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Acidic Properties of Benzimidazoles and Substituent Effects. IV.[1] Relationship between the Acidities of N′-(Substituted Phenyl)arylamidines and Ring Closures to Imidazole

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2-Arylbenzimidazole and 5-substituted derivatives were synthesized by condensation at *p*-substituted-*o*-phenylene nitrogens with 2- or 4-picoline in the presence of sulfur or with a carboxylic acid group in the presence of polyphosphoric acid. Imidazole cyclizations from N′-(*o*, *m* or *p*-substituted-phenyl)arylamidines were also investigated, using sodium hypochlorite to react with N-arylamidines at pH 3 to afford the corresponding imino chlorides in higher yields. The chlorides were heated with an excess of sodium carbonate *in situ* for cyclization to an imidazole. Their cyclizing efficiencies to benzimidazoles decreased in correlation with the order of pK_a values due to the dissociation of the amidino site in alkaline aqueous buffers.

The acidities of 7-substituted-2-arylbenzimidazoles formed by ring closure at the position *ortho* to the substituent on the aniline ring in N′-(*m*-substituted-phenyl)arylamidines and those of compounds formed by the ring closure of N′-(*o*-substituted-phenyl)-arylamidines fitted the Taft equation for which steric hindrances are negligible ($\log K/K_{CH_3}=\rho^*\sigma^*$). On the other hand, the acidities of 5-substituted-2-arylbenzimidazoles formed by ring closure at the position *para* to the substituent on the aniline ring in N′-(*m*-substituted-phenyl)arylamidines, by ring closure of N′-(*p*-substituted-phenyl)arylamidines and by ring closure of *p*-substituted-*o*-phenylene diamines with a carboxylic acid group fitted the Hammett equation using σ_{para} ($\rho=1.3$).

Keywords——benzimidazole cyclizations from *p*-substituted-*o*-phenylene diamines with a carboxylic acid group in the presence of polyphosphoric acid; benzimidazole cyclizations from N′-(*o*, *m*, or *p*-substituted phenyl)arylamidines; measurement of acid dissocn. constants of N′-(substituted phenyl)arylamidines; Taft equation for acidities of 7-substituted-2-arylbenzimidazoles; Hammett equation for acidities of 5-substituted-2-arylbenzimidazoles

In previous studies the preparation of a series of 2-heterocycle-benzimidazole derivatives was carried out by the condensations of *o*-phenylene nitrogens with an active methyl group in the presence of sulfur and with a carboxylic acid group under high temperature conditions, but efforts to prepare benzimidazoles having an electron-withdrawing substituent met with only limited success.[3]

In the present work, benzimidazole cyclizations from N′-(substituted-phenyl)arylamidines have been investigated by methods that take advantage of the effect of the substituent in the benzene ring.

In ring closures of N′-(*o*, *m* or *p*-substituted-phenyl)arylamidines, N′-(*m*-substituted-phenyl)arylamidines afford isomeric benzimidazoles, 7-substituted benzimidazoles (*ortho*-type) and 5-substituted benzimidazoles (*para*-type). The acidity of N-arylamidines was observed to be related to the imidazole cyclization. The procedures were improved by the addition of polyphosphoric acid (PPA) in the condensation of *o*-phenylene nitrogens with a

1) Part III: M. Ichikawa, S. Nabeya, K. Muraoka, and T. Hisano, *Org. Prep. Proced. Int.*, **10** (5), 205 (1978).
2) Location: *Oe-hon-machi, Kumamoto 862, Japan.*
3) *a*) T. Hisano and H. Koga, *Yakugaku Zasshi*, **91**, 180 (1971); *b*) M. Ichikawa and T. Hisano, *Chem. Pharm. Bull.* (Tokyo), **25**, 358 (1977).

carboxylic acid group. The acid dissociation constants of benzimidazoles formed by these synthetic methods were also evaluated by spectrophotometry and a correlation of these acidities with substituent groups became apparent.

