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Synthesis and Antiinflammatory Activity of N^1-(Substituted phenyl)pyridinecarboxamidines

TAKUZO HISANO,*,[a] MASANOBU TASAKI,[a] KONOSUKE TSUMOTO,[a] TOSHIKAZU MATSUOKA,[a] and MASATAKA ICHIKAWA[b]

Faculty of Pharmaceutical Sciences, Kumamoto University,[a] 5–1 Oe-honmachi, Kumamoto 862, Japan and Faculty of Pharmacy & Pharmaceutical Sciences, Fukuyama University,[b] 985 Higashimura-cho, Fukuyama, Hiroshima 729–02, Japan

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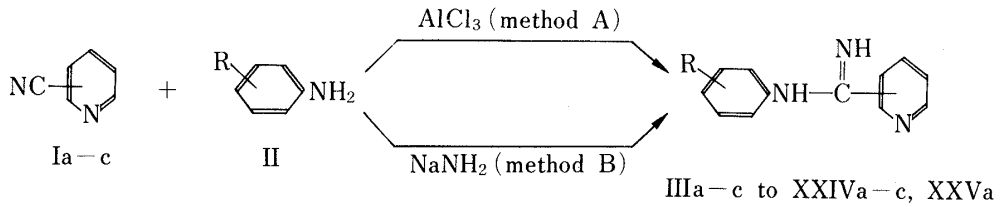
A series of N^1-(substituted phenyl)pyridinecarboxamidines was synthesized by the condensation of substituted anilines with cyanopyridines in the presence of aluminum chloride or sodium amide and these compounds were evaluated for antiinflammatory activity by the carrageenin-induced rat paw edema assay. In the synthesis of N^1-alkoxyphenyl pyridinecarboxamidines, it was found that *o*-alkoxyanilines reacted with aluminum chloride to afford *o*-aminophenol, while *m*- and *p*-alkoxyanilines were scarcely dealkylated. Sodium amide was successfully used for the condensation of *o*-alkoxyanilines with cyanopyridines. Among several active derivatives, N^1-(2,4-dichlorophenyl)pyridinecarboxamidine and N^1-(4-chlorophenyl)-pyridinecarboxamidine exhibited significant antiinflammatory activities.

Keywords——N^1-(substituted phenyl)pyridinecarboxamidine; aluminum chloride; sodium amide; structure–activity; antiinflammatory activity; carrageenin-induced rat paw edema assay

Some nonacidic 2-substituted benzazoles, 2-(dichlorophenyl)benzoxazole[1] and 2-(2-pyridyl)benzimidazoles[2] have efforts were therefore made to prepare a group of nonacidic pyridinecarboxamidines in an attempt to obtain a new class of antiinflammatory agents with reduced gastrointestinal irritation.[3]

A series of N^1-(substituted phenyl)pyridinecarboxamidines was prepared by the condensation of substituted anilines with cyanopyridines in the presence of aluminum chloride (method A) or in the presence of sodium amide (method B) and evaluated for antiinflammatory activity by means of the carrageenin-induced rat paw edema assay.



a: 2-pyridyl; b: 3-pyridyl; c: 4-pyridyl

Chart 1

Chemistry

The reaction of anilines and cyanopyridines in the presence of aluminum chloride (method A) was employed first: the nitrile and the amine were simply heated together in an inert solvent such as *sym*-tetrachloroethane, as described in the previous report.[4] At the end of the reaction the amidine-aluminum chloride complex was decomposed with 5 N sodium

hydroxide. However, there were some cases where this method was not applicable. *o*-Alkoxyanilines failed to give the expected N^1-(*o*-alkoxyphenyl)pyridinecarboxamidines, and resinous substances were formed during the reaction under these conditions. Pursuing this point, we heated an equimolar mixture of *o*-, *m*- or *p*-alkoxyanilines and aluminum chloride in tetrachloroethane, and it was found that *o*-alkoxyanilines were converted into *o*-aminophenol, while *m*- and *p*-alkoxyanilines scarcely gave the corresponding aminophenols.

