299.1643[d]		
23o	2	4-OCH_2CF_3	3	1	55	202—207	G	$C_{17}H_{18}F_3N_3O_2 \cdot HCl \cdot 0.6H_2O$	50.96	5.08	10.49	50.84	4.88	10.42
23q	2	3-OCH_2CF_3	2	1	76	135—137	C	$C_{17}H_{18}F_3N_3O_2$	57.79	5.13	11.89	57.99	5.18	11.84
24a	3	4-OCH_3	2	1	92	Oil	—	$C_{16}H_{19}N_3O_2$	285.1477			285.1473[d]		
24b	3	4-CH_3	2	1	71	Oil	—	$C_{16}H_{19}N_3O$	269.1528			269.1532[d]		
24c	3	4-CF_3	2	1	97	Oil	—	$C_{16}H_{16}F_3N_3O$	323.1245			323.1251[d]		
24d	3	4-Cl	2	1	85	Amorphous	D	$C_{15}H_{16}ClN_3O \cdot HCl$	289.0982			289.0985[d]		
24e	3	4-OCH_3	3	1	90	138—140	F	$C_{16}H_{19}N_3O_2 \cdot HCl \cdot 0.3H_2O$	58.73	6.35	12.84	58.85	6.39	12.80
24g	3	4-OH	2	1	85	151—153 (dec.)	B	$C_{15}H_{17}N_3O \cdot HCl \cdot 0.5H_2O$	56.87	6.05	13.26	56.68	6.11	13.14
24h	3	4-OCH_2CF_3	2	1	90	218—219	B	$C_{17}H_{18}F_3N_3O_2 \cdot HCl$	52.38	4.91	10.78	52.47	4.89	10.71
24i	3	4-OCH_2CH_3	2	1	100	229—230 (dec.)	B	$C_{17}H_{21}N_3O_2 \cdot 2HCl$	54.85	6.23	11.29	54.98	6.16	11.28
24j	3	4-$O(CH_2)_2CH_3$	2	1	100	Oil	—	$C_{18}H_{23}N_3O_2$	313.1790			313.1778[d]		
24k	3	4-$OCH(CH_3)_2$	2	1	100	Oil	—	$C_{18}H_{23}N_3O_2$	313.1790			313.1789[d]		
24l	3	4-OCH_2–$CH=CH_2$	2	1	98	Oil	—	$C_{18}H_{21}N_3O_2$	311.1634			311.1629[d]		
24m	3	4-$O(CH_2)_7CH_3$	2	1	94	180—182 (dec.)	B	$C_{23}H_{33}N_3O_2 \cdot 2HCl$	60.52	7.73	9.21	60.53	7.67	9.22
24q	3	3-OCH_2CF_3	2	1	75	165—168	H	$C_{17}H_{18}F_3N_3O_2$	57.79	5.13	11.89	57.63	5.22	11.80
25a	4	4-OCH_3	2	1	81	213—214	B	$C_{16}H_{19}N_3O_2 \cdot HCl \cdot 0.5H_2O$	58.09	6.40	12.70	58.30	6.20	12.66
25b	4	4-CH_3	2	1	95	Oil	—	$C_{16}H_{19}N_3O$	269.1528			269.1552[d]		
25e	4	4-OCH_3	3	1	96	247—249	B	$C_{16}H_{19}N_3O_2 \cdot HCl$	59.72	6.26	13.06	59.57	6.20	12.93
25h	4	4-OCH_2CF_3	2	1	100	228—232	B	$C_{17}H_{18}F_3N_3O_2 \cdot HCl$	52.38	4.91	10.78	52.35	5.08	10.78
25i	4	4-OCH_2CH_3	2	1	71	105—107	—	$C_{17}H_{21}N_3O_2$	299.1634			299.1626[d]		
25o	4	4-OCH_2CF_3	3	1	82	210—212	B	$C_{17}H_{18}F_3N_3O_2 \cdot HCl$	52.38	4.91	10.78	52.35	5.08	10.78
26	2	4-OCH_2CF_3	2	0	94	85—86	C	$C_{16}H_{16}F_3N_3O_2$	56.64	4.75	12.38	56.64	4.68	12.27
27	3	4-OCH_2CF_3	2	0	91	135—140	B	$C_{16}H_{16}F_3N_3O_2 \cdot HCl \cdot 0.2H_2O$	50.66	4.62	11.08	50.37	4.60	11.06
29[c]	3	4-CH_3	2	1	89	Oil	—	$C_{16}H_{19}N_3O_2$	285.1477			285.1479[d]		

a) Isolated yield of chromatographically pure product. *b*) Abbreviations for the solvents used are as follows: A, MeOH–acetone; B, MeOH–ether; C, AcOEt–hexane; D, ether; E, acetone–ether; F, MeOH–AcOEt; G, EtOH–hexane; H, AcOEt. *c*) Pyridine *N*-oxide. *d*) High mass data.

how the binding positions of the substituents R^1 and R^2 on the benzene ring affected the activity. The (2,4-disubstituted phenyl)pyridines (type I) were more effective than the other types (types II and III). In the type I compounds, the activity was affected by the binding position of the disubstituted phenyl group on the pyridine ring. That is to say, the activities of 4-phenylpyridines (**25a, b**) were less than those of the corresponding 2- and 3-phenylpyridines (**23a, b** and **24a, b**). The substituent in the former case might influence interactions of the molecules concerned with the drug receptor, and there are differences of lipophilicity (π value of the 4-pyridyl group: 0.32). Pyridine *N*-oxide (**29**) remarkably reduced the activity.

Compounds **23h**, **24h**, **26** and **27** were examined to see how the carbon-chain length of the substituent R^2 influenced the activity. The activities of the 3-aminobutyramido compounds (**23h**, **24h**) were more potent than those of the 2-aminopropionamido compounds (**26**, **27**). We assumed the activities to be influenced by the basicity of the amino group; the pK_a values of 2-aminopropionamido derivatives are smaller than those of 3-aminobutyramido derivatives.[4]

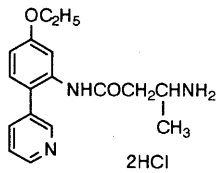
On the basis of the above-mentioned structure–activity studies, 3-[4-substituted-2-(3-aminobutyramido)phenyl]-pyridines were tested to determine whether modification at the 4-position of the benzene ring in this series of compounds could improve the antiarrhythmic activity in the chloroform-mouse test. First, the most suitable length of carbon-chain of the alkoxy group at the 4-position in 3-[2-(3-aminobutyramido)phenyl]pyridines (**24a**, **24h**—**m**) was elucidated. The 2,2,2-trifluoroethoxy group and

TABLE V. Biological Data for (Substituted Aminoalkylamidophenyl)pyridines (**23**—**27** and **29**)

