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Synthesis of Benzoxazoles, Benzothiazoles and Benzimidazoles and Evaluation of Their Antifungal, Insecticidal and Herbicidal Activities

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Benzoxazoles, benzothiazoles and benzimidazoles having substituents on the azole and benzene nuclei were synthesized evaluated for antifungal, insecticidal and herbicidal activities. It was found that benzimidazoles tended to exhibit antifungal activity while benzothiazoles tended to show herbicidal activity. Chloro, trifluoromethyl, methoxy and ethoxy groups at the 5 position were potent substituents, and the 2-pyridyl group at the 2 position is a common structural unit. Among several active derivatives, 7-chloro-2-(2-pyridyl)benzimidazole and 2-(2-pyridyl)-5-trifluoromethylbenzothiazole exhibited significant activity against *Panonycus citri*.

Keywords—cyclization; benzoxazole; benzothiazole; benzimidazole; Willgerodt-Kindler reaction; pyridinecarbothioanilide; N^1-arylpyridinecarboxamidine; antifungal activity; insecticidal activity; herbicidal activity

Diverse synthetic methods to obtain compounds having a thiazole, oxazole or imidazole ring system have been investigated.[1-7] Numerous benzazoles have been prepared and evaluated for biological activities useful in an agricultural context, such as antifungal, insecticidal and herbicidal activities.

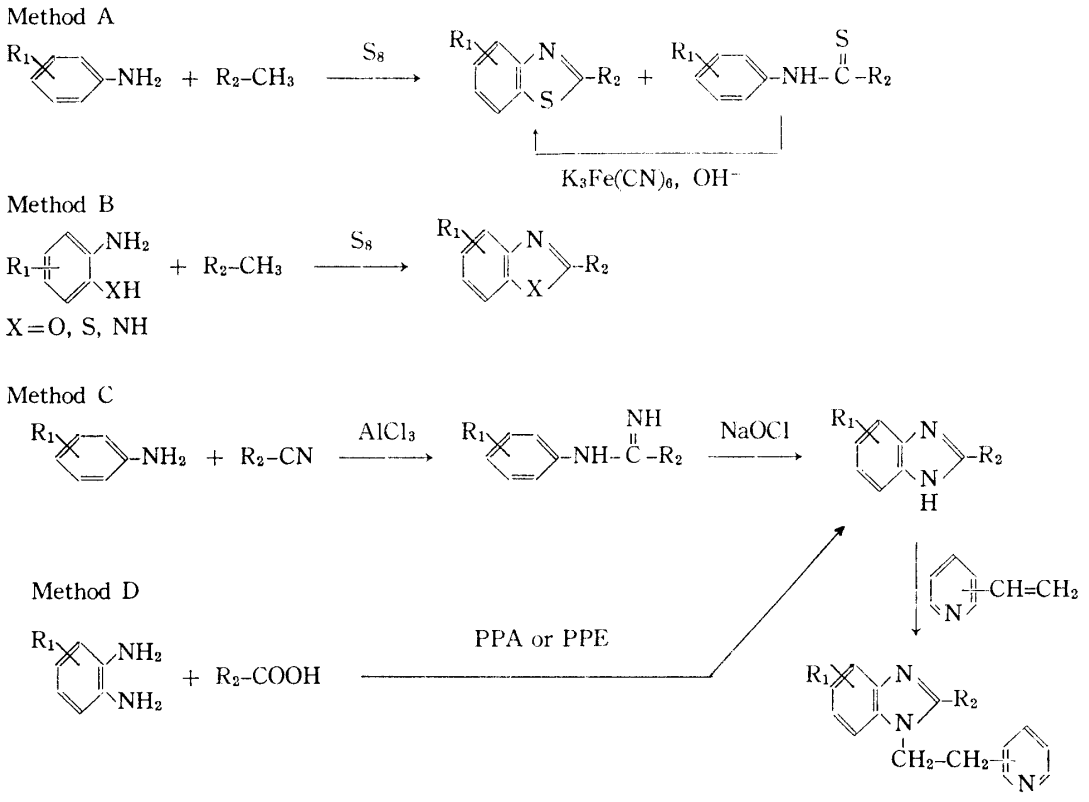
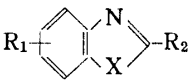
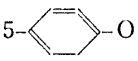
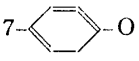


Chart 1

Table I. 