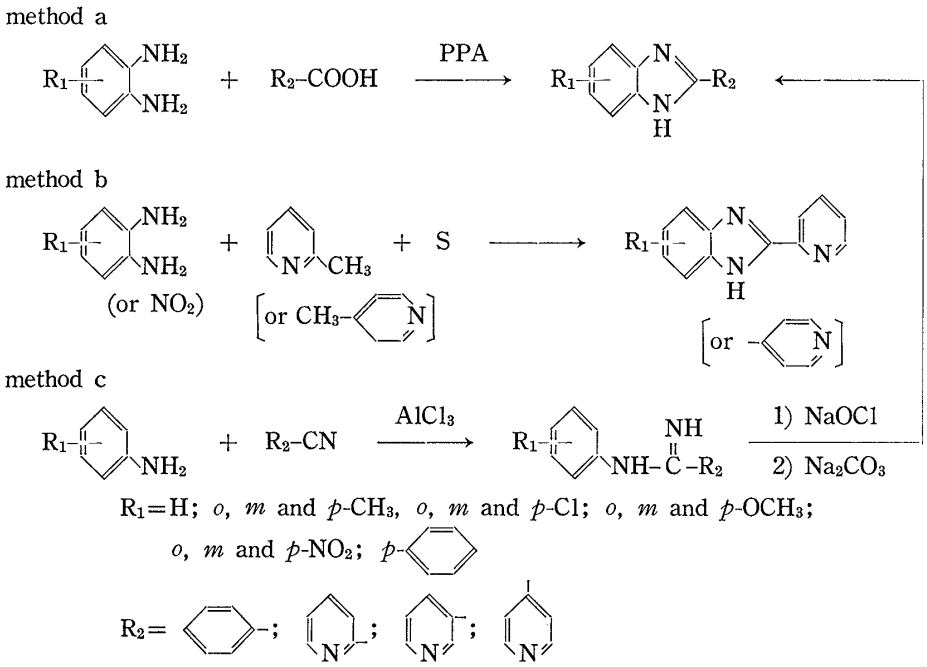


Chart 1

Experimental

Preparation of N′-(Substituted-phenyl)picolylamidines——As a typical run, 13.3 g (0.1 mol) of powdered anhyd. $AlCl_3$ was gradually added to a solution of 0.1 mole of a mono-substituted aniline and 10.4 g (0.1 mole) of 2-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_2CO_3 and HCl gas was then introduced into the extract in an ice bath, during which period a crystalline hydrochloride of the amidine separated. The crystalline mass was collected by suction and dissolved in 200 ml 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 (Table I).

Imidazole Cyclizations——The yield for each given set of conditions of method c is given in Table II. Comparisons of methods a and b are shown in Table III.

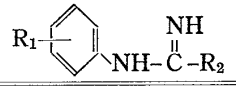
Method a: To a mixture of 0.03 mol of substituted-*o*-phenylene diamine and 4.31 g (0.035 mol) of picolinic acid, 7 g of PPA was added and then the mixture was heated at 170—180° for 3 hr. The reaction mixture was poured into ice-water and neutralized with Na_2CO_3. The precipitate was collected by suction and further treated with 5% NaOH aq. soln. to liberate H_3PO_4. The crystalline mass was collected by suction, washed with H_2O, dried and recrystallized to give an analytical sample (Table III).

Method b: The procedures described in our earlier report[3b] were used as a general method.

Method c: In general, the amidine (0.02 mol) was dissolved in 90 ml of 50% MeOH aq. soln. and adjusted with 10% HCl to pH 3.0. To the solution was added dropwise 13 ml of 10% NaOCl aq. soln. during 5 min at 10—20,° and the mixture was stirred for a further 20 min. Na_2CO_3 (4 g) was added as a saturated aqueous solution and the mixture was heated for 1 hr under reflux. When the reaction was over, the reaction solution was kept overnight below 10° to separate the benzimidazole, which was purified by recrystallization in the same manner as in methods a and b (Table IV).

The ring closure of N′-(*m*-substituted phenyl)arylamidines afforded isomeric benzimidazoles (*ortho*- and *para*-type compounds) as follows: when the above reaction was over, the reaction solution was kept overnight below 10° to separate the isomeric benzimidazoles. In general, the isolation of isomers can be carried out by fractional recrystallization, in which 7-substituted-2-arylbenzimidazoles (*ortho*-type) separated first. The filtrate was concentrated to give a crystalline mass of the crude 5-substituted materials (*para*-type). A mixture of isomeric methyl-benzimidazoles (XIVx,z and XVIIx,z) was dissolved in a small portion of benzene for chromatography on 70 g of Al_2O_3 (300 mesh), with a mixture of benzene and petr. benzine as the eluent, since their methyl-benzimidazoles proved difficult to crystallize by fractional recrystallization. From the fraction eluted first, a crude crystalline mass of the *ortho*-type compounds (XIVx, XVIIx) was obtained