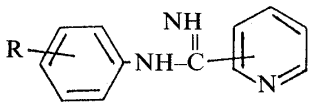
Since substituted anilines metallized with sodium have often been used for the condensation with *o*-substituted benzonitriles,[3,5] sodium amide was tested as a catalyst in the reaction of *o*-alkoxyanilines with cyanopyridines. In method B, *o*-alkoxyanilines were successfully condensed with 2-, 3- and 4-cyanopyridines after reaction with one equivalent of sodium amide in liquid ammonia.

The infrared (IR) spectra of the amidines thus obtained displayed C=N and NH absorptions at 1648—1616 cm^{-1}, and 3480—3415 and 3385—3240 cm^{-1} in accordance with previous reports.[4,6] The NMR spectra showed a broad hydrogen peak at δ 7.00—6.00 due to the two protons of the amidino group, which disappeared readily upon the addition of D_2O.

Antiinflammatory Activity

All the N^1-(substituted phenyl)pyridinecarboxamidines were screened for antiinflammatory activity in the carrageenin-induced rat paw edema test and were compared to ibuprofen. The compounds which exhibited antiinflammatory activity in the initial screening test are given in Table II, and the following structure–activity relationships can be deduced. Introduction of a halogeno substituent at the 4 position of the benzene ring enhances the activity. Chloro and fluoro groups appear to be more effective. On the other hand, the activity is remarkably sensitive to positional changes on the pyridine nucleus site, and the 2-pyridinecarboxamidine moiety is a common structural unit. The nitrogen base of the pyridine nucleus, therefore, appears to have an important role in the activity. Among several active compounds, N^1-(2,4-dichlorophenyl)-2-pyridinecarboxamidine (XXIIa) was very effective for the initial 3 h after administration, then its action became that of a muscle relaxant. N^1-(4-Chlorophenyl)-2-pyridinecarboxamidine (IXa) had no muscle relaxant action, and was

TABLE I. Analytical Data for N^1-(Substituted phenyl)pyridinecarboxamidines



Compd. No.	R	mp (°C)	Appearance (Recryst. solvent)	Yield (%) Method A	Yield (%) Method B	Formula	Analysis (%) Calcd (Found) C	H	N
IIIa	H	bp 136[4] (3 Torr)	Light yellow liquid	87		$C_{12}H_{11}N_3$	73.07 (72.84)	5.62 (5.88)	21.30 (21.57)
IIIb	H	131—132.5	Colorless plates (Acetone–*n*-hexane)	60		$C_{12}H_{11}N_3$	73.07 (72.98)	5.62 (5.78)	21.30 (21.60)
IIIc	H	147—149	Colorless needles (Acetone–*n*-hexane)	75		$C_{12}H_{11}N_3$	73.07 (73.25)	5.62 (5.40)	21.30 (21.31)
IVa	2-CH_3	68—69[4]	Colorless needles (*n*-Hexane)	70		$C_{13}H_{13}N_3$	73.91 (73.80)	6.20 (6.39)	19.89 (19.92)
IVb	2-CH_3	122—124	Colorless plates (Acetone–*n*-hexane)	50		$C_{13}H_{13}N_3$	73.91 (73.96)	6.20 (6.40)	19.89 (19.81)

TABLE I. (continued)