Compd. No.	% inhibition of chloroform-induced V.F. in mouse		Symptons			
			100 mg/kg *p.o.*			
	100 mg/kg *p.o.* ($N^{a)}$)	30 mg/kg *p.o.* ($N^{a)}$)	Sedation[d]	Tremor	Convulsion	Ataxia
23a	100 (10)	80 (10)	+	−	−	−
23b	100 (10)	90 (10)	++	+	−	−
23c	100 (10)	80 (10)	++	+	−	−
23d	100 (10)	80 (10)	++	+	−	+
23e	90 (10)	60 (10)	+	−	−	−
23f	50 (10)	ND	−	−	−	−
23h	100 (10)	100 (10)	++	−	−	−
23i	90 (10)	80 (10)	++	−	−	−
23o	−(6)[b]	60 (6)	−	−	−	−
23q	100 (10)	50 (10)	−	−	−	−
24a	80 (10)	70 (10)	−	−	−	−
24b	100 (10)	80 (10)	−	−	−	−
24c	90 (10)	70 (10)	−	−	−	−
24d	40 (5)	ND	−	−	−	−
24e	57 (7)	ND	−	−	−	−
24g	10 (10)	ND	−	−	−	−
24h	100 (10)	100 (10)	−	+	+	+
24i	100 (10)	100 (10)	++	−	−	−
24j	100 (9)[c]	90 (10)	++	+	−	−
24k	100 (10)	70 (10)	−	−	−	−
24l	100 (10)	70 (10)	−	−	−	−
24m	40 (10)	ND	−	−	−	−
24q	90 (10)	30 (10)	++	−	−	−
25a	20 (10)	ND	−	−	−	−
25b	40 (10)	ND	−	−	−	−
25e	20 (10)	ND	++	−	−	−
25h	90 (10)	80 (10)	−	−	−	−
25i	90 (10)	40 (10)	−	−	−	−
25o	80 (10)	ND	−	−	−	−
26	25 (10)	ND	++	−	−	−
27	80 (10)	ND	+	−	−	−
29[e]	40 (5)	ND	−	−	−	−
Mexiletine	100 (10)	50 (10)	−	+	+	+

a) Number of mice used. *b*) Dead (%) 50. *c*) Dead (%) 10. *d*) +: weak sedation, ++: sedation. *e*) Pyridine *N*-oxide. ND, not done.

ethoxy group were most effective. A less lipophilic group, namely methoxy, and slightly more lipophilic ones such as *n*-propoxy, isopropoxy and allyloxy slightly decreased the effect and a more lipophilic group such as octyloxy dramatically diminished it. Secondly, compounds **23b**—**d**, **24b**—**d**, **g** and **25b** were examined to see how a substituent R^1 other than an alkoxy group on the benzene ring would affect the activity. Introduction of a methyl group, which has electron-releasing nature similar to that of an alkoxy group, at the 4-position of the benzene ring retained the activity, which was comparable to those of **24h** and **24i** themselves. The 4-trifluoromethyl compounds (**23c**, **24c**) also retained the activity despite the electron-attracting nature of the trifluoromethyl group. In contrast, the 3-[4-hydroxy-2-(3-aminobutyramido)phenyl]pyridine (**24g**) showed considerably reduced activity. This is considered to be because the π value of the hydroxy group (-0.67) is very low. It is particularly noteworthy that the 4-chloro compound (**24d**) had almost no effect even though **23d** had potent activity; this was an interesting result that had no parallel in the case of 2- and 3-(disubstituted phenyl)pyridines. As far as the substituent R^1 is concerned, it appears that the combination of appropriate bulkiness and adequate lipophilicity (π value) of the substituent R^1 is necessary for potent activity, whereas electronic effects are of little importance.



K-953 (**24i** • 2HCl)

Fig. 3

Finally, three compounds (**23h**, **24h**, **i**) were found to be twice as active as mexiletine (III). The antiarrhythmic activities of these compounds were further examined at 10 mg/kg *p.o.* in the chloroform-mouse test. The order of activity for inhibition of ventricular fibrillation (V.F.) at the dose of 10 mg/kg *p.o.* was **24h** (60% inhibition), **24i** (50%) and **23h** (40%), while that of the CNS activity in mice, as shown in Table V, was **24h** > **24i** = **23h**. In comparison with mexiletine (III), **24i** has a weak CNS activity in mice. On the basis of these results, compound **24i** (2HCl salt) was selected for further evaluation as K-953 (Fig. 3).

The antiarrhythmic activities of optical isomers of K-953 (**24i**·2HCl) were next examined at 30 mg/kg *p.o.* in the chloroform-mouse test. The order of activity was *S*(+)-K-953 (90% inhibition) > (±)-K-953 (80%) > *R*(−)-K-953 (60%).

Furthermore, K-953 (10^{-5}, 3×10^{-5} M) showed a shortened duration of action potential and a reduced maximum rate of rise of phase 0 ($\overset{\infty}{V}_{max}$) in a concentration-dependent manner, suggesting that K-953 can be classified as a class I B agent in the Vaughan Williams classification. During rapid stimulation trains at 4 Hz in a preparation treated with K-953 (3×10^{-5} M), a slow onset of decrease in $\mathring{V}_{max}$ of the action potential was observed. The calculated time constant for the onset rate was $0.080\pm0.006\,AP^{-1}$, indicating that K-953 can be classified as a slow drug as regards the kinetics of sodium channel blocking action.

In conclusion, we have described a new class of antiarrhythmic agents, the disubstituted phenylpyridine derivatives, and evaluated the relationship between antiarrhythmic activity and Hansch's π value of the substituent on the benzene nucleus. The antiarrhythmic activity of the disubstituted phenylpyridine derivatives is greatly influenced by Hansch's π value of the substituent on the benzene nucleus. Among the compounds tested, **24i** has a potent antiarrhythmic activity with low CNS side effects. Compound **24i** has a class I B electrophysiological character and showed a slow kinetic RDB of the sodium channel in cardiac muscle.

Experimental

Melting points were determined on a Büchi 530 melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Shimadzu IR-435 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL JNM-FX200 or FX-270 spectrometer unless otherwise noted and chemical shifts are given in ppm with tetramethylsilane as an internal standard. Electron impact mass spectra (EI-MS) and high-resolution mass spectra (HR-MS) were recorded on a JMS-D-300 spectrometer.

Materials L-(+)-3-aminobutanoic acid and D-(−)-3-aminobutanoic acid were donated by Daiichi Pure Chemicals Co., Ltd., Tokyo, Japan.

3-Methoxy-2-nitroaniline (11)[8] A solution of 3-methoxy-2-nitrobenzoic acid (96%) (**9**) (10.338 g, 50.3 mmol) in *tert*-BuOH (15 ml) containing Et_3N (0.71 ml, 50.9 mmol) was treated with DPPA (1.1 ml,

TABLE VI. Spectral Data for Phenylpyridines (**2a—f**, **3a—f**, **4a—c** and **6—8**)