Compd. No.	R_1	R_2	X	mp (lit.) (°C)	Appearance (Recryst. solvent)	Yield (%)	Method of prepn.	Formula	Analysis (%) Calcd (Found) C	H	N
1	5-Cl	2-Pyridyl	S	171—173 (171—173)[3]	Colorless needles (EtOH)	0.2 19.2[a]	A				
2	5-F_3C	2-Pyridyl	S	161—163 (161—163)[3]	Colorless prisms (EtOH)	0.8 22.1[a]	A				
3	5-CH_3O	2-Pyridyl	S	126—127 (127)[3]	Colorless prisms (EtOH)	39.7 18.6[a]	A				
4	5-C_2H_5O	2-Pyridyl	S	120—121 (120—121)[3]	Colorless needles (EtOH)	50.0 49.0[a]	A				
5	5- 	2-Pyridyl	S	123—125 (123—125)[3]	Colorless prisms (EtOH)	13.6 17.3[a]	A				
6	7-Cl	2-Pyridyl	S	126—128 (126—128)[3]	Colorless prisms (EtOH)	56.8[a]	A				
7	7-F_3C	2-Pyridyl	S	120—122 (121—122)[3]	Colorless needles (EtOH)	42.7[a]	A				
8	7-CH_3O	2-Pyridyl	S	145—147 (145—147)[3]	Colorless prisms (EtOH)	25.8[a]	A				
9	7-C_2H_5O	2-Pyridyl	S	103—105 (104—106)[3]	Colorless prisms (EtOH)	29.1[a]	A				
10	7- 	2-Pyridyl	S	90—92 (91— 93)[3]	Colorless prisms (EtOH)	60.5[a]	A				
11	5-Cl	4-Pyridyl	S	178—179 (178—179)[4]	Colorless prisms (Benzene)	6.1 14.0[a]	A				
12	5-F_3C	4-Pyridyl	S	151—153 (153—155)[4]	Colorless needles (Benzene)	12.0 12.0[a]	A				
13	5-CH_3O	4-Pyridyl	S	131—133 (132—133)[4]	Colorless prisms (Benzene)	44.7 15.3[a]	A				
14	5-C_2H_5O	4-Pyridyl	S	127—128 (127—128)[4]	Colorless needles (Benzene)	37.8 19.9[a]	A				
15	7-Cl	4-Pyridyl	S	167—168 (167—168)[4]	Colorless prisms (Benzene)	30.0[a]	A				
16	7-F_3C	4-Pyridyl	S	187—189 (187—189)[4]	Colorless prisms (Benzene)	48.0[a]	A				
17	7-CH_3O	4-Pyridyl	S	127—129 (129—131)[4]	Colorless prisms (Benzene)	30.7[a]	A				
18	7-C_2H_5O	4-Pyridyl	S	106—108 (106—108)[4]	Colorless prisms (Benzene)	40.9[a]	A				
19	H	2-Quinolyl	S	199—201 (199—201)[1]	Colorless prisms (Benzene)	70.2	B				
20	H	2-Benzothiazolyl	S	303—305 (304—305)[1]	Colorless plates (Toluene)	32.1	B				

