single spot on TLC, but decomposed on standing. λ_{max}^{EtOH} 224, 284, 292 nm, λ_{min} 246, 290 nm. IR (CCl_4); 3470 cm^{-1} (NH). Mass Spectrum *m/e* (rel. intens); 253, 251 (33, M^+), 238, 236 (100, M−Me). NMR (CCl_4) δ 1.57 (s, 3-*t*-Bu), 6.8—7.8 (m, arom H and NH). Elution with CH_2Cl_2 gave **2a** (137 mg, 24%) which was identical with the sample obtained above.

5a (490 mg) was refluxed with EtOH (10 ml)–10% HCl (5 ml) for 3 hr. The usual work-up gave a brown oil (390 mg) which was separated by silica gel column and preparative TLC to give **3a** (129 mg), **1a** (24 mg), **4a** (27 mg) and **2a** (123 mg). These were identical with the samples obtained above (IR).

The bromination of **1b** (540 mg) under the same condition for 5 hr recovered 1b and NBS quantitatively.

Bromination of 1c with NBS in CCl_4–BPO——A mixture of **1c** (1.37 g, 6 mmol), NBS (1.07 g, 6 mmol), and BPO (5 mg) in CCl_4 (30 ml) was refluxed for 3 hr under N_2 stream. After cooling insoluble succinimide (526 mg) was removed by filtration and the filtrate was evaporated to leave an oil (1.87 g) which was separated by silica gel column. The first fraction eluted with hexane gave **7** (574 mg, 31%) which was identical with the above sample (IR and mmp). The second fraction eluted the same solvent gave **1c** (651 mg 48%). Elution with CH_2Cl_2 gave **8** (146 mg). The next fraction eluted with the same solvent gave **9** (119 mg).

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Acidic Properties of Benzimidazoles and Substituent Effects. II.[1] The Substituent Effect on the Imidazole Formation from *p*-Substituted-*o*-phenylenediamines and on the Acid Dissociation of the Benzimidazoles

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2-(2-Pyridyl)benzimidazole and 5(or 6)-substituted derivatives were synthesized by the condensation of *p*-substituted-*o*-phenylene diamines with α-picoline in the presence of sulfur or with picolinic acid. These acid dissociation constants were measured in aqueous buffers at 20° by spectrophotometry and fitted the Hammett equation with the use of σ_{para} (ρ=1.3).

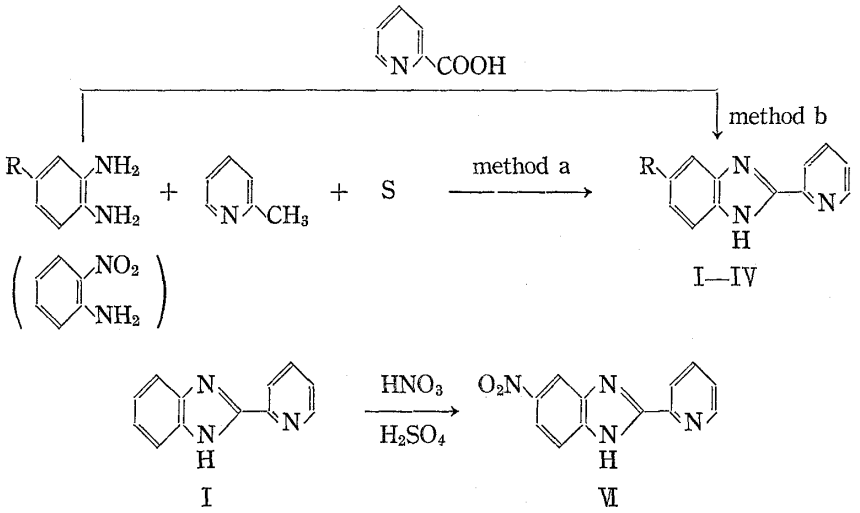
On the other hand, 2-(2-pyridyl)benzimidazole was nitrated to give its mono-nitro compound which was identical with 5(or 6)-nitro-2-(2-pyridyl)benzimidazole obtained from *p*-nitro-*o*-phenylene diamine. The correlation of the position of substituent groups with their effects for the acidity of 2-(2-pyridyl)benzimidazoles was discussed.