Compd. No.	R	mp (°C)	Appearance (Recryst. solvent)	Yield (%) Method A	Yield (%) Method B	Formula	Analysis (%) Calcd (Found) C	H	N
IVc	2-CH_3	175—176	Colorless needles (Acetone–*n*-hexane)	64		$C_{13}H_{13}N_3$	73.91 (73.88)	6.20 (6.50)	19.89 (19.72)
Va	3-CH_3	54—55[4)]	Colorless prisms (*n*-Hexane)	61		$C_{13}H_{13}N_3$	73.91 (74.10)	6.20 (6.15)	19.89 (19.95)
Vb	3-CH_3	137—138.5	Colorless plates (Benzene)	52		$C_{13}H_{13}N_3$	73.91 (74.06)	6.20 (6.23)	19.89 (19.77)
Vc	3-CH_3	122—123	Light yellow prisms (Benzene)	50		$C_{13}H_{13}N_3$	73.91 (73.69)	6.20 (6.17)	19.89 (19.99)
VIa	4-CH_3	52—53[4)]	Colorless needles (*n*-Hexane)	72		$C_{13}H_{13}N_3$	73.91 (73.88)	6.20 (6.21)	19.89 (19.67)
VIb	4-CH_3	154—155	Colorless plates (Acetone–*n*-hexane)	70		$C_{13}H_{13}N_3$	73.91 (73.78)	6.20 (6.39)	19.89 (19.88)
VIc	4-CH_3	108—109.5	Colorless needles (Acetone–*n*-hexane)	75		$C_{13}H_{13}N_3$	73.91 (74.03)	6.20 (6.42)	19.89 (20.11)
VIIa	2-Cl	63—64[4)]	Colorless needles (*n*-Hexane)	67		$C_{12}H_{10}ClN_3$	62.21 (62.51)	4.35 (4.14)	18.14 (18.42)
VIIb	2-Cl	86—88	Colorless needles (Acetone–*n*-hexane)	40		$C_{12}H_{10}ClN_3$	62.21 (62.37)	4.35 (4.48)	18.14 (17.93)
VIIc	2-Cl	115—117	Colorless prisms (Acetone–*n*-hexane)	58		$C_{12}H_{10}ClN_3$	62.21 (62.43)	4.35 (4.24)	18.14 (18.38)
VIIIa	3-Cl	86—87[4)]	Colorless needles (Acetone–*n*-hexane)	57		$C_{12}H_{10}ClN_3$	62.21 (62.50)	4.35 (4.34)	18.14 (18.42)
VIIIb	3-Cl	187—188	Colorless plates (Acetone–*n*-hexane)	46		$C_{12}H_{10}ClN_3$	62.21 (61.98)	4.35 (4.29)	18.14 (18.18)
VIIIc	3-Cl	141—142	Light yellow prisms (Benzene)	35		$C_{12}H_{10}ClN_3$	62.21 (62.49)	4.35 (4.33)	18.14 (17.88)
IXa	4-Cl	80—82[4)]	Colorless prisms (Acetone–*n*-hexane)	84		$C_{12}H_{10}ClN_3$	62.21 (62.41)	4.35 (4.49)	18.14 (17.92)
IXb	4-Cl	186—188	Colorless prisms (Acetone–*n*-hexane)	46		$C_{12}H_{10}ClN_3$	62.21 (62.38)	4.35 (4.21)	18.14 (17.97)
IXc	4-Cl	113—114	Colorless needles (Acetone–*n*-hexane)	66		$C_{12}H_{10}ClN_3$	62.21 (62.29)	4.35 (4.58)	18.14 (18.42)
Xa	2-Br	68—70	Colorless needles (Acetone–*n*-hexane)	63		$C_{12}H_{10}BrN_3$	52.20 (52.41)	3.65 (3.72)	15.22 (15.51)
Xb	2-Br	105—107	Colorless needles (Acetone–*n*-hexane)	37		$C_{12}H_{10}BrN_3$	52.20 (52.38)	3.65 (3.75)	15.22 (15.47)
Xc	2-Br	146—148	Colorless prisms (Acetone–*n*-hexane)	40		$C_{12}H_{10}BrN_3$	52.20 (52.43)	3.65 (3.90)	15.22 (15.43)
XIa	3-Br	75.5—76.5	Colorless needles (Acetone–*n*-hexane)	54		$C_{12}H_{10}BrN_3$	52.20 (51.90)	3.65 (3.40)	15.22 (15.25)
XIb	3-Br	208.5—210	Colorless prisms (Benzene–MeOH)	44		$C_{12}H_{10}BrN_3$	52.20 (52.26)	3.56 (3.54)	15.22 (15.04)

TABLE I. (continued)