Compd. No.	IR (KBr) cm^{-1}	^1H-NMR ($CDCl_3$) δ (ppm)
2a	1518, 1343	3.94 (3H, s), 7.2—8.2 (6H, m), 8.7—9.0 (1H, m)
2b	1525, 1358	2.50 (3H, s), 7.1—7.7 (4H, m), 7.7—8.0 (2H, m), 8.6—8.8 (1H, m)
2c	1541, 1364, 1322	7.3—8.1 (5H, m), 8.22 (1H, s), 8.74 (1H, d, J=5 Hz)
2d	1527, 1358	7.2—8.1 (6H, m), 8.6—8.8 (1H, m)
2e	1521, 1354	3.92 (3H, s), 7.1—7.9 (6H, m), 8.66 (1H, dd, J=5, 2 Hz)
2f	1531, 1370	3.98 (3H, s), 7.0—7.9 (6H, m), 8.5—8.8 (1H, m)
3a	1506, 1354	3.94 (3H, s), 7.1—7.5 (3H, m), 7.5—7.8 (2H, m), 8.3—8.8 (2H, br s)
3b	1521, 1356	2.53 (3H, m), 7.4—7.8 (3H, m), 7.8—8.1 (2H, m), 8.5—8.8 (2H, m)[b]
3c	1534, 1355, 1323	7.3—7.9 (3H, m), 8.01 (1H, d, J=8 Hz), 8.32 (1H, s), 8.65 (1H, d, J=3 Hz), 8.75 (1H, dd, J=5, 2.5 Hz)
3d	1514, 1355	7.3—7.7 (4H, m), 7.99 (1H, d, J=2 Hz), 8.57 (1H, d, J=1.5 Hz), 8.67 (1H, dd, J=5, 1.5 Hz)
3e	1527, 1350	3.94 (3H, s), 7.0—8.0 (5H, m), 8.5—8.8 (2H, m)
3f	1522, 1371	3.95 (3H, s), 7.00 (1H, d, J=8.3 Hz), 7.11 (1H, d, J=8.3 Hz), 7.34 (1H, dd, J=8, 5 Hz), 7.51 (1H, t, J=8.3 Hz), 7.70 (1H, dt, J=8, 2 Hz), 8.6—8.7 (2H, m)
4a	1527, 1353	3.92 (3H, s), 7.2—7.5 (4H, m), 7.54 (1H, d, J=2 Hz), 8.6—8.8 (2H, br s)
4b	1528, 1368[a]	2.53 (3H, m), 7.2—7.5 (3H, m), 7.58 (1H, d, J=8 Hz), 7.88 (1H, s), 8.6—8.9 (2H, m)
4e	1524, 1347	4.08 (3H, s), 7.29 (1H, d, J=8 Hz), 7.4—7.7 (2H, m), 7.91 (1H, dd, J=8, 2 Hz), 8.19 (1H, d, J=2 Hz), 8.7—8.9 (2H, m)
6	1603, 1460, 1244, 1020	3.86 (3H, s), 6.9—7.1 (2H, m), 7.1—7.2 (1H, m), 7.6—7.8 (2H, m), 7.9—8.0 (2H, m), 8.65 (1H, d, J=5 Hz)
7	1605, 1471, 1250, 1026	3.86 (3H, s), 7.03 (2H, d, J=8 Hz), 7.2—7.5 (1H, m), 7.56 (2H, d, J=8 Hz), 7.7—8.0 (1H, m), 8.30 (1H, dd, J=5, 2.5 Hz), 8.87 (1H, d, J=2.5 Hz)
8	1604, 1483, 1254, 1032	3.87 (3H, s), 6.9—7.1 (2H, m), 7.4—7.7 (4H, m), 8.6—8.7 (2H, m)

a) Film. *b*) Solvent: CD_3OD.

51.0 mmol), and the mixture was stirred at 100 °C for 4 h. After cooling to room temperature, the resulting mixture was extracted with AcOEt. The extract was washed with water, then dried, and the solvent was removed. The residue was chromatographed on a silica gel column with hexane–AcOEt (5 : 1, v/v) to give **10** (11.49 g, 81%), which was recrystallized from petroleum ether to afford pale yellow needles, mp 99—100 °C. IR (KBr): 3400, 1729, 1609, 1507, 1419, 1349, 1272, 1154, 1044, 781 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.53 (9H, s), 3.92 (3H, s), 6.73 (1H, d, J=8 Hz), 7.41 (1H, t, J=8 Hz), 7.58 (1H, br s), 7.81 (1H, d, J=8 Hz).

The column was further eluted with hexane–AcOEt (5 : 1—4 : 1, v/v) to give **11** (0.881 g, 10%), which was crystallized from benzene–petroleum ether to afford bright yellow prisms, mp 117—120 °C (lit.[8] 124—124.5 °C). IR (KBr): 3419, 3348, 1635, 1605, 1576, 1512, 1449, 1359, 1335, 1269, 1135, 1079, 853, 780 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 3.90 (3H, s), 5.02 (2H, br s), 6.37 (2H, t, J=8 Hz), 7.20 (1H, t, J=8 Hz).

A solution of **10** (11.50 g, 42.9 mmol) in MeOH (90 ml) was acidified with 6 N HCl (15 ml), and the mixture was refluxed for 30 min. The solvent was removed, then the residue was made alkaline with 25% NaOH, and extracted with AcOEt. The extract was dried over anhydrous Na_2SO_4 and evaporated to dryness to give **11** (6.71 g, 93%) as yellow crystals.

Compounds **2a—f**, **3a—f**, **4a**, **b**, **e** and **6—8** were prepared by the methods described in the literature.[7,10] Yields and physical properties are shown in Table I. Spectral data are shown in Table VI.

3-(4-Hydroxy-2-nitrophenyl)pyridine (3g) A solution of **3a** (1.235 g, 5.4 mmol) in 47% HBr (10 ml) was stirred at 120 °C for 8 h, then adjusted to pH 3—4 with 50% NaOH, neutralized with powdered $NaHCO_3$, and extracted with AcOEt. The organic layer was dried, and the solvent was removed. The residue was recrystallized from AcOEt to give **3g** (477 mg) as yellow prisms. The mother liquor was purified by column chromatography on silica gel with $CHCl_3$–MeOH (50 : 1, v/v) to give **3g** (331 mg). The total yield of **3g** was 808 mg (69%), mp 189—191 °C (dec.) (acetone). IR (KBr): 1517, 1346 cm^{-1}. ^1H-NMR (CD_3OD) δ: 7.15 (1H, dd, J=8, 2.5 Hz), 7.2—7.9 (4H, m), 8.4—8.7 (2H, m). *Anal.* Calcd for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.38; H, 3.82; N, 12.78.

Other phenols were similarly obtained.

2-(4-Hydroxy-2-nitrophenyl)pyridine (**2g**): Pale yellow prisms, yield 70%, mp 182—185 °C (AcOEt–hexane). IR (KBr): 1528, 1306 cm^{-1}. ^1H-NMR (CD_3OD) δ: 7.18 (1H, dd, J=8, 2.5 Hz), 7.3—7.7 (4H, m), 7.8—8.1 (1H, m), 8.5—8.7 (1H, m). *Anal.* Calcd for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.17; H, 3.76; N, 12.95.

4-(4-Hydroxy-2-nitrophenyl)pyridine (**4g**): A pale brown powder, yield 47%, mp 240—246 (dec.) (MeOH). IR (KBr): 1525, 1350 cm^{-1}. ^1H-NMR (CD_3OD) δ: 7.18 (1H, dd, J=8, 2.5 Hz), 7.3—7.6 (4H, m), 8.4—8.9 (2H, m). *Anal.* Calcd for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 60.93; H, 3.74; N, 12.68.