Keywords——benzimidazole cyclization between *p*-substituted-*o*-phenylenediamines and α-picoline in the presence of sulfur; benzimidazole cyclization between *p*-substituted-*o*-phenylenediamines and picolinic acid; nitration of 2-(2-pyridyl)benzimidazole; measurement of acid dissocn. constants of 2-(2-pyridyl)-5-substituted-benzimidazoles; correlation of substituent constants and acidities of 2-(2-pyridyl)-5-substituted-benzimidazoles

Earlier, we have reported the synthesis of 2-(2-pyridyl)benzimidazole derivatives with a substituent in 1-position,[3] and the relationship between acid dissociation constants and hydrogen bond equilibrium constants of 2-substituted-benzimidazoles has been studied in rela-

1) Part I: T. Hisano and M. Ichikawa, *Chem. Pharm. Bull.* (Tokyo), **22**, 1923 (1974).
2) Location: *Oe-honmachi, Kumamoto, 862, Japan.*
3) T. Hisano and M. Ichikawa, *Yakugaku Zasshi*, **91**, 1136 (1971).

tion to the reactivity at N-1 of the benzimidazole ring.[1] In the present work the substituent effects on the imidazole cyclization between *p*-substituted-*o*-phenylenediamines and picolinic acid and on the acid dissociations of the 2-(2-pyridyl)benzimidazoles have been examined. No previous measurements of this type exist.



R=H, CH_3, OCH_3, Cl, $COOC_2H_5$, NO_2

Chart 1

Experimental

Preparations of 5-Substituted-2-(2-pyridyl)benzimidazoles——2-(2-Pyridyl)benzimidazoles were prepared by the methods described below and Table I lists the compounds investigated, their melting points and the analytical data.

Method a: According to our earlier report,[4] a mixture of α-picoline (0.1 mole), *p*-substituted-*o*-phenylenediamine (0.1 mole), and sulfur (0.3 mole) was heated at 170° for 10 hr. After the reaction was over, the reaction mixture was concentrated *in vacuo* to be made gummy. The residue was extracted with hot ethanol. The extract was evaporated *in vacuo* and recrystallized after purification with an active charcoal.

Method b: A mixture of picolinic acid (0.1 mole) and *p*-substituted-*o*-phenylenediamine (0.1 mole) was heated at 190° for 24 hr. After the reaction was over, the reaction mixture was extracted with hot ethanol. The extract was evaporated *in vacuo* and recrystallized with an active charcoal.

Nitration of 2-(2-Pyridyl)benzimidazole——To a solution of 2-(2-pyridyl)benzimidazole (0.01 mole) in 10 ml of H_2SO_4, 2 ml of HNO_3 (d: 1.38) was added dropwise below 5° and was stirred for 1 hr. After stirring at 50° for 30 min, the reaction mixture was poured into 50 ml of an ice water and the separated crystalline mass was collected by suction. The crystals were extracted with hot benzene and the extract was evaporated *in vacuo*. The residue was recrystallized from EtOH, giving VI (mp 211—212°) as light brown powder in 51% yield. *Anal.* Calcd. for $C_{12}H_8O_2N_4$: C, 60.00; H, 3.37; N, 23.32. Found: C, 60.23; H, 3.42; N, 23.31. Mol. wt. Calcd.: 240. Found: 240 (by mass analysis), which was identical with 5-nitro-2-(2-pyridyl)benzimidazole prepared by method b in all respects.