Compd. No.	R_1	R_2	X	mp (iit.) (°C)	Appecrance (Recryst. solvent)	Yield (%)	Method of prepn.	Formula	Analysis (%) Calcd (Found) C	H	N
21	H	2-Benzimidazolyl	S	295—296 (295—296)[1]	Yellow prisms (EtOH)	58.7	B				
22	H	2-Benzimidazolyl	O	240—242 (241-242.5)[1]	Colorless needles ($EtOH-H_2O$)	13.5	B				
23	H	2-Benzothiazolyl	O	186—187 (186—187)[1]	Colorless needles (EtOH)	18.3	B				
24	H	2-Quinolyl	O	179—180 (179—180)[1]	Colorless needles (EtOH)	67.0	B				
25	H	2-Pyridyl	O	104—106 (105—106)[1]	Colorless needles ($EtOH-H_2O$)	33.0	B				
26	H	4-Pyridyl	O	130—131 (130—131)[1]	Colorless needles ($EtOH-H_2O$)	30.1	B				
27	H	2-Quinoly	NH	194—195 (194.5-195)[6]	Colorless needles (Benzene)	65.9	B				
28	H	4-Quinolyl	NH	218—220 (219.5-220)[6]	Colorless needles ($MeOH-H_2O$)	65.0	B				
29	H	2-Pyridyl	NH	218—219 (219.5-220)[6]	Colorless needles (Benzene)	79.7	B				
30	H	4-Pyridyl	NH	242—244	Colorless needles ($EtOH-H_2O$)	95.0	D[6]	$C_{12}H_9N_3$	73.85 (73.81	4.61 4.85	21.54 21.80)
31	H	4-Pyridyl	NH	214—216 (216-216.5)[6]	Colorless needles (H_2O)	62.2	B				
32	5-CH_3	2-Pyridyl	NH	158—159 (159—160)[7]	Colorless needles (*n*-Hexane–Acetone)	60.0	C				
33	5-CH_3	3-Pyridyl	NH	230—232	Colorless needles (*n*-Hexane–Acetone)	90.0	C	$C_{13}H_{11}N_3$	74.62 (74.58	5.30 5.46	20.08 20.05)
34	5-CH_3	4-Pyridyl	NH	208—209	Colorless needles (*n*-Hexane–Acetone)	94.0	C	$C_{13}H_{11}N_3$	74.62 (74.37	5.30 5.24	20.08 20.03)
35	5-CH_3O	2-Pyridyl	NH	133—134 (133-134)[7]	Colorless needles (*n*-Hexane–Acetone)	33.0	D[b]				
36	5-CH_3O	3-Pyridyl	NH	180—182	Colorless needles (*n*-Hexane–Acetone)	9.0	D[b]	$C_{13}H_{11}N_3O$	69.32 (69.08	4.92 4.88	18.66 18.78)
37	5-CH_3O	4-Pyridyl	NH	200—201	Colorless needles (EtOH)	61.0	B	$C_{13}H_{11}N_3O$	69.32 (69.55	4.92 4.77	18.66 18.90)
38	5-C_2H_5O	2-Pyridyl	NH	125—126	Colorless needles (*n*-Hexane–Acetone)	50.0	B	$C_{14}H_{13}N_3O$	70.27 (70.38	5.45 5.21	17.56 17.81)
39	5-C_2H_5O	3-Pyridyl	NH	181—183	Colorless needles (*n*-Hexane–Acetone)	10.0	D[b]	$C_{14}H_{13}N_3O$	70.27 (70.05	5.48 5.37	17.56 17.56)