Compd. No.	R	mp (°C)	Appearance (Recryst. solvent)	Yield (%) Method A	Yield (%) Method B	Formula	Analysis (%) Calcd (Found) C	H	N
XIc	3-Br	163—164	Light yellow prisms (Benzene–MeOH)	41		$C_{12}H_{10}BrN_3$	52.20 (52.32)	3.56 (3.52)	15.22 (15.33)
XIIa	4-Br	85—86	Light yellow needles (Acetone–*n*-hexane)	53		$C_{12}H_{10}BrN_3$	52.20 (52.21)	3.56 (3.48)	15.22 (15.01)
XIIb	4-Br	186—188	Colorless plates (Acetone–*n*-hexane)	37		$C_{12}H_{10}BrN_3$	52.20 (52.39)	3.56 (3.87)	15.22 (15.29)
XIIc	4-Br	138—139	Colorless prisms (Acetone–*n*-hexane)	48		$C_{12}H_{10}BrN_3$	52.20 (52.47)	3.56 (3.77)	15.22 (15.48)
XIIIa		75—76	Light yellow plates (*n*-Hexane)	79		$C_{12}H_{10}FN_3$[a]			
XIIIb		179—180	Colorless plates (Acetone)	60		$C_{12}H_{10}FN_3$[a]			
XIIIc		99—101	Colorless needles (Acetone–*n*-hexane)	41		$C_{12}H_{10}FN_3$[a]			
XIVa	2-OCH_3	94	Colorless needles (Acetone–*n*-hexane)	—	81	$C_{13}H_{13}N_3O$	68.70 (68.93)	5.77 (5.84)	18.49 (18.73)
XIVb	2-OCH_3	104—105	Colorless prisms (Acetone–*n*-hexane)	—	61	$C_{13}H_{13}N_3O$	68.70 (68.67)	5.77 (5.73)	18.49 (18.27)
XIVc	2-OCH_3	124—124.5	Colorless leaflets (Acetone–*n*-hexane)	—	65	$C_{13}H_{13}N_3O$	68.70 (68.89)	5.77 (5.81)	18.49 (18.26)
XVa	3-OCH_3	65—66	Colorless prisms (Ether–*n*-hexane)	63	63	$C_{13}H_{13}N_3O$	68.70 (68.48)	5.77 (5.51)	18.49 (18.37)
XVb	3-OCH_3	128—129	Colorless prisms (Acetone–*n*-hexane)	54	72	$C_{13}H_{13}N_3O$	68.70 (68.88)	5.77 (5.77)	18.49 (18.19)
XVc	3-OCH_3	147—148.5	Light yellow prisms (Acetone)	53	74	$C_{13}H_{13}N_3O$	68.70 (68.90)	5.77 (5.79)	18.49 (18.25)
XVIa	4-OCH_3	78.5—80	Colorless needles (Ether–*n*-hexane)	75	70	$C_{13}H_{13}N_3O$	68.70 (68.53)	5.77 (5.56)	18.49 (18.19)
XVIb	4-OCH_3	143—144	Colorless needles (Acetone–*n*-hexane)	32	79	$C_{13}H_{13}N_3O$	68.70 (68.61)	5.77 (5.49)	18.49 (18.20)
XVIc	4-OCH_3	148—149	Pale yellow prisms (Benzene–MeOH)	36	81	$C_{13}H_{13}N_3O$	68.70 (68.73)	5.77 (5.51)	18.49 (18.20)
XVIIa	2-OC_2H_5	63—64	Colorless needles (Ether)	—	69	$C_{14}H_{15}N_3O$	69.69 (69.93)	6.27 (6.37)	17.41 (17.44)
XVIIb	2-OC_2H_5	65—66	Colorless prisms (Ether)	—	70	$C_{14}H_{15}N_3O$	69.69 (69.85)	6.27 (6.42)	17.41 (17.58)
XVIIc	2-OC_2H_5	106—107	Pale yellow prisms (Acetone–*n*-hexane)	—	78	$C_{14}H_{15}N_3O$	69.69 (69.90)	6.27 (6.30)	17.41 (17.41)
XVIIIa	4-OC_2H_5	94—95	Pale yellow needles (Acetone–*n*-hexane)	73	67	$C_{14}H_{15}N_3O$	69.69 (69.89)	6.27 (6.16)	17.41 (17.17)
XVIIIb	4-OC_2H_5	128—130	Colorless plates (Acetone–*n*-hexane)	57	61	$C_{14}H_{15}N_3O$	69.69 (69.58)	6.27 (6.32)	17.41 (17.30)