Spectrophotometric Evaluation of Dissociation Constants——The acid dissociation constants of 2-(2-pyridyl)benzimidazoles were evaluated spectrophotometrically by using a Hitachi EPS-3T at 20°±1 according to the previous report.[1] A Hitachi-Horiba Model F-7ss type pH meter was used for pH measurements. Stock solutions of these compounds (1.0×10^{-2} M) were prepared by dissolving a weighed sample of each 2-(2-pyridyl)benzimidazoles in 50 ml of EtOH and then were diluted with an aqueous buffer so that the final solution had a concentration in the range 2.00 to 4.00×10^{-5} M. The benzimidazoles were dissolved in a buffered solution (pH 7.40) to ensure that all solutes were in the undissociated form and in a buffered solution (pH 11.00) in order to give complete dissociation of the solute. Other solutions were made in buffers whose pH's were near to the pK_a of the compound. By measuring the absorbance of the above solutions (with the same total

4) T. Hisano and H. Koga, *Yakugaku Zasshi*, **91**, 180 (1971).

concentration of the solute) at the wave-length of maximum absorbance of the dissociated form, the pK_a was calculated by the use of equation (1)[1,5,6]

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

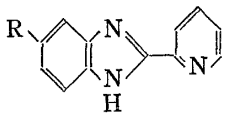
where $D_{[H^+]}$ is the absorbance of the buffered solution at a given pH and D_A and D_B are the absorbance of the solutions of the completely undissociated and dissociated forms of the solute, respectively. In the range 9 to 12, a mixture of 0.05 M $Na_2B_4O_7$ and 0.1 N NaOH was used, while for pH <9 a mixture of 0.05 M $Na_2B_4O_7$ and 0.1 N HCl was adopted.[7]

The pK_a values reported in Table II are the average of at least four determinations. The measurement is accurate within 1%.

Results and Discussion

Although method a is possible to yield 2-(2-pyridyl)benzimidazole from *o*-nitroaniline as well as *o*-phenylenediamine, it is unlikely to form the corresponding benzimidazoles from *o*-nitroanilines having a substituent group at the *para*-position and from *p*-nitro-*o*-phenylenediamine. Therefore, as indicated in Table I, the compounds investigated were prepared from *p*-substituted-*o*-phenylenediamine by method b.

Table I. Chemical Properties of 2-(2-Pyridyl)benzimidazole Derivatives



Compd. No.	R	mp (lit.) (°C)	Appearance (recryst. solvent)	Formula	Analysis (%) Calcd. (found) C	H	N	Synthetic method	Yield (%)
I	H	219—220 (219—220)[1]	colorless needles (benzene)					A[a]	80
								B	62
II	CH_3	158—160	colorless plates [pet. benzine–$(CH_3)_2CO$]	$C_{13}H_{11}N_3$	74.62 (74.81)	5.30 (5.29)	20.08 (20.23)	A	62
								B	60
III	OCH_3	133—134	colorless needles [pet. benzine–$(CH_3)_2CO$]	$C_{13}H_{11}ON_3$	69.32 (69.44)	4.92 (4.90)	18.66 (18.72)	A	32
								B	43
IV	Cl	141	colorless needles (benzene)	$C_{12}H_8N_3Cl$	62.76 (62.76)	3.51 (3.59)	18.30 (18.58)	A	43
								B	41
V	$COOC_2H_5$	175—177	colorless needles (benzene–EtOH)	$C_{15}H_{11}O_2N_3$	67.39 (67.30)	4.91 (4.88)	15.73 (15.60)	A	—
								B	65
VI	NO_2	211—212	light brown powder (EtOH)	$C_{12}H_8O_2N_4$	60.00 (59.80)	3.37 (3.40)	23.32 (23.16)	A	—
								B	38

a) gave I in 60% yield by use of *o*-nitro aniline as a starting material

Among these reactions, as noted previously,[8] the position of a substituent group in the benzimidazoles obtained is obscure. In order to make this point clearer, relationship between substituent constants and acidities of 2-(2-pyridyl)-5(or 6)-substituted-benzimidazoles has been investigated.