2-(4-Hydroxy-3-nitrophenyl)pyridine (**2n**): Yellow needles, yield 81%, mp 112—116 °C (EtOH–hexane). IR (KBr): 1528, 1324 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 7.2—7.6 (2H, m), 7.6—8.0 (2H, m), 8.32 (1H, dd, J=8, 2.5 Hz), 8.6—8.9 (2H, m), 10.65 (1H, s). *Anal.* Calcd for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 60.93; H, 3.57; N, 12.88.

4-(4-Hydroxy-3-nitrophenyl)pyridine (**4n**): Pale orange needles, yield 76%, mp 211—213 °C (MeOH). IR (KBr): 1525, 1348 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 7.31 (1H, d, J=9 Hz), 7.50 (2H, dd, J=6, 1.5 Hz), 7.89 (1H, dd, J=9, 2.5 Hz), 8.42 (1H, d, J=2.5 Hz), 8.71 (2H, d, J=6 Hz), 10.68 (1H, br s). *Anal.* Calcd for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.15; H, 3.73; N, 12.90.

2-(3-Hydroxy-2-nitrophenyl)pyridine (**2p**): Pale yellow leaflets, yield 38%, mp 153—155 °C (AcOEt). IR (KBr): 1579, 1525, 1372, 1316 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 7.0—7.7 (5H, m), 7.7—8.0 (1H, m), 8.6—8.8 (1H, m), 9.6—10.2 (1H, m). *Anal.* Calcd for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.50; H, 3.73; N, 12.95.

3-(3-Hydroxy-2-nitrophenyl)pyridine (**3p**): Orange prisms, yield 86%, mp 230—238 °C (MeOH). IR (KBr): 1574, 1514, 1320 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 6.88 (1H, d, J=8 Hz), 7.23 (1H, d, J=8 Hz), 7.37 (1H, dd, J=7, 5 Hz), 7.5—7.7 (2H, m), 8.54 (1H, d, J=2.5 Hz), 8.65 (1H, dd, J=5, 1.5 Hz), 9.99 (1H, br s). *Anal.* Calcd for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.29; H, 3.79; N, 12.84.

3-[2-Nitro-4-(2,2,2-trifluoroethoxy)phenyl]pyridine (3h) 2,2,2-Trifluoroethyl trifluoromethanesulfonate (1.68 g, 7.2 mmol) was added to a solution of **3g** (649 mg, 3.0 mmol) in DMF (6 ml) containing K_2CO_3 (622 mg, 4.5 mmol), and the reaction mixture was stirred at 50 °C for 1 h, then allowed to cool to room temperature. AcOEt (60 ml) was added, and the mixture was washed with water. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated to give a dark brown oil. The oil was chromatographed on silica gel with $CHCl_3$ to give **3h** (765 mg, 85%) as a pale yellow oil. IR (film): 1618, 1528, 1354, 1290, 1262, 1227, 1162, 1074, 971, 811, 712 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 4.50 (2H, q, J=8 Hz), 7.2—7.8 (5H, m), 8.5—8.8 (2H, m). HR-MS: Calcd for $C_{13}H_9F_3N_2O_3$ 298.0565, Found 298.0566.

Other 2,2,2-trifluoroethoxy derivatives were similarly obtained.

3-(4-Ethoxy-2-nitrophenyl)pyridine (3i) Ethyl iodide (1.46 ml, 18.3 mmol) was added to a solution of **3g** (3.8 g, 17.6 mmol) in DMF (38 ml) containing K_2CO_3 (2.84 g, 20.5 mmol), and the mixture was stirred overnight at room temperature, then poured into water. This mixture was extracted with ether. The extract was washed with water and brine in that order, and dried over anhydrous Na_2SO_4. The solvent was removed, and the residue was purified by column chromatography on silica gel with

AcOEt–hexane (1 : 4—1 : 3, v/v). The eluate was evaporated, and the residue was recrystallized from AcOEt–hexane (1 : 2, v/v) to give **3i** (4.36 g, 81%) as light yellow prisms, mp 61—63 °C. IR (KBr): 1621, 1521, 1342, 1284, 1049, 869, 712 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, t, J=7 Hz), 4.14 (2H, q, J=7 Hz), 7.19 (1H, dd, J=8.3, 2.5 Hz), 7.31 (1H, d, J=8.3 Hz), 7.33 (1H, dd, J=8.0, 5 Hz), 7.48 (1H, d, J=2.5 Hz), 7.60 (1H, ddd, J=8.0, 2.5, 1.5 Hz), 8.55 (1H, d, J=1.5 Hz), 8.63 (1H, dd, J=5, 1.5 Hz). *Anal.* Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.84; H, 4.94; N, 11.51.

Other ethoxy derivatives were similarly obtained.

3-(2-Nitro-4-*n*-propoxyphenyl)pyridine (3j) *n*-Propyl bromide (677 mg, 5.5 mmol) was added to a solution of **3g** (1.08 g, 5.0 mmol) in DMF (10 ml) containing K_2CO_3 (829 mg, 6.0 mmol), and the mixture was stirred at 70 °C for 30 min. The reaction mixture was treated in a manner similar to that described above to afford **3j** (1.099 g, 85%) as a pale brown oil. IR (KBr): 3361, 1617, 1523, 1465, 1348, 1226, 809, 713 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (3H, t, J=7 Hz), 1.87 (2H, sext, J=7 Hz), 4.03 (2H, t, J=7 Hz), 7.19 (1H, dd, J=8.3, 2.5 Hz), 7.28 (1H, d, J=8.3 Hz), 7.3—7.4 (1H, m), 7.48 (1H, d, J=2.5 Hz), 8.62 (1H, dd, J=5, 2 Hz). HR-MS: Calcd for $C_{14}H_{14}N_2O_3$ 258.1004, Found 258.1004.

3-(4-Isopropoxy-2-nitrophenyl)pyridine (3k) Isopropyl iodide (0.204 ml, 2.0 mmol) was added to a solution of **3g** (422 mg, 2.0 mmol) in DMF (10 ml) containing K_2CO_3 (303 mg, 2.2 mmol), and the mixture was stirred at 40 °C for 6 h. The reaction mixture was treated in a manner similar to that described above to afford **3k** (536 mg, quant.) as a yellow oil. IR (film): 1620, 1526, 1460, 1350, 1286, 1109 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (6H, d, J=7 Hz), 4.72 (1H, m), 7.22 (1H, dd, J=9, 2.5 Hz), 7.3—7.5 (2H, m), 7.55 (1H, d, J=2.5 Hz), 7.7 (1H, m), 8.6—8.8 (2H, m). HR-MS: Calcd for $C_{14}H_{14}N_2O_3$ 258.1004, Found 258.1006.

3-(4-Allyloxy-2-nitrophenyl)pyridine (3l) Allyl bromide (0.942 ml, 10.9 mmol) was added to a solution of **3g** (2.0 g, 9.3 mmol) in DMF (20 ml) containing K_2CO_3 (1.5 g, 10.9 mmol), and the mixture was stirred at 70 °C for 30 min. The reaction mixture was treated in a manner similar to that described above to afford **3l** (1.73 g, 73%) as pale yellow prims, mp 79—81 °C (AcOEt–hexane). IR (KBr): 1621, 1521, 1342, 1284, 1226, 1049, 869, 712 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, t, J=7 Hz), 4.14 (2H, q, J=7 Hz), 7.19 (1H, dd, J=8.3, 2.5 Hz), 7.31 (1H, d, J=8.3 Hz), 7.33 (1H, dd, J=7.8, 4.9 Hz), 7.48 (1H, d, J=2.5 Hz), 7.60 (1H, ddd, J=7.8, 2.5, 1.5 Hz), 8.55 (1H, d, J=1.5 Hz), 8.63 (1H, dd, J=4.9, 1.5 Hz). *Anal.* Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.74; H, 4.78; N, 10.85.