TABLE I. (continued)

Compd. No.	R	mp (°C)	Appearance (Recryst. solvent)	Yield (%) Method A	Yield (%) Method B	Formula	Analysis (%) Calcd (Found) C	H	N
XVIIIc	4-OC_2H_5	146—148	Pale yellow prisms (Acetone)	63	84	$C_{14}H_{15}N_3O$	69.69 (69.49)	6.27 (6.35)	17.41 (17.66)
XIXa	4-OC_3H_7	62—63	Colorless prisms (Acetone–*n*-hexane)	60		$C_{15}H_{17}N_3O$	70.56 (70.46)	6.71 (6.78)	16.46 (16.59)
XIXb	4-OC_3H_7	137—137.5	Colorless plates (Acetone–*n*-hexane)	47		$C_{15}H_{17}N_3O$	70.56 (70.61)	6.71 (6.83)	16.46 (16.73)
XIXc	4-OC_3H_7	113—114	Colorless needles (Acetone–*n*-hexane)	50		$C_{15}H_{17}N_3O$	70.56 (70.31)	6.71 (6.54)	16.46 (16.71)
XXa	4-$OCH(CH_3)_2$	81—83	Colorless needles (Acetone–*n*-hexane)	30		$C_{15}H_{17}N_3O$	70.56 (70.81)	6.71 (6.54)	16.46 (16.72)
XXb	4-$OCH(CH_3)_2$	129—131	Colorless needles (Acetone–*n*-hexane)	20		$C_{15}H_{17}N_3O$	70.56 (70.30)	6.71 (6.43)	16.46 (16.56)
XXc	4-$OCH(CH_3)_2$	118—120	Colorless needles (Acetone–*n*-hexane)	27		$C_{15}H_{17}N_3O$	70.56 (70.82)	6.71 (6.91)	16.46 (16.22)
XXIa	3-CF_3	63—64	Colorless prisms (*n*-Hexane)	35		$C_{13}H_{10}F_3N_3$ [b]			
XXIb	3-CF_3	168—169.5	Colorless plates (Acetone–*n*-hexane)	3		$C_{13}H_{10}F_3N_3$ [b]			
XXIc	3-CF_3	148.5—150	Colorless needles (Acetone–*n*-hexane)	3		$C_{13}H_{10}F_3N_3$ [b]			
XXIIa	2,4-Cl	80—81	Colorless needles (*n*-Hexane)	92		$C_{12}H_9Cl_2N_3$	54.16 (54.42)	3.41 (3.39)	15.79 (15.89)
XXIIb	2,4-Cl	108—110	Colorless prisms (Acetone–*n*-hexane)	23		$C_{12}H_9Cl_2N_3$	54.16 (54.25)	3.41 (3.47)	15.79 (16.01)
XXIIc	2,4-Cl	129.5—131	Colorless prisms (Acetone–*n*-hexane)	26		$C_{12}H_9Cl_2N_3$	54.16 (54.45)	3.41 (3.30)	15.79 (15.74)
XXIIIa	2,6-Cl	99.5—101	Colorless prisms (*n*-Hexane)	60		$C_{12}H_9Cl_2N_3$	54.16 (54.06)	3.41 (3.21)	15.79 (15.79)
XXIIIb	2,6-Cl	73—74	Colorless plates (Acetone–*n*-hexane)	11		$C_{12}H_9Cl_2N_3$	54.16 (54.42)	3.41 (3.67)	15.79 (15.49)
XXIIIc	2,6-Cl	157.5—159	Colorless plates (Acetone–*n*-hexane)	19		$C_{12}H_9Cl_2N_3$	54.16 (53.95)	3.41 (3.62)	15.79 (15.81)
XXIVa	3,4-Cl	112—113	Light yellow needles (Acetone–*n*-hexane)	81		$C_{12}H_9Cl_2N_3$	54.16 (53.89)	3.41 (3.27)	15.79 (15.82)
XXIVb	3,4-Cl	200—201	Colorless plates (Benzene)	15		$C_{12}H_9Cl_2N_3$	54.16 (54.44)	3.41 (3.40)	15.79 (16.02)
XXIVc	3,4-Cl	157—158	Colorless prisms (Benzene)	24		$C_{12}H_9Cl_2N_3$	54.16 (53.90)	3.41 (3.63)	15.79 (15.59)
XXVa	2,4,6-Cl	116—117	Colorless prisms (Acetone–*n*-hexane)	57		$C_{12}H_8Cl_3N_3$	47.95 (48.01)	2.68 (2.65)	13.98 (14.03)