TABLE I. N′-Arylamidines



Compd. No.	R_1	R_2	mp (°C) (lit.)	Appearance	Recrystn. solvent	Yield (%)	IR ν_{max}^{KBr} (cm^{-1}) N–H		C=N	NMR (in DMSO) 2H, br. s., –NH– and C=NH): τ	Formula	Analysis (%) Calcd. (Found) C	H	N
I	H	Phenyl	111—112 (111—112)[a]	Colorless needles	*n*-Hexane-$(CH_3)_2CO$	84	3460	3340	1615	3.74				
IIx	*o*-CH_3	Phenyl	105—106	Colorless needles	*n*-Hexane	84	3445	3286	1631	4.00	$C_{14}H_{14}N_2$	79.96 (79.79	6.71 6.90	13.33 13.42)
IIy	*m*-CH_3	Phenyl	107	Colorless needles	*n*-Hexane	87	3440	3285	1630	3.79	$C_{14}H_{14}N_2$	79.96 (79.89	6.71 6.82	13.33 13.24)
IIz	*p*-CH_3	Phenyl	98—99 (98—99)[b]	Colorless needles	*n*-Hexane	92	3450	3285	1630	3.81	$C_{14}H_{14}N_2$	79.96 (80.01	6.71 6.58	13.33 13.57)
IIIx	*o*-Cl	Phenyl	117—119	Colorless needles	*n*-Hexane-$(CH_3)_2CO$	85	3415	3240	1623	3.70	$C_{13}H_{11}ClN_2$	67.39 (67.19	4.63 4.92	12.33 12.55)
IIIy	*m*-Cl	Phenyl	115—117	Colorless needles	*n*-Hexane-$(CH_3)_2CO$	89	3440	3280	1630	3.57	$C_{13}H_{11}ClN_2$	67.39 (67.54	4.63 4.92	12.33 12.03)
IIIz	*p*-Cl	Phenyl	116—117 (117)[b]	Colorless needles	*n*-Hexane-$(CH_3)_2CO$	96	3485	3335	1610	3.63	$C_{13}H_{11}ClN_2$	67.39 (67.38	4.63 4.61	12.33 12.34)
IV	H	2-Pyridyl	bp 136 (3 mmHg)	Light yellow liquid		87	3460	3355	1637	4.20	$C_{12}H_{11}N_3$	73.07 (72.84	5.62 5.88	21.30 21.57)
Vx	*o*-CH_3	2-Pyridyl	68.5—69	Colorless needles	*n*-Hexane	89	3445	3260	1626	3.69	$C_{13}H_{13}N_3$	73.91 (73.80	6.20 6.39	19.89 19.92)
Vy	*m*-CH_3	2-Pyridyl	54—55	Colorless needles	*n*-Hexane	63	3430	3265	1622	3.55	$C_{13}H_{13}N_3$	73.91 (73.76	6.20 6.38	19.89 19.79)
Vz	*p*-CH_3	2-Pyridyl	52—53	Colorless needles	*n*-Hexane	86	3440	3275	1628	3.56	$C_{13}H_{13}N_3$	73.91 (73.88	6.20 6.21	19.89 19.67)
VIx	*o*-Cl	2-Pyridyl	64—64	Colorless prisms	*n*-Hexane	70	3480	3360	1642	3.38	$C_{12}H_{10}ClN_3$	62.21 (62.51	4.35 4.14	18.14 17.89)
VIy	*m*-Cl	2-Pyridyl	86—87	Colorless needles	*n*-Hexane	79	3480	3370	1640	3.30	$C_{12}H_{10}ClN_3$	62.21 (62.07	4.35 4.57	18.14 17.90)
VIz	*p*-Cl	2-Pyridyl	81—82	Colorless prisms	*n*-Hexane	67	3455	3360	1635	3.40	$C_{12}H_{10}ClN_3$	62.21 (62.42	4.35 4.49	18.14 17.92)
VIIy	*m*-OCH_3	2-Pyridyl	66—67	Colorless prisms	*n*-Hexane	58	3450	3335	1643	[c]	$C_{13}H_{13}N_3O$	68.70 (68.48	5.77 5.51	18.49 18.37)
VIIz	*p*-OCH_3	2-Pyridyl	80—82	Colorless needles	*n*-Hexane	77	3465	3355	1643	3.55	$C_{13}H_{13}N_3O$	68.70 (68.48	5.77 5.65	18.49 18.22)
VIIIx	*o*-NO_2	2-Pyridyl	75—76	Light yellow needles	*n*-Hexane-$(CH_3)_2CO$	47	3465	3340	1637	—[d]	$C_{12}H_{10}N_4O_2$	59.50 (59.31	4.16 4.32	23.13 22.96)
VIIIy	*m*-NO_2	2-Pyridyl	117.5—118.5	Light yellow needles	*n*-Hexane-$(CH_3)_2CO$	73	3465	3355	1643	3.08	$C_{12}H_{10}N_4O_2$	59.50 (59.70	4.16 4.34	23.13 23.23)
VIIIz	*p*-NO_2	2-Pyridyl	179—180	Light yellow prisms	*n*-Hexane-$(CH_3)_2CO$	65	3450	3345	1648	3.05	$C_{12}H_{10}N_4O_2$	59.50 (59.28	4.16 4.11	23.13 23.23)
IXz	*p*-Phenyl	2-Pyridyl	124.5—125	Light yellow plates	*n*-Hexane-$(CH_3)_2CO$	64	3480	3385	1634	3.38	$C_{18}H_{14}N_3$	79.10 (78.84	5.45 5.53	15.10 15.37)

a) S. Tanimoto and T. Ishibashi, *Yukigoseikagaku*, **28**, 1073 (1970). *b*) M. Osone, S. Tanimoto and R. Oda, *Yukigoseikagaku*, **24**, 562 (1966).
c) The two-proton signals for -NH- and C–NH are masked by a part of the armoatic proton signals at 3.16 to 3.63.
d) The solubility of VIIIx was too small to give a measurable signal. Two proton signals for the amindo site in F_3CCOOD are masked by aromatic proton signals at 1.33 to 2.33 and the remaindr is one hydrogen as a doublet of doublets at 0.96, ascribed to the α-position of the pyridine nucleus.

in each case. An exception was the ring closure of N′-(*m*-anisyl)picolylamidine (VIIy). First, 2-(2-pyridyl)-5-methoxybenzimidazole (XVIIIz) precipitated from the reaction solution (pH *ca.* 10) and then 2-(2-pyridyl)-7-methoxybenzimidazole (XVIIIx) gradually precipitated after adjusting the pH with dil. HCl to around neutrality.

Spectrophotometric Evaluation of Acid Dissociation Constants——The acid dissociation constants of N-arylamidines and benzimidazoles were evaluated spectrophotometrically using a Hitachi EPS-3T unit at 20°±1 according to the previous report.[3b] A Hitachi-Horiba F-7ss type pH meter was used for pH measurements. Stock solutions of these compounds of 1.0×10^{-2} M each were prepared by dissolving a weighed sample in 50 ml of EtOH and then diluting with an aqueous buffer so that the final concentration was in the range of 2.00 to 4.00×10^{-5} M. The amidines were dissolved in buffered solutions (pH 9.00) to ensure that all solutes were in the undissociated form, and in a buffered solution (pH 12.00) in order to ensure complete dissociation of the solutes. Other solutions were made up in buffers whose pH's were near the pKa values of the compounds. The benzimidazoles were also dissolved in the above buffers under the same conditions, using buffer of pH 7.40 for the undissociated form of the solutes and buffer of pH 11.00 for the completely dissociated form of 2-pyridyl-benzimidazoles. By measuring the absorbance of the above solutions (with the same total concentration of the solute) at the wavelength of maximum absorbance of the dissociated form, the pKa could be calculated by the use of equation (1)[3b,4]