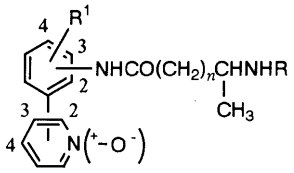
3-(2-Nitro-4-*n*-octyloxyphenyl)pyridine (3m) *n*-Octyl bromide (1.07 g, 5.5 mmol) was added to a solution of **3g** (1.0 g, 4.6 mmol) in DMF (6 ml) containing K_2CO_3 (0.767 g, 5.5 mmol) and KI (0.768 g, 4.6 mmol), and the mixture was stirred at 70 °C for 1 h. The reaction mixture was treated in a manner similar to that described above to afford **3m** (1.52 g, quant.) as a pale yellow oil. IR (film): 1618, 1527, 1465, 1349, 1287, 1227 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.7—2.1 (15H, m), 4.07 (2H, t, J=7 Hz), 7.1—7.8 (5H, m), 8.5—8.8 (2H, m).

Hydrochloride Salt of **3m**: mp 173—176 °C (AcOEt–EtOH–Et_2O), pale yellow needles. *Anal.* Calcd for $C_{19}H_{25}ClN_2O_3$: C, 62.35; H, 6.91; N, 7.68. Found: C, 62.38; H, 7.00; N, 7.71.

Yields and physical properties of the (alkoxy nitrophenyl)pyridines are summarized in Table II.

Aniline compounds (**12a—f, h, i, o, q, 13a—e, g—m, q** and **14a, b, e, h, i, o**) were synthesized by the method reported by Coates *et al.*[10] Yields

TABLE VII. Yields and Physical Data for (*N*-Protected Aminoalkylamidophenyl)pyridines (**18—22** and **28**)[a]



Compd. No.	Position of pyridine	R^1	NHCO(CH$_2$)$_n$CHNHR CH$_3$ Position	n	R	Yield[b] (%)	mp (°C)	Recrystn. solvent[c]	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
18a	2	4-OCH_3	2	1	Boc	84	147—148	A	$C_{21}H_{27}N_3O_4 \cdot 0.1H_2O$	65.13	7.08	10.85	65.05	7.13	10.98
18b	2	4-CH_3	2	1	Boc	97	153—155	A	$C_{21}H_{27}N_3O_3$	68.27	7.37	11.37	68.19	7.28	11.29
18c	2	4-CF_3	2	1	Boc	70	157—158	A	$C_{21}H_{24}F_3N_3O_3$	59.57	5.71	9.92	59.67	5.85	9.97
18d	2	4-Cl	2	1	Boc	92	162—165	B	$C_{20}H_{24}ClN_3O_3$	61.61	6.20	10.78	61.44	6.21	10.74
18e	2	4-OCH_3	3	1	Boc	79	155—156	A	$C_{21}H_{27}N_3O_4$	65.44	7.06	10.90	65.51	7.11	10.94
18f	2	3-OCH_3	2	1	Boc	69	178—181	A	$C_{21}H_{27}N_3O_4$	65.44	7.06	10.90	65.26	7.21	10.82
18h	2	4-OCH_2CF_3	2	1	Boc	98	97—99	D	$C_{22}H_{26}F_3N_3O_4$	58.27	5.78	9.27	58.10	5.69	9.21
18i	2	4-OCH_2CH_3	2	1	TFA	82	132—133	A	$C_{19}H_{20}F_3N_3O_3$	57.72	5.10	10.63	57.81	5.06	10.57
18o	2	4-OCH_2CF_3	3	1	Boc	88	140—141	A	$C_{22}H_{26}F_3N_3O_4$	58.27	5.78	9.27	58.47	5.80	9.24
18q	2	3-OCH_2CF_3	2	1	Boc	23	160—161	B	$C_{22}H_{26}F_3N_3O_4$	58.27	5.78	9.27	58.35	5.75	9.15
19a	3	4-OCH_3	2	1	Boc	87	166—169	A	$C_{21}H_{27}N_3O_4 \cdot 0.1H_2O$	65.13	7.08	10.85	64.91	7.12	10.91
19b	3	4-CH_3	2	1	Boc	100	145—148	A	$C_{21}H_{27}N_3O_3$	68.27	7.37	11.37	68.52	7.17	11.38
19c	3	4-CF_3	2	1	Boc	54	208—212	A	$C_{21}H_{24}F_3N_3O_3$	59.57	5.71	9.92	59.76	5.81	9.92
19d	3	4-Cl	2	1	Boc	52	189—191	A	$C_{20}H_{24}ClN_3O_3 \cdot 0.1H_2O$	61.33	6.23	10.73	61.27	6.30	10.57
19e	3	4-OCH_3	3	1	Boc	82	148—150	A	$C_{21}H_{27}N_3O_4$	65.44	7.06	10.90	65.48	7.02	10.86
19g	3	4-OH	2	1	Boc	89	214—216	C	$C_{17}H_{16}F_3N_3O_3$	55.59	4.39	11.44	55.72	4.39	11.50
19h	3	4-OCH_2CF_3	2	1	Boc	73	153—154	A	$C_{22}H_{26}F_3N_3O_4$	58.27	5.78	9.27	58.40	5.77	9.29
19i	3	4-OCH_2CH_3	2	1	TFA	81	164—166	B	$C_{19}H_{20}F_3N_3O_3$	57.72	5.10	10.63	57.63	4.98	10.76
19j	3	4-$OCH_2CH_2CH_3$	2	1	TFA	90	153—154	A	$C_{20}H_{22}F_3N_3O_3$	58.68	5.42	10.26	58.69	5.33	10.17
19k	3	4-$OCH(CH_3)_2$	2	1	TFA	84	164—166	A	$C_{20}H_{22}F_3N_3O_3$	58.68	5.42	10.26	58.74	5.47	10.20
19l	3	4-OCH_2–CH=CH_2	2	1	TFA	85	152—154	A	$C_{20}H_{20}F_3N_3O_3$	58.97	4.95	10.31	58.77	4.90	10.35
19m	3	4-$O(CH_2)_7CH_2$	2	1	TFA	87	127—130	A	$C_{25}H_{32}F_3N_3O_3$	62.62	6.73	8.76	62.43	6.85	8.71
19q	3	3-OCH_2CF_3	2	1	Boc	72	152—154	A	$C_{22}H_{26}F_3N_3O_4$	58.27	5.78	9.27	57.99	5.55	9.22
20a	4	4-OCH_3	2	1	Boc	75	94—96	A	$C_{21}H_{27}N_3O_4 \cdot 0.1H_2O$	65.13	7.08	10.85	65.10	7.35	10.55
20b	4	4-CH_3	2	1	Boc	97	157—158	B	$C_{21}H_{27}N_3O_3$	68.27	7.37	11.37	68.27	7.37	11.33
20e	4	4-OCH_3	3	1	Boc	73	168—169	A	$C_{21}H_{27}N_3O_4$	65.44	7.06	10.90	65.37	7.01	10.83
20h	4	4-OCH_2CF_3	2	1	Boc	48	187—188	A	$C_{22}H_{26}F_3N_3O_4$	58.27	5.78	9.27	58.47	5.79	9.30
20i	4	4-OCH_2CH_3	2	1	TFA	87	183—185	A	$C_{19}H_{20}F_3N_3O_3$	57.72	5.10	10.63	57.69	5.09	10.58
20o	4	4-OCH_2CF_3	3	1	Boc	75	98—103	A	$C_{22}H_{26}F_3N_3O_4$	58.27	5.78	9.27	58.09	5.81	9.19
21	2	4-OCH_2CF_3	2	0	Boc	93	146—147	E	$C_{21}H_{24}F_3N_3O_4$	57.40	5.50	9.56	57.50	5.57	9.54
22	3	4-OCH_2CF_3	2	0	Boc	76	149—152	A	$C_{21}H_{24}F_3N_3O_4$	57.40	5.50	9.56	57.24	5.46	9.60
28[d]	3	4-CH_3	2	1	Boc	87	172—173	A	$C_{21}H_{27}N_3O_4$	65.44	7.06	10.90	65.34	7.09	10.77