a) MS for $C_{12}H_{10}FN_3$: Calcd *m/e*: 215; Found: 215. *b*) MS for $C_{13}H_{10}F_3N_3$: Calcd *m/e*: 265; Found: 265.

TABLE II. Antiinflammatory Activity of N^1-(Substituted phenyl)pyridincarboxamidines

Compound No.	Antiinflammatory act.[a] at 50 mg/kg *p.o.*	Inhibition (%)	Compound No.	Antiinflammatory act.[a] at 50 mg/kg *p.o.*	Inhibition (%)
Control	77.2±2.3		XIIIc	97.7±6.7	Inact.
IIIa	74.3±5.5	3.8	XIVa	75.1±6.0	2.7
IIIb	82.2±7.1	Inact.	XIVb	77.7±5.4	Inact.
IIIc	75.9±4.2	1.7	XIVc	74.1±4.3	4.0
IVa	71.2±5.2	7.8	XVa	86.6±5.5	Inact.
IVb	75.1±6.0	2.7	XVb	88.7±4.5	Inact.
IVc	74.2±3.3	3.9	XVc	85.7±4.5	Inact.
Va	75.4±4.8	2.3	XVIa	85.5±3.9	Inact.
Vb	76.7±3.8	Inact.	XVIb	78.0±5.1	Inact.
Vc	82.8±1.2	Inact.	XVIc	75.1±5.7	2.7
VIa	75.1±8.5	2.7	XVIIIa	74.0±8.2	4.1
VIb	78.7±4.5	Inact.	XVIIIb	82.8±4.4	Inact.
VIc	70.9±5.2	8.2	XVIIIc	78.6±2.8	Inact.
VIIa	69.3±8.9	10.2	XIXa	79.1±2.3	Inact.
VIIb	74.1±4.3	4.0	XIXb	77.7±4.1	Inact.
VIIc	83.3±4.0	Inact.	XIXc	69.8±2.6	9.6
VIIIa	86.6±6.6	Inact.	XXa	78.7±7.3	Inact.
VIIIb	76.2±5.0	1.3	XXb	74.4±5.2	3.6
VIIIc	83.5±9.6	Inact.	XXc	70.1±2.7	9.2
IXa	50.4±5.6	34.7[b]	XXIa	74.1±4.9	4.0
IXb	70.5±4.4	8.7	XXIb	71.0±4.1	8.0
IXc	75.2±3.5	2.6	XXIc	64.2±6.4	16.8[b]
Xa	71.3±4.1	7.6	XXIIa	45.5±4.3	41.1[b]
Xb	76.4±5.3	Inact.	XXIIb	81.7±4.9	Inact.
Xc	76.0±1.7	1.6	XXIIc	75.2±3.6	2.6
XIa	77.7±5.4	Inact.	XXIIIa	71.3±4.4	7.6
XIb	75.2±4.3	2.6	XXIIIb	81.2±3.6	Inact.
XIc	80.7±4.1	Inact.	XXIIIc	79.8±2.1	Inact.
XIIa	71.3±7.4	7.6	XXIVa	75.7±4.9	1.9
XIIb	76.0±3.9	1.6	XXIVb	74.3±3.5	3.8
XIIc	71.1±4.2	7.9	XXIVc	79.4±5.9	Inact.
XIIIa	69.2±7.5	10.4	XXVa	81.6±3.3	Inact.
XIIIb	81.8±6.8	Inact.	Ibuprofen	43.9±4.6	43.1[b]

a) Values indicate the percent edema intensity (mean±standard error; $n=5$) 3 h after carrageenin injection.
b) Significant difference from control ($p<0.01$).

slightly less active as an antiinflammatory than the 2,4-dichloro compound (XXIIa).