Compd. No.	R_1	R_2	X	mp (lit.) (°C)	Appearance (Recryst. solvent)	Yield (%)	Method of prepn.	Formula	Analysis (%) Calcd (Found) C	H	N
40	5-C_2H_5O	4-Pyridyl	NH	203—204	Colorless needles (Acetone)	40.0	B	$C_{14}H_{13}N_3O$	70.27 (70.27	5.48 5.55	17.56 17.59)
41	5-Cl	2-Pyridyl	NH	140—141 (140—141)[7]	Colorless prisms (Benzene)	64.0	C				
42	5-Cl	3-Pyridyl	NH	240—242	Colorless needles (EtOH–H_2O)	45.0	D	$C_{12}H_8ClN_3$	62.76 (62.56	3.51 3.73	18.30 18.45)
43	5-Cl	4-Pyridyl	NH	306—307	Colorless needles (EtOH–H_2O)	40.3	D	$C_{12}H_8ClN_3$	62.76 (62.88	3.51 3.66	18.30 18.12)
44	5-NO_2	2-Pyridyl	NH	211—212 (211—212)[7]	Light yellow powder (EtOH)	24.5	C				
45	5-C_2H_5OOC	2-Pyridyl	NH	175—177 (175—177)[7]	Colorless needles (Benzene–EtOH)	65.0	D				
46	7-CH_3	2-Pyridyl	NH	142—144 (144–144·5)[7]	Colorless needles (Benzene)	22.0	C				
47	7-CH_3	3-Pyridyl	NH	245—247	Colorless needles (*n*-Hexane–Acetone)	82.0	C	$C_{13}H_{11}N_3$	74.62 (74.61	5.30 5.21	20.08 20.10)
48	7-CH_3	4-Pyridyl	NH	178—180	Colorless needles (*n*-Hexane–Acetone)	67.0	C	$C_{13}H_{11}N_3$	74.62 (74.43	5.30 5.25	20.08 20.23)
49	7-CH_3O	2-Pyridyl	NH	100—102 (100—102)[7]	Colorless needles (*n*-Hexane–Acetone)	13.0	C				
50	7-Cl	2-Pyridyl	NH	130—132 (132—133)[7]	Colorless prisms (Benzene)	23.0	C				
51	7-Cl	3-Pyridyl	NH	240—242	Colorless needles (EtOH–H_2O)	45.2	D	$C_{12}H_8ClN_3$	62.76 (62.65	3.51 3.73	18.30 18.45)
52	7-Cl	4-Pyridyl	NH	234—236	Colorless needles (EtOH–H_2O)	93.2	C	$C_{12}H_8ClN_3$	62.76 (63.01	3.51 3.54	18.30 18.52)
53	7-NO_2	2-Pyridyl	NH	214—215 (214—215)[7]	Light yellow needles (EtOH)	38.0	C				
54	H	2-Pyridyl	*N*-[2-(2-Pyridyl) ethyl]	80—81 (80—81)[9]	Colorless needles (EtOH–H_2O)	63.3					
55	H	2-Pyridyl	*N*-[2-(4-Pyridyl) ethyl]	108—110 (110)[9]	Colorless needles (*n*-Hexane–Acetone)	65.0					
56	5-Cl	2-Pyridyl	*N*-[2-(2-Pyridyl) ethyl]	92—94 (95)[9]	Colorless needles (*n*-Hexane–Acetone)	82.0					
57	5-Cl	2-Pyridyl	*N*-[2-(4-Pyridyl) ethyl]	113—114 (114)[9]	Colorless needles (*n*-Hexane–Acetone)	65.8					

Compd. No.	R_1	R_2	X	mp (lit.) (°C)	Appearance (Recryst. solvent)	Yield (%)	Method of prepn	Formula	Analysis (%) Calcd (Found) C	H	N
58	5-NO_2	2-Pyridyl	*N*-[2-(2-Pyridyl) ethyl]	137 (137)[9]	Light yellow needles (*n*-Hexane–Acetone)	63.8					
59	5-NO_2	2-Pyridyl	*N*-[2-(4-Pyridyl) ethyl]	160—162 (163)[9]	Light yellow needles (*n*-Hexane–Acetone)	40.6					
60	7-Cl	2-Pyridyl	*N*-[2-(2-Pyridyl) ethyl]	114—116 (116)[9]	Colorless needles (*n*-Hexane)	53.0					
61	7-Cl	2-Pyridyl	*N*-[2-(4-Pyridyl) ethyl]	147—148 (148)[9]	Colorless needles (*n*-Hexane–Acetone)	44.8					
62	7-NO_2	2-Pyridyl	*N*-[2-(2-Pyridyl) ethyl]	161—162 (163)[9]	Yellow needles (*n*-Hexane–Acetone)	8.7					
63	7-NO_2	2-Pyridyl	*N*-[2-(4-Pyridyl) ethyl]	166—167 (167)[9]	Light yellow prisms (*n*-Hexane–Acetone)	1.4					

a) *N*-(*m*-substituted phenyl) thiopyridinecarboxamides were used as starting materials and were cyclized to thiazoles by $K_3Fe(CN)_6$.
b) PPE was used as the condensing agent.