a) NMR and IR spectra consistent with the assigned structures were obtained in all cases. *b*) Isolated yield of chromatographically pure product. *c*) Abbreviations for the solvents used are as follows: A AcOEt–hexane; B, AcOEt; C, AcOEt–MeOH; D, EtOH–hexane; E, ether–hexane; F, MeOH. *d*) Pyridine *N*-oxide.

TABLE VIII. Spectral Data for (Substituted Aminoalkylamidophenyl)pyridines (**23**—**27** and **29**)

Compd. No.	Salt	IR cm^{-1}	^{1}H-NMR δ (ppm)
23a	HCl	1665 (KBr)	1.38 (3H, d, J=6 Hz), 2.80 (2H, d, J=6 Hz), 3.6—4.0 (4H, m), 6.84 (1H, dd, J=8, 3 Hz), 7.2—8.2 (5H, m), 8.6—8.8 (1H, m) (CD_3OD)
23b	—	1675 (KBr)	1.16 (3H, d, J=6 Hz), 1.54 (2H, s), 2.43 (3H, s), 3.3—3.7 (1H, m), 7.02 (1H, d, J=8 Hz), 7.2—8.0 (4H, m), 8.46 (1H, s), 8.6—8.8 (1H, m), 12.30 (1H, br s) ($CDCl_3$)
23c	HCl	1666 (KBr)	1.40 (3H, d, J=6 Hz), 2.82 (2H, d, J=6 Hz), 3.6—4.0 (1H, m), 7.3—8.2 (5H, m), 8.7—8.9 (2H, m) (CD_3OD)
23d	HCl	1684 (KBr)	1.39 (3H, d, J=6 Hz), 2.79 (2H, d, J=6 Hz), 3.6—4.0 (1H, m), 7.2—8.2 (5H, m), 8.47 (1H, d, J=2 Hz), 8.7—8.9 (1H, m) (CD_3OD)
23e	HCl	1662 (KBr)	1.22 (3H, d, J=6 Hz), 1.66 (2H, br s), 2.32 (1H, dd, J=16, 8 Hz), 2.54 (1H, dd, J=16, 4 Hz), 3.3—3.6 (1H, m), 3.92 (3H, s), 7.00 (1H, d, J=8 Hz), 7.1—8.0 (4H, m), 8.6—8.8 (1H, m), 9.03 (1H, d, J=2 Hz), 9.55 (1H, br s) ($CDCl_3$)
23f	—	1671 (KBr)	1.06 (3H, d, J=6 Hz), 1.48 (2H, br s), 2.0—2.5 (2H, m), 3.1—3.4 (1H, m), 3.91 (3H, s), 6.9—7.9 (6H, m), 8.5—8.7 (1H, m), 9.0—9.5 (1H, m) ($CDCl_3$)
23h	HCl	1666 (KBr)	1.41 (3H, d, J=6 Hz), 2.81 (2H, d, J=6 Hz), 3.6—4.0 (1H, m), 4.61 (2H, q, J=8 Hz), 6.94 (1H, dd, J=8, 3 Hz), 7.3—8.1 (4H, m), 8.17 (1H, d, J=3 Hz), 8.6—8.9 (1H, m) (CD_3OD)
23i	—	1670 ($CHCl_3$)	1.18 (3H, d, J=6 Hz), 1.43 (3H, t, J=6 Hz), 4.17 (2H, q, J=6 Hz), 6.7—8.7 (7H, m) ($CDCl_3$)
23o	HCl	1662 (KBr)	1.44 (3H, d, J=7 Hz), 2.87 (2H, d, J=7 Hz), 3.5—4.0 (1H, m), 4.73 (2H, q, J=8 Hz), 7.2—8.8 (7H, m) (CD_3OD)
23q	—	1670 (KBr)	1.11 (3H, d, J=6 Hz), 1.41 (2H, br s), 2.1—2.5 (2H, m), 3.1—3.5 (1H, m), 4.48 (2H, q, J=8 Hz), 6.9—8.8 (7H, m), 9.7—10.1 (1H, m) ($CDCl_3$)
24a	—	1671 (film)	1.10 (3H, d, J=6 Hz), 1.32 (2H, s), 2.0—2.6 (2H, m), 2.8—3.4 (1H, m), 3.88 (3H, s), 6.78 (1H, dd, J=8, 3 Hz), 7.16 (1H, d, J=8 Hz), 7.3—7.9 (2H, m), 8.06 (1H, d, J=3 Hz), 8.5—8.8 (2H, m) ($CDCl_3$)
24b	—	1655 (film)	1.25 (3H, d, J=6 Hz), 2.42 (3H, d, J=6 Hz), 2.59 (2H, d, J=6 Hz), 3.4—3.7 (1H, m), 7.3—8.1 (5H, m), 8.5—8.7 (2H, m) (CD_3OD)
24c	—	1674 (film)	1.00 (2H, br s), 1.09 (3H, d, J=6 Hz), 2.12 (1H, dd, J=16, 8 Hz), 2.38 (1H, dd, J=16, 4 Hz), 2.9—3.3 (1H, m), 7.2—7.9 (4H, m), 8.6—8.9 (3H, m), 10.85 (1H, m) ($CDCl_3$)
24d	HCl	1662 (KBr)	1.27 (3H, d, J=7 Hz), 2.61 (2H, d, J=6 Hz), 3.4—3.7 (1H, m), 7.44 (2H, s), 7.5—8.1 (3H, m), 8.5—8.9 (2H, m) (CD_3OD)
24e	HCl	1663 (KBr)	1.44 (3H, d, J=6 Hz), 2.8—3.0 (2H, m), 3.6—4.0 (1H, m), 3.97 (3H, s), 7.19 (1H, d, J=8 Hz), 7.4—8.9 (6H, m) (CD_3OD)
24g	HCl	1642 (KBr)	1.08 (3H, d, J=6 Hz), 2.3—2.7 (2H, m), 6.77 (1H, dd, J=8, 2 Hz), 6.93 (1H, d, J=2 Hz), 7.17 (1H, d, J=8 Hz), 7.3—7.5 (1H, m), 7.71 (1H, dt, J=8, 1 Hz), 8.04 (2H, br s), 8.4—8.6 (2H, m), 9.72 (1H, s), 9.83 (1H, br s) (DMSO-d_6)
24h	HCl	1679 (KBr)	1.27 (3H, d, J=6 Hz), 2.61 (2H, d, J=6 Hz), 3.4—3.8 (1H, m), 4.61 (2H, d, J=8 Hz), 7.09 (1H, dd, J=8, 3 Hz), 7.30 (1H, d, J=3 Hz), 7.40 (1H, d, J=8 Hz), 7.4—8.1 (2H, m), 8.4—8.8 (2H, m) (CD_3OD)