Experimental

All melting points are uncorrected. IR spectra were recorded on a Nippon Bunko DS-701G infrared spectrophotometer and ^{1}H-NMR spectra were taken with a JNM-C-60H machine in *ca.* 4% (w/v) dimethyl sulfoxide (DMSO)-d_6 with tetramethylsilane as an internal standard. Mass spectra (MS) were taken with JEOL JMS-01SG spectrometer. The results of experiments involving the two general methods (A and B) are summarized in Table I.

Preparation of N^1-(Substituted phenyl)pyridinecarboxamidines——Method A: In general, 13.3 g (0.1 mol) of powdered anhyd. $AlCl_3$ was gradually added to a solution of 0.1 mol of a substituted aniline and 10.4 g (0.1 mol) of a cyanopyridine in 40 ml of *sym*-tetrachloroethane, and the mixture was then refluxed for 30 min. After cooling, the reaction mixture was poured into 1000 ml of 5 N NaOH aq. soln. and extracted with 300 ml of dichloromethane. The extract was dried over anhyd. Na_2SO_4 and HCl gas was then introduced into the extract in an ice bath, during which period the crystalline hydrochloride of the amidine separated. The crystalline mass was collected by suction and dissolved in a small amount of H_2O. The aqueous solution was neutralized with Na_2CO_3 to separate the crude amidine, which was recrystallized to give an analytical sample.

Method B: Powdered $Fe(NO_3)_3 \cdot 9H_2O$ (0.2 g) was added to 350 ml of liq. NH_3 with stirring and then 2.3 g (0.1 mol) of powdered sodium was added gradually over 10 min, during which period granular sodium amide separated. A suspension of 0.1 mol of an alkoxyaniline in 50 ml of Et_2O was added to the above mixture in portions and the whole was stirred for 3 h. A suspension of 10.4 g (0.1 mol) of a cyanopyridine in 100 ml of Et_2O was then added in portions over a period of 10 min, and the resulting mixture was stirred for 3 h, then quenched with 5.4 g of NH_4Cl. Excess liq. NH_3 was allowed to evaporate off, and the residue was treated with 100 ml of Et_2O then 100 ml of H_2O with shaking. The separated product was collected by suction and recrystallized to give an analytical sample. In addition, the filtrate was extracted with three 100 ml portions of Et_2O and the extract was concentrated to give a tarry residue. The residue was recrystallized to give the amidine (Table I).

Dealkylation of Alkoxyanilines with Aluminum Chloride Catalyst——As a typical run, 6.7 g (0.05 mol) of powdered anhyd. $AlCl_3$ was added to a solution of 6.2 g (0.05 mol) of *o*-anisidine in 22 ml of *sym*-tetrachloroethane and the mixture was refluxed for 30 min. The reaction mixture was poured into 500 ml of 5 N NaOH aq. soln. and extracted with CH_2Cl_2 to remove unchanged *o*-anisidine. The alkaline aqueous layer was neutralized with HCl to pH 7 and extracted with CH_2Cl_2. The extract was dried over anhyd. K_2CO_3 and concentrated *in vacuo*. The residue was triturated with a small amount of a mixture of Et_2O–petr. ether to give an analytical sample, mp 173—174 °C, which gave no depression of the mp with *o*-aminophenol (mp 174 °C). The IR, nuclear magnetic resonance (NMR) and MS were identical with those of *o*-aminophenol.

o-Phenetidine was reacted with anhyd. $AlCl_3$ in the same manner as above to afford *o*-aminophenol in 30% yield.

Assay for Antiinflammatory Activity——Measurement of activity on carrageenin-induced rat hind paw edema[7] was performed as follows. A group of 7 male rats of the Wistar strain (130—150 g) was used for each compound. A suspension (10 ml/kg) in 0.5% tragacanth gum–saline solution was administered *p.o.* to rats, then after 1 h, 1% carrageenin in physiological saline solution (0.1 ml) was injected into subplantar tissue of the right hind paw. The difference in foot-pad thickness was measured every hour, according to the method of Aonuma *et al.*[8]

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