$$pK_a = pH - \log (D_{[H^+]}-D_A)/(D_B-D_{[H^+]}) \quad (1)$$

where $D_{[H^+]}$ is the absorbance of the buffered solution at a given pH and D_A and D_B are the absorbance of the solutions of the completely undissociated and dissociated forms of the solute, respectively. In the pH range of 9 to 12, a mixture of 0.05 M $Na_2B_4O_7$ and 0.1 N NaOH was used, while for pH <9 a mixture of 0.05 M $Na_2B_4O_7$ and 0.1 N HCl was adopted.[5]

The pK_a values reported in Tables V for amidines and VI for benzimidazoles are the averages of at least four determinations. The measurements are accurate within 1%.

Results and Discussion

Synthetic Methods

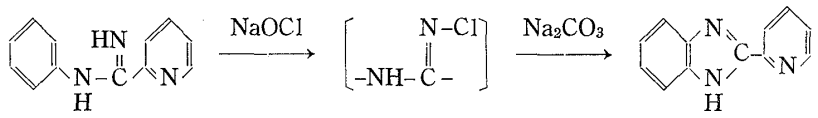
The use of PPA (method a) brought about a considerable reduction in time requirement and also shortened the purification procedure; yields of benzimidazoles showed about 20% augmentation in comparison with drastic condensations at the *o*-phenylene nitrogens at elevated temperatures.[3] However, the addition of PPA to the condensation of *p*-nitro-*o*-phenylene diamine with picolinic acid resulted in the production of resinous substances. The question of the effect of electron-withdrawing substituents in such a condensation remains open. Although method b can yield 2-(2- or 4-pyridyl)benzimidazoles from *o*-nitroaniline as well as *o*-phenylene diamine, it is unlikely to yield the corresponding benzimidazoles from *o*-nitroanilines having a substituent group.

For the preparation of amidines by method c, mono-substituted-anilines were condensed with 2-cyanopyridine in the presence of aluminum chloride. The infrared (IR) spectra of N′-(substituted-phenyl)picolylamidines exhibited two secondary amine absorptions ($\nu_{C=NH}$ and ν_{-NH-}) at about 3300 and 3400 cm^{-1} (Table I), similar to those of N-substituted trichloroacetamidines as reported by Grivas *et al.*[6]

The NMR spectra in 4% dimethylsulfoxide (DMSO) also showed a broad single hydrogen peak at τ 3.00 to 4.00 for two protons of the amidino group; this disappeared readily immediately upon the addition of D_2O. The amidines should be converted to intermediary N-chloro-compounds by sodium hypochlorite as a prerequisite for successful imidazole cyclization: the methanolic solution of amidines was adjusted to pH 3.0 and then 10% sodium hypochlorite added dropwise at 10 to 20°, during which period the tarry N-chloro-amidines were separated. This chlorination could be followed by the disappearance of the positive chlorine response

4) H.H. Jaffe and M. Orchin, "Theory and Application of Ultra Violet Spectroscopy," John Wiley and Sons, Inc., New York, 1966, p. 560; J.P. Idoux, U. S. Cantwell, J. Hinton, S.O. Nelson and P. Hollier, *J. Org. Chem.*, **39**, 3946 (1974).
5) L. Meites, "Handbook of Analytical Chemistry," McGraw-Hill, London, 1963, section 11-7.
6) J.C. Grivas and A. Taurins, *Canad. J. Chem.*, **37**, 795 (1959).

TABLE II. Reaction Conditions of Ring Closure to Imidazole by Method C



IV XI

pH	Reaction conditions[a] Temperature (°C)	Time (hr)	Product (XI)[b] Yield (%)
1—2	10—20	1	19.0
3	10—20	1	75.0
4—5	10—20	1	59.0
6	10—20	1	56.0
7—8	10—20	1	56.0

a) See method c in "Experimental". The maximum yields obtained are shown.
b) Compound XI, mp 219—220° as colorless needles (from benzene), was identical with 2-(2-pyridyl)-benzimidazole prepared by method a in all respects.

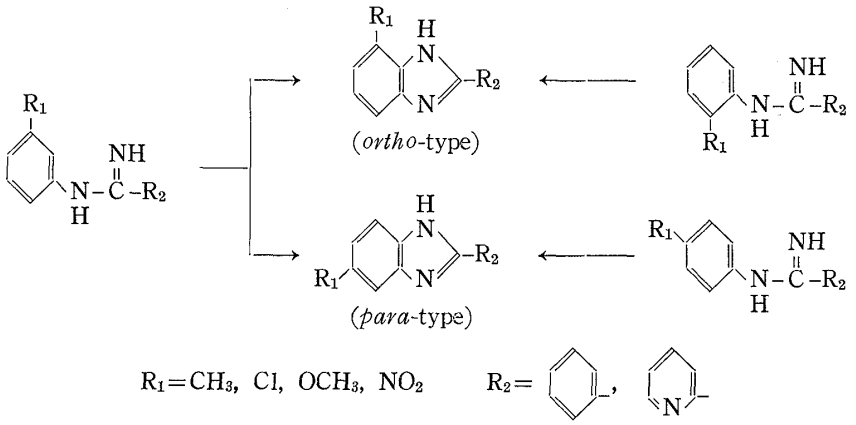
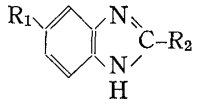