5) E. Pelizzetti and C. Verdi, *J. Chem. Soc.* (Perkin II), **1973**, 808; J.P. Idoux, U.S. Cantwell, J. Hinton, S.O. Nelson, and P. Hollier, *J. Org. Chem.*, **39**, 3946 (1974).
6) H.H. Jaffe and M. Orchin, "Theory and Application of Ultra Violet Spectroscopy," John Wiley & Sons, Inc., New York, 1966, p. 560.
7) L. Meites, "Handbook of Analytical Chemistry," McGraw-Hill, London, 1963, section 11-7.
8) M.W. Partridge and H.A. Turner, *J. Chem. Soc.*, **1958**, 2086; S. Tanimoto, S. Shimojo, and R. Oda, *Yuki Gosei Kagaku Shi*, **26** (2), 151 (1968); E.A. Averkin, C.C. Beard, C.A. Dvorak, J.A. Edwards, J.H. Fried, J.G. Kilian, and R.A. Schiltz, *J. Med. Chem.*, **18**, 1164 (1975).

The ultraviolet absorption (UV) spectra of 2-(2-pyridyl)benzimidazole derivatives in the buffers of various pH containing less than 1% ethanol were observed with one isosbestic point and their acid dissociation constants were measured according to the previous report.[1] The pK_a, λ_{max}, and log ε values of the undissociated form of the benzimidazoles are listed in Table II.

Table II. Dissociation Constants and Spectrophotometric Data of 2-(2-Pyridyl)benzimidazoles at 20°±1

Compound	λ_{max} (nm)	log ε_{max}	pK_v
I	307	4.39	10.18[a]
II	313	4.40	10.39
III	322	4.36	10.50
IV	313	4.38	9.91
V	313	4.45	9.53
VI	330	4.07	9.05

a) reported,[1] 10.17 at 25°

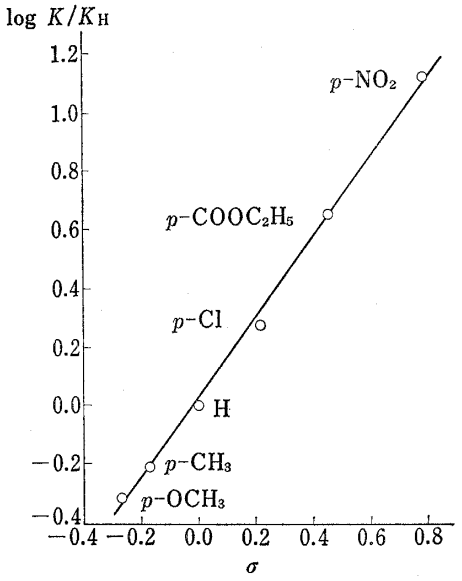


Fig. 1. Correlation of log K/K_H and σ_{para}

Figure 1 shows that the pK_a data for 2-(2-pyridyl)benzimidazoles substituted in the benzene ring can be correlated by means of the Hammett equation (2) with σ_{para} values, where K_H is the equilibrium constant of unsubstituted 2-(2-pyridyl)benzimidazole, and a ρ value of 1.3 is observed.

$$\log K/K_H = \rho\sigma \qquad (2)$$

On the other hand, the nitration of 2-(2-pyridyl)benzimidazole gave a mono-nitro compound ($C_{12}H_8O_2N_4$), which was identical with 5-nitro-2-(2-pyridyl)benzimidazole (VI) prepared from *p*-nitro-*o*-phenylenediamine by the mixed melting point test and spectral measurements (UV, IR, and NMR).

From these data, it seems reasonable to point out that a substituent group in the *para*-position of *o*-phenylenediamine would result in occupying a *para*-site for a reaction center (–NH–) on the acidic property of benzimidazoles. The nitro group substitution contributes to give such desired acidity. It would be possible to design the acidity of benzimidazoles.

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