24i	2HCl	1671 (KBr)	1.27 (3H, d, J=8 Hz), 1.46 (3H, t, J=7 Hz), 2.75 (2H, d, J=7 Hz), 3.70 (1H, m), 4.62 (2H, q, J=7 Hz), 7.18 (1H, d, Hz), 7.23 (1H, dd, J=8, 2 Hz), 7.62 (1H, d, J=8 Hz), 8.25 (1H, dd, J=8, 5 Hz), 8.7—9.0 (3H, m) (D_2O)
24j	—	1671 (film)	1.05 (3H, t, J=7 Hz), 1.08 (3H, d, J=7 Hz), 1.36 (1H, m), 4.00 (2H, t, J=8 Hz), 6.77 (1H, dd, J=8, 3 Hz), 7.15 (1H, d, J=8 Hz), 7.3—7.4 (1H, m), 7.72 (1H, d, J=8 Hz), 8.03 (1H, d, J=3 Hz), 8.5—8.7 (2H, m) ($CDCl_3$)
24k	—	1664 (film)	1.08 (3H, d, J=8 Hz), 1.37 (6H, d, J=6 Hz), 2.16 (1H, dd, J=15, 9 Hz), 2.40 (1H, dd, J=15, 4 Hz), 3.16 (1H, m), 4.66 (1H, m), 6.73 (1H, dd, J=8, 3 Hz), 7.15 (1H, d, J=8 Hz), 7.3—7.9 (2H, m), 8.6—8.8 (2H, m) ($CDCl_3$)
24l	—	1668, 1650 ($CHCl_3$)	1.08 (3H, d, J=6 Hz), 4.65 (2H, d, J=6 Hz), 5.3—5.6 (2H, m), 6.0—6.4 (1H, m), 6.8—8.8 (7H, m) ($CDCl_3$)
24m	2HCl	1679 (KBr)	0.8—2.0 (15H, m), 1.27 (3H, d, J=7 Hz), 2.77 (2H, d, J=7 Hz), 3.5—4.3 (3H, m), 6.9—7.2 (2H, m), 7.47 (1H, d, J=8 Hz), 8.0—8.9 (4H, m) (D_2O)
24q	—	1663 (KBr)	1.02 (3H, d, J=6 Hz), 2.25 (2H, d, J=6 Hz), 3.1—3.4 (1H, m), 4.62 (2H, q, J=8 Hz), 7.1—8.0 (5H, m), 8.5—8.7 (2H, m) (CD_3OD)
25a	HCl	1693 (KBr)	1.28 (3H, d, J=7 Hz), 2.64 (2H, d, J=7 Hz), 3.5—3.8 (1H, m), 3.87 (3H, s), 6.99 (1H, dd, J=8, 3 Hz), 7.16 (1H, d, J=3 Hz), 7.39 (1H, d, J=9 Hz), 7.4—7.7 (2H, m), 8.4—8.8 (2H, m) (CD_3OD)
25b	—	1660 (film)	1.10 (3H, d, J=6 Hz), 1.20 (2H, br s), 2.0—2.6 (5H, m), 3.0—3.4 (1H, m), 6.9—7.5 (4H, m), 8.13 (1H, s), 8.6—8.9 (2H, m), 9.9—10.2 (1H, m) ($CDCl_3$)
25e	HCl	1689 (KBr)	1.46 (3H, d, J=6 Hz), 2.92 (2H, d, J=6 Hz), 4.01 (3H, s), 7.23 (1H, d, J=8 Hz), 7.69 (1H, dd, J=8, 2 Hz), 7.8—9.0 (5H, m) (CD_3OD)
25h	HCl	1687 (KBr)	1.28 (3H, d, J=7 Hz), 2.63 (1H, d, J=6 Hz), 3.5—3.8 (1H, m), 4.62 (2H, q, J=8 Hz), 7.10 (1H, dd, J=8, 3 Hz), 7.30 (1H, d, J=3 Hz), 7.36 (1H, d, J=8 Hz), 7.4—7.7 (2H, m), 8.5—8.8 (2H, m) (CD_3OD)
25i	—	1668 ($CHCl_3$)	1.10 (3H, d, J=6 Hz), 1.43 (3H, t, J=6 Hz), 4.12 (2H, q, J=6 Hz), 6.8—8.7 (7H, m) ($CDCl_3$)
25o	HCl	1688 (KBr)	1.45 (3H, d, J=6 Hz), 2.88 (2H, d, J=6 Hz), 3.6—4.0 (1H, m), 4.74 (2H, q, J=8 Hz), 7.32 (1H, d, J=8 Hz), 7.6—7.9 (3H, m), 8.36 (1H, d, J=3 Hz), 8.5—8.8 (2H, m) (CD_3OD)
26	—	1675 (KBr)	1.45 (3H, d, J=8 Hz), 1.60 (2H, s), 3.5—3.9 (1H, m), 4.48 (2H, q, J=8 Hz), 6.84 (1H, dd, J=8, 2 Hz), 7.2—8.1 (4H, m), 8.48 (1H, d, J=2 Hz), 8.6—8.8 (1H, m) ($CDCl_3$)
27	HCl	1683 (KBr)	1.40 (3H, d, J=7 Hz), 4.08 (1H, q, J=7 Hz), 4.64 (2H, d, J=8 Hz), 7.16 (1H, dd, J=8, 2 Hz), 7.29 (1H, d, J=8 Hz), 7.4—8.8 (1H, m) (CD_3OD)
29[a]	—	1665 (film)	1.13 (3H, d, J=7 Hz), 2.21 (1H, dd, J=16, 9 Hz), 2.40 (1H, dd, J=16, 4 Hz), 2.41 (3H, s), 3.1—3.2 (1H, m), 7.02 (1H, d, J=8 Hz), 7.12 (1H, d, J=8 Hz), 7.2—7.4 (2H, m), 8.02 (1H, s), 8.1—8.2 (1H, m), 10.55 (1H, br s) ($CDCl_3$)

a) Pyridine *N*-oxide.

and physical properties are summarized in Table III.

2-[2-(*N*-Boc-3-aminobutyramido)-4-methoxy)phenyl]pyridine (18a) *N*-Boc-3-aminobutanoic acid **15** (1.280 g) and WSC (1.21 g) were added to a solution of **12a** (967 mg, 4.8 mmol) in CH_2Cl_2 (15 ml), and the solution was stirred at room temperature for 3 h. The reaction mixture was washed with water, and the solvent was evaporated. The residue was chromatographed on silica gel with $CHCl_3$. The eluate was evaporated, and the residue was recrystallized from AcOEt–hexane to give **18a** (1.574 g, 84%) as pale yellow prisms.