Chart 2

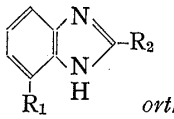
TABLE III. Yields of 5-Substituted-2-arylbenzimidazoles formed by Methods A and B

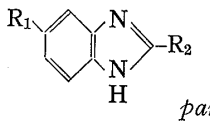


Compd. No.	R_1	R_2	mp (lit.) (°C)	Appearance (Recryst. solvent)	Synthetic method	Yield (%)
X	H	Phenyl	285 (285)[a]	Colorless prisms (benzene)	A	90
XI	H	2-Pyridyl	219—220 (219—220)[b]	Colorless needles (benzene)	A B[d]	80 75
XII	H	3-Pyridyl	249—251 (252—254)[c]	Colorless needles (EtOH)	A	91
XIII	H	4-Pyridyl	216 (216)[a]	Colorless needles (EtOH–H_2O)	A B	85 62
XVIz	*p*-CH_3	2-Pyridyl	159—160 (158—160)[b]	Colorless plates [petr. benzine-$(CH_3)_2CO$]	A B	80 62
XVIIz	*p*-Cl	2-Pyridyl	140—141 (141)[b]	Colorless needles (benzene)	A B	60 43
XVIIIz	*p*-OCH_3	2-Pyridyl	133—134 (133—134)[b]	Colorless needles [petr. benzine-$(CH_3)_2CO$]	A B	50 32

a) Ref. 8. *b*) Ref. 3*b*.
c) D.W. Hein, R.J. Alheim and J.J. Leavitt, *J. Am. Chem. Soc.*, **79**, 427 (1957).
d) gave XI in 60% yield with *o*-nitroaniline as a strating material.

TABLE IV. Yields and Analytical Data of 5-Substituted-2-arylbenzimidazoles (*para*-type) and 7-Substituted-2-arylbenzimidazoles (*ortho*-type) prepared by Method C


ortho-type


para-type

Starting material	R_1	R_2	*ortho*-type Compd. No.	*ortho*-type Yield (%)	*ortho*-type mp (°C) (lit.)	*para*-type Compd. No.	*para*-type Yield (%)	*para*-type mp (°C) (lit.)
IIx	CH_3	Phenyl	XIVx	54.0	248—250 (251—252)[a]			
IIIx	Cl	Phenyl	XVx	79.0	228 (227—228)[b]			
Vx	CH_3	2-Pyridyl	XVIx	75.0	144—144.5			
VIx	Cl	2-Pyridyl	XVIIx	75.0	132—133			
VIIIx	NO_2	2-Pyridyl	XIXx	60.0	214—215			
IIy	CH_3	Phenyl	XIVx	31.5	248—250	XIVz	52.2	243 (241—243)[c]
IIIy	Cl	Phenyl	XVx	32.0	228	XVz	66.0	209—210 (210)[c]
Vy	CH_3	2-Pyridyl	XVIx	22.0	144—144.5 (144—144.5)[e]	XVIz	60.0	159—160 (158—160)[d,e]
VIy	Cl	2-Pyridyl	XVIIx	23.0	132—133	XVIIz	64.0	140—141 (141)[d]
VIIy	OCH_3	2-Pyridyl	XVIIIx	13.0	100—102 (100—102)[e]	XVIIIz	32.0	133—134 (133—134)[d,e]
VIIIy	NO_2	2-Pyridyl	XIXx	24.5	214—215 (214—215)[e]	XIXz	38.0	211—212 (211—212)[d,e]
IIz	CH_3	Phenyl				XIVz	92.0	243
IIIz	Cl	Phenyl				XVz	94.0	209—210
Vz	CH_3	2-Pyridyl				XVIz	84.0	159—160
VIz	Cl	2-Pyridyl				XVIIz	95.0	140—141
VIIz	OCH_3	2-Pyridyl				XVIIIz	—	
VIIIz	NO_2	2-Pyridyl				XIXz	18.0	211—212
IXz	Phenyl	2-Pyridyl				XXz	43.0	164—165

Compd. No.	Appearance (Recrystn. solvent)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XIVx	Colorless needles (benzene)	$C_{14}H_{12}N_2$	79.96	6.71	13.33	79.90	6.82	13.36
XVx	Colorless prisms [*n*-hexane–$(CH_3)_2CO$]	$C_{13}H_9ClN_2$	68.28	3.97	12.27	68.41	4.06	12.14
XVIx	Colorless needles [*n*-hexane–$(CH_3)_2CO$]	$C_{13}H_{11}N_3$	74.62	5.31	20.08	74.36	5.44	20.20
XVIIx	Colorless prisms (benzene)	$C_{12}H_8ClN_2$	62.76	3.51	18.30	62.66	3.57	18.21
XVIIIx	Colorless needles [*n*-hexane–$(CH_3)_2CO$]	$C_{13}H_{11}N_3O$	69.32	4.92	18.66	69.08	4.87	18.75
XIXx	Light yellow needles (EtOH)	$C_{12}H_8N_4O_2$	60.00	3.37	23.32	59.78	3.47	23.07
XIVz	Colorless needles (benzene)	$C_{14}H_{12}N_2$	79.96	6.71	13.33	79.87	6.59	13.52
XVz	Colorless needles (benzene)	$C_{13}H_9ClN_2$	68.28	3.97	12.27	68.13	3.87	12.31
XVIz	Colorless needles [*n*-hexane–$(CH_3)_2CO$]	$C_{13}H_{11}N_3$	74.62	5.30	20.08	74.81	5.29	20.23
XVIIz	Colorless prisms (benzene)	$C_{12}H_8ClN_2$	62.76	3.51	18.30	62.71	3.59	18.17
XVIIIz	Colorless needles [*n*-hexane–$(CH_3)_2CO$]	$C_{13}H_{11}N_3O$	69.32	4.92	18.66	69.44	4.91	18.72
XIXz	Light yellow powder (EtOH)	$C_{12}H_8N_4O_2$	60.00	3.37	23.32	59.80	3.46	23.16
XXz	Colorless prisms	$C_{18}H_{13}N_3$	79.68	4.83	15.49	79.46	4.77	15.29

a) E. Haruki, T. Inaike and E. Imoto, *Bull. Chem. Soc.*, **4**, 1361 (1968). *b*) F. Montanari and R. Passerini, *Boll. Sci. Facolta Chim. Ind. Bologna.* **11**, 42 (1953) [*C.A.*, **48**, 643 (1954)]. *c*) M. Osone, S. Tanimoto and R. Oda, *Yukigosei-kagaku*, **24**, 562 (1966). *d*) Ref. 3*b*. *e*) Ref. 1.

with potassium iodide-starch paper. The NMR spectra of N-chloro-amidines in 4% DMSO showed a broad single hydrogen peak at τ −0.5 to −1.0 for one proton of the secondary amino site, characteristic of such N-chloroamidines, while the hydrogen peak at τ 3.00 to 4.00 for two protons disappeared. Thus, an excess of sodium carbonate was added to the reaction solution containing N-chloro-amidines, then the imidazole cyclization was accomplished by heating. The reactivity of chlorine generated from sodium hypochlorite in acidic solutions apparently has an effect on the ring closure (Table II). It would seem that the formation of N-chloro-amidines plays an important role in the initial stage of this reaction.

In our preliminary experiments, attempts were made to cyclize several N′-(*m*-substituted-phenyl)picolylamidines which would permit closure of the imidazole ring to either the 2- or the 6-position of the aniline ring. It was noted that there was a mixture of isomeric benzimidazoles in the reaction processes.[1] In this context, an alternative to this cyclization was the use of a *meta*-directing substituent group. The isomers, 5-substituted-2-arylbenzimidazoles (*para*-type) and 7-substituted-2-arylbenzimidazoles (*ortho*-type), were successfully isolated by a combination of activated alumina column chromatography and fractional crystallization and subjected to elemental analysis as shown in Table IV. One of them, that was usually separated from the mother liquor, was found to be identical with the 5-substituted-2-(2-pyridyl)-benzimidazole structure[3b] formed from *p*-substituted-*o*-phenylene diamines

Table V. Acid Dissociation Constants and Spectrophotometric Data of N′-(Substituted phenyl)picolylamidines and Benzimidazoles at 20°±1

Compound No.	λ_{max} (nm)	log ε_{max}	pK_a
IV	272	3.98	11.23
Vx	271	4.03	11.37
Vy	272	3.95	11.29
Vz	272	3.99	11.31
VIx	272	4.00	11.11
VIy	272	4.01	11.02
VIz	272	4.16	11.13
VIIy	274	3.96	11.10
VIIz	272	3.99	11.35
VIIIx	270	3.96	11.07
VIIIy	273	4.22	10.86
VIIIz	303	4.03	10.79
X	241	4.21	11.41
XI	240	4.22	10.18[a]
XII	242	4.08	11.31
XIII	243	3.88	10.28[b]
XIVx	242	4.32	12.08
XIVz	251	4.06	11.82
XVx	246	4.25	10.93
XVz	307	4.34	10.86
XVIx	308	4.34	10.36
XVIz	313	4.40	10.39[a]
XVIIx	307	4.25	10.20
XVIIz	313	4.38	9.91[a]
XVIIIx	310	4.03	10.45
XVIIIz	322	4.36	10.50[a]
XIXx	288	4.16	9.89
XIXz	303	4.07	9.05[a]
XXz	325	3.97	10.21
XXIz	313	4.45	9.53[c]

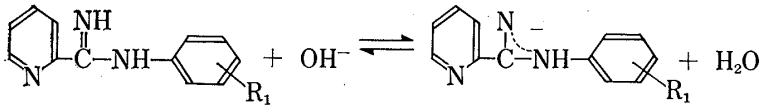
a) Ref. 3*b* (20°): XI, 10.18; XVIz, 10.39; XVIIz, 9.91; XVIIIz, 10.50; XIXz, 9.05.
b) reported,[8] 10.27 at 25°.
c) Data for 2-(2-pyridyl)-5-carboethoxybenzimidazole (XXIz) are taken from Ref. 3*b*.

and picolinic acid and from N′-(*p*-substituted-phenyl)picolylamidines on the basis of mixed melting point tests and comparisons of their spectral data (IR, NMR and UV). The other isomer was found to be a 7-substituted benzimidazole structure from the values of elemental analysis and the similarities of IR and NMR spectra, in addition to its being identical in all respects with the benzimidazoles formed from N′-(*o*-substituted-phenyl)picolylamidines. It is difficult to obtain N′-(*o*-methoxy-phenyl)picolylamidine in this reaction because *o*-anisidine was demethylated by aluminum chloride to give *o*-aminophenol. Thus, the ring closure occurred at the positions *para* and *ortho* to the substituent on the aniline ring and cyclization to the *para* position was always preferred to that to the *ortho* position. The structures of a series of 2-phenyl-benzimidazoles were assigned in a completely analogous manner.