Other compounds (**18b—f, h, o, q, 19a—e, h, q** and **20a, b, e, h, o**) were similarly obtained. Compounds **21** and **22** were synthesized in a similar manner using *N*-Boc alanine **17** instead of *N*-Boc-3-aminobutanoic acid **15** as the reagent.

3-[4-Ethoxy-2-(*N*-TFA-3-aminobutyramido)phenyl]pyridine (19i) A solution of *N*-TFA-3-aminobutyryl chloride **16** (3.08 g, 14.2 mmol) [prepared from *N*-TFA-3-aminobutanoic acid (2.82 g, 14.2 mmol) and oxalyl chloride (1.63 ml, 18.7 mmol) in the presence of DMF (2 drops) in benzene (37 ml)] in tetrahydrofuran (THF) (20 ml) was added to a solution of **13i** (2.03 g, 9.5 mmol) and Et_3N (1.83 ml, 13.1 mmol) in THF (20 ml), and the mixture was stirred overnight at room temperature. The solvent was removed, and the residue was extracted with AcOEt. The extract was washed with water, saturated $NaHCO_3$, water, and brine in that order, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was recrystallized from AcOEt to give **19i** (3.04 g, 81%) as colorless needles.

Other compounds (**18i, 19j—m** and **20i**) were similarly obtained.

3-[2-(*N*-Boc-3-aminobutyramido)-4-methyl)phenyl]pyridine *N*-Oxide (28) A solution of **19b** (449 mg, 1.2 mmol) in $CHCl_3$ (9 ml) was treated with 80% *m*-CPBA (395 mg, 2.3 mmol), and the solution was stirred overnight at room temperature. The reaction mixture was chromatographed on a silica gel column with $CHCl_3$–MeOH (30 : 1, v/v). The eluate was evaporated, and the residue (crude **28**: 410 mg, 87%) was recrystallized from AcOEt–hexane to give **28** (310 mg, 66%) as a colorless powder.

Yields and physical properties of compounds **18—22** and **28** are summarized in Table VII.

2-[2-(3-Aminobutyramido)-4-methoxyphenyl]pyridine (23a) A solution **18a** (1.50 g, 3.9 mmol) in MeOH (39 ml) was acidified with 6 N HCl (6.5 ml), and the solution was stirred at 80 °C for 1 h, then allowed to cool. The solvent was removed, and the residue was neutralized with dilute NaOH. The solution was extracted with AcOEt, then the extract was dried, and the solvent was evaporated off. The residue was chromatographed on a silica gel column with $CHCl_3$–MeOH (saturated with NH_3) (30 : 1, v/v) to give **23a** (994 mg, 89%) as a yellow oil. EI-MS *m/z*: 285 (M^+). Recrystallization of its hydrochloride salt from MeOH–acetone gave a colorless crystalline powder.

3-[2-(3-Aminobutyramido)-4-ethoxyphenyl]pyridine (24i) A solution of **19i** (5.52 g, 14.0 mmol) in MeOH (30 ml)–water (50 ml) was treated with K_2CO_3 (2.32 g, 16.8 mmol), and the mixture was stirred at 70 °C for 4 h. After cooling, the reaction mixture was concentrated, and the residue was extracted with AcOEt. The extract was washed with water, dried, and evaporated to dryness. The residue was chromatographed on a silica gel column with $CHCl_3$–MeOH (saturated with NH_3) (50 : 1—30 : 1, v/v) to give **24i** (4.27 g, quant.) as a pale yellow oil. Recrystallization of the dihydrochloride salt from MeOH–ether gave a colorless crystalline powder.

Yields and physical properties of compounds **23—27** and **29** are summarized in Table IV and the spectral data in Table VIII.

Optically active **24i** was synthesized by the same method as that described for **24i**.

S(−)-3-(Trifluoroacetamido)butanoic Acid: Yield 97%, mp 113—114 °C (ligroin–hexane), $[\alpha]_D^{22}$ −6.5° (*c* = 1, MeOH).

R(+)-3-(Trifluoroacetamido)butanoic Acid: Yield 97%, mp 110—111 °C (ligroin), $[\alpha]_D^{22}$ +6.7° (*c* = 1, MeOH).

S(−)-3-[4-Ethoxy-2-(*N*-TFA-3-aminobutyramido)phenyl]pyridine: Yield 94%, mp 173—174 °C (AcOEt), $[\alpha]_D^{22}$ −7.7. (*c* = 1, MeOH).

R(+)-3-[4-Ethoxy-2-(*N*-TFA-3-aminobutyramido)phenyl]pyridine: Yield 90%, mp 174.5—175.5 °C (AcOEt), $[\alpha]_D^{22}$ +7.5° (*c* = 1, MeOH).

S(+)-3-[2-(3-Aminobutyramido)-4-ethoxyphenyl]pyridine Dihydrochloride: Yield 89%, mp 234—237 °C (dec.) (MeOH–EtOH (1 : 1)), $[\alpha]_D^{22}$ +10.7° (*c* = 2, MeOH).

R(−)-3-[2-(3-Aminobutyramido)-4-ethoxyphenyl]pyridine Dihydrochloride: Yield 94%, mp 238—241 °C (dec.) (MeOH–EtOH (1 : 1)), $[\alpha]_D^{22}$ −11.0° (*c* = 2, MeOH).

Analytical HPLC was carried out on an ULTRON ES-OVM packed column (4.6 × 150 mm) at 30 °C, with phosphate buffer (0.02 M, pH 7.0)–MeCN–MeOH (20 : 1 : 1) unless otherwise stated (flow rate; 1 ml/min), with ultraviolet (UV) detection at 265 nm. Retention times: (±)-K-953: t_R 11.06 and 13.54 min; *S*(+)-K-953: t_R 11.06 min; *R*(−)-K-953: t_R 13.54 min.

Biological Test ICR-strain mice having a body weight of 20 to 35 g (10 per group) were used, and the test compound was administered orally at a dose of 100 mg/kg (30 mg/kg). The mice were put in a 1-liter beaker, and observed for 20 min. Then, they were placed in a vessel saturated with chloroform vapor. After they had stopped breathing, the mice were taken out of the vessel and the electrocardiogram (lead II) was recorded by using a memory oscilloscope (VC-10, Nihon Koden) and a linear corder (WTR_{331}, Watanabe Measuring Instrument Co., Ltd.). The occurrence of ventricular fibrillation was evaluated from the electrocardiogram. The results are shown in Table V as percent V.F. inhibition.

For the study of electrophysiological properties of K-953 (**24i**), a standard microelectrode technique was adopted. Action potentials were measured in electrically driven papillary muscles (1 Hz) isolated from guinea pigs, and superfused with oxygenated Tyrode's solution with and without K-953 (10^{-5} and 3×10^{-5} M). The maximum rate of rise of action potential ($\dot{V}_{max}$) was also measured for determination of the sodium channel blocking kinetic constant during perfusion with 3×10^{-5} M K-953 with rapid stimulation at the rate of 4 Hz.

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