Substituent groups appear to affect the cyclizing efficiency of the N-arylamidines, since the yields of benzimidazoles having electron-withdrawing substituents decreased. The drop in basicity of the amidine site could account for a decrease in reactivity for chlorination.

Substituent Effects on Acidities

In order to examine the influence of substituent groups of *N′*-(*o*, *m* or *p*-substituted-phenyl)picolylamidines on their acidities, we sought to measure their acid dissociation constants by spectrophotometry. The ultraviolet (UV) absorption spectra of the amidines in buffers of various pH values containing less than 1% ethanol were found to have one isobestic point, and their acid dissociation constants were measured. The pK_a, λ_{max} and log ε values of the undissociated form are listed in Table V.



(2)

$$\log K/K_H = \rho\sigma \qquad (3)$$

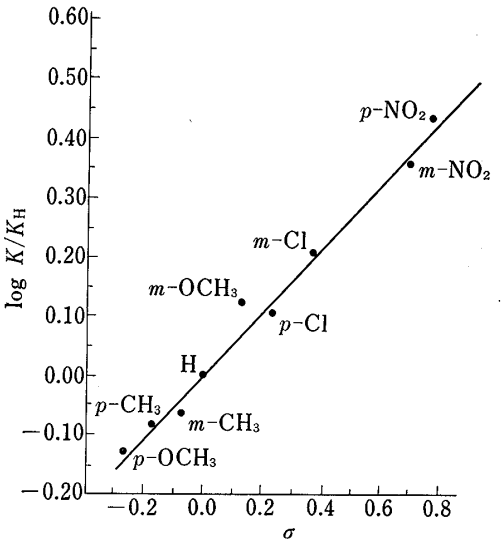


Fig. 1. Correlation of log K/K_H and σ using the Hammett Ea Equation

Figure 1 shows that the pK_a data for N′-phenyl-picolylamidines substituted at the *meta*- or *para*-position of the aniline ring fit the Hammett equation (3), where K_H is the equilibrium constant of unsubstituted N′-phenyl-picolylamidine (IV) in the reaction (2).

The slope of the linear plot is 0.7. The acidity of amidines increases with increasing electron-withdrawing power of a substituent group in the aniline ring, while their cyclizing efficiencies to benzimidazoles decrease correspondingly in the order of the acidities. The weakness of substituent effects suggests that the substituent groups are distant from the reaction center yielding the characteristic imino form whose hydrogen dissociates in solution.

With regard to the influence of substituent groups on the tautomeric equilibria of the imidazole ring, benzimidazoles prepared by methods a, b and c were spectrophotometrically evaluated in various pH buffers. UV spectra of 7-substituted-benzimidazoles (*ortho*-type) dissolved in ethanol-water exhibited characteristic absorption in the range of 240 to 260 nm, while 5-substituted ones (*para*-type) showed a discernible shoulder on the shorter wavelength side of the main absorption band.[3b] In alkaline buffers where the hydrogen ion derived from the unchanged acid (-NH-) is lost by dissociation, dissociated forms of *ortho*-type compounds absorbed light at about 250 and 320 nm with two isobestic points at about 280 and 300 nm. These phenomena appear to be rather specific for *ortho*-type benzimidazoles. Their pK_a values

were determined under the same conditions as those of amidines and are listed with the λ_{max} and log ε values of the undissociated form in Table V.

These substituent effects on acidity were analyzed by means of the Taft equation (4), where K_{CH_3} is the equilibrium constant of 2-(2-pyridyl)-7-methylbenzimidazole (XVIx).

$$\log K/K_{CH_3} = \rho^*\sigma^* \qquad (4)$$

Equation (4) has been applied successfully to equilibria or reaction series in which steric hindrances are negligible, such as the dissociation of carboxylic acids.[7] This equation could also be successfully applied in the case of our *ortho*-type compounds in which steric effects (Es) appear to be absent. The Taft (σ^*) plot for the ionizations of *ortho*-type benzimidazoles was linear and its slope (ρ^*) was found to be 0.45 (Fig. 2).

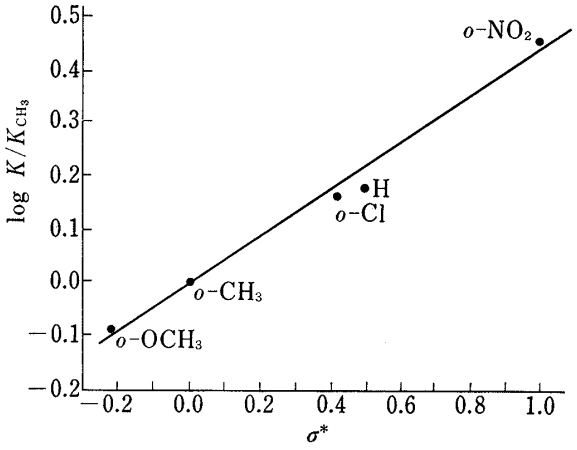


Fig. 2. Correlation of log K/K_{CH_3} and σ^* for the Acidity of 7-Substituted-2-(2-pyridyl)-benzimidazoles using the Taft Equation

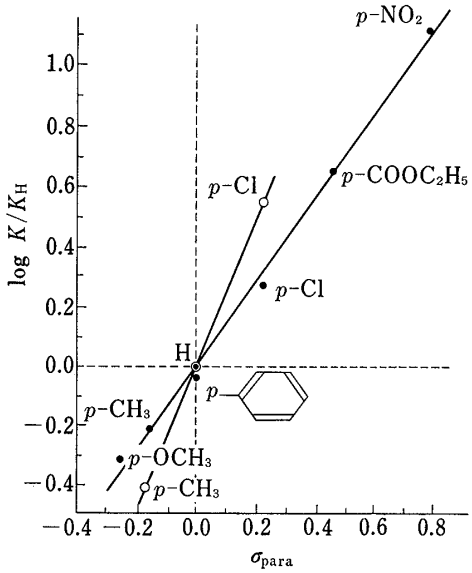


Fig. 3 A Hammett Plot for the Acidities of 5-Substituted 2-Phenyl- and 2-(2-Pyridyl)benzimidazoles

—○—, 5-substituted-2-phenylbenzimidazoles.
—●—, 5-substituted-2-(2-pyridyl)benzimidazoles.

In preliminary experiments, we have observed that the substituent groups on compounds completely analogous to the *para*-type-structure act as σ_{para} in connection with their acidities using the Hammett equation,[3b] so benzimidazoles prepared systematically from N′-(*o*, *m* or *p*-substituted-phenyl)arylamidines by method c should provide useful information for attempts to rationalize the behavior of acidity with respect to substituent groups. The *para*-type compounds prepared by methods a and c were dissolved in buffers of various pH containing less than 1% alcohol, and their pK_a values were determined under the same conditions as for those of N-arylamidines. Each pair in the same series of substituent groups appeared to be identical in all spectral data. Thus, the Hammett equation (3) could be applied successfully to correlate their acid dissociation constants. The Hammett (σ_{para}) plot for the ionization was linear, and the ρ value was 1.3, in agreement with that described in our previous report.[3b] These substituent effects tend to fluctuate rather widely in 5-substituted-2-phenylbenzimidazoles (ρ=2.2) (Fig. 3).

In a series of pyridyl groups at the second position of the imidazole ring, changes in the electron-withdrawing powers have a fairly large effect upon the acid dissociation constants.

7) E. Maccarone, A. Mamo, G. Musumarra, G. Scarlata, and G.A. Tomaselli, *J. Org. Chem.*, **42**, 3024 (1977); A. Arcoria, S. Fisichella, S. Occhipirti and G. Scarlata, *Ann. Chim.* (Rome), **64**, 95 (1974).

The effects, in increasing order (pK_a), are as follows: β-pyridyl, XII (11.31) $<\gamma$-pyridyl, XIII (10.28)[8] $<\alpha$-pyridyl, XI (10.18). The β-pyridyl group has the weakest effect, but exerts an effect rather similar to that of the phenyl group (11.41).

Among imidazole cyclizations from N′-(*o*, *m* or *p*-substituted-phenyl)arylamidines, the hydrogen atom in the imidazole ring produced should be favorably located so that their acidities might correlate with the directing effects of substituent groups: the 2-aryl-7-substituted-benzimidazole structures would occur predominantly in the ring closure of N′-(*o*-substituted-phenyl)arylamidines and the 2-aryl-5-substituted-benzimidazole structures in the ring closure of N′-(*p*-substituted-phenyl)arylamidines. In addition, both structures might be involved in the closure of the imidazole ring of N′-(*m*-substituted-phenyl)arylamidines, no matter what the potential tautomeric structure *meta* to a substituent group might be.

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8) T. Hisano and M. Ichikawa, *Chem. Pharm. Bull.* (Tokyo), **22**, 1923 (1974).

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Interaction of Chlorpromazine-Hydrochloride with Lecithin Vesicles detected by the Use of Carbon-13 Nuclear Magnetic Resonance

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The interaction of chlorpromazine-HCl with lecithin vesicles was investigated by carbon-13 nuclear magnetic resonance spectroscopy. Signal broadening of the drug induced by its addition to a vesicle–water (D_2O) solution indicated the incorporation of the drug into the vesicle membrane. In the absence of the drug, two resolved signals arising from the carbonyl carbons of the external and internal layers of the vesicle were observed with 0.3 ppm shift difference, but the difference became almost undetectable on addition of the drug. This phenomenon suggests that the incorporated chlorpromazine was located near the carbonyl carbons in the vesicle membrane. Displacement of a trivalent cation from the membrane surface by chlorpromazine-HCl was confirmed by the observation that the upfield shift of exterior choline methyl carbons initially induced by the addition of a shift reagent, Yb^{3+}, to the vesicle solution was canceled out when a sufficient amount of the drug was added to the sample solution.

Keywords——chlorpromazine-hydrochloride; lecithin vesicles; drug interaction; ^{13}C NMR study; shift reagent

Previously we investigated the interaction of a tranquilizer, chlorpromazine-HCl, with lecithin vesicles by proton magnetic resonance (^1H NMR) spectroscopy to obtain fundamental information on the drug interaction with biological membranes. We reported that chlorpromazine-HCl interacted with the polar part of the vesicle membrane surface, displacing the divalent ion Mn^{2+} and trivalent ion Eu^{3+}.[2] In this study, we have analyzed the same inter-

1) Location: *5 Nakauchicho, Misasagi, Yamashina-ku, Kyoto, 607, Japan.*

2) K. Kitamura, T. Takahashi, K. Hozumi, and T. Sato, *Chem. Pharm. Bull.* (Tokyo), **26**, 256 (1978).