Our previous papers[1-6] presented a convenient synthetic method to obtain benzothiazoles, benzoxazoles and benzimidazoles substituted with a 2-pyridyl or 4-pyridyl group at the 2 position by means of the modified Willgerodt–Kindler reaction (methods A and B), in which a mixture of picolines and anilines was heated in the presence of sulfur. However, the Willgerodt–Kindler reaction cannot be used in the synthesis of benzazoles having a chloro substituent, since dechlorination occurred during the cyclization process with chloroanilines.[3,4] In the synthesis of 2-(3-pyridyl) derivatives, 3-picoline is unreactive under the reaction conditions used. Therefore, two further synthetic methods were employed (Chart 1). Firstly, N^1-(substituted phenyl)pyridinecarboxamidines obtained from anilines and cyanopyridines were cyclized to imidazole (method C).[7] Secondly, pyridinecarboxylic acids were used as the starting material and heated with *o*-phenylenediamines in the presence of polyphosphoric acid (PPA) or polyphosphate ester (PPE) to give the corresponding benzimidazoles (method D).[7] All the compounds tested are listed in Table I.

Experimental

All melting points are uncorrected. The structures of all the compounds were supported by their infrared (IR) (Nippon Bunko DS-701G) and nuclear magnetic resonance (NMR) (JEOL JNM-C-60H) spectra. All compounds were analyzed for C, H and N and the results were within 0.3% of calculated theoretical values. Typical examples of methods A, B, C and D are given below.

Method A——1) A mixture of 0.25 mol of a substituted aniline, 0.25 mol of 2-picoline and 0.62 mol of sulfur was heated on an oil bath at 170°C for 10 h. After cooling, the reaction mixture was extracted with 500 ml of EtOH under reflux for 30 min and the extract was concentrated to yield a crystalline mass. The crystalline mass was extracted with 10% KOH aq. soln. on a water bath and the alkaline solution was neutralized with dil. HCl to separate the corresponding thioanilide. On the other hand, the benzothiazole, which remained insoluble in the alkaline solution, was collected by suction, washed with H_2O, dried and recrystallized before use for the biological tests.

2) A solution of 20 g of an *N*-(*m*-substituted phenyl)-2-pyridinecarbothioamide and 24.2 g of NaOH on 350 ml of H_2O was added dropwise to suspention of 88 g of powdered $K_3Fe(CN)_6$ in 220 ml of H_2O at 60—

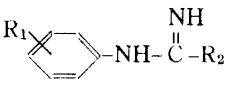
70°C during 2 h with stirring. After completion of the addition, the mixture was stirred for an additional 2 h, and 60 g of K_2CO_3 was added to the reaction mixture. The mixture was kept at 50—60°C for another hour, then cooled and extracted with ether. The ether layer was dried over anhyd. Na_2SO_4 and the ether was removed by evaporation. The residue was dissolved in benzene and chromatographed over silica gel (50 g) with benzene and a mixture of benzene and CH_2Cl_2 (2: 1) as eluents. 5-Substituted benzothiazole was obtained from the benzene eluate, and then 7-substituted benzothiazole was eluted with benzene–CH_2Cl_2 (2: 1). Each fraction was concentrated *in vacuo* and the residue was purified by recrystallization before use of the biological tests.

Method B——A mixture of 0.06 mol of *o*-phenylenediamine, 0.05 mol of 2-picoline and 0.15 mol of sulfur was heated on an oil bath at 160—170°C for 10 h, during which period considerable H_2S was generated. When the reaction was over, the reaction mixture was cooled to room temperature and extracted with 200 ml of EtOH on a water bath. The extract was concentrated *in vacuo* and the residue was purified by recrystallization to give the corresponding benzimidazole.

In order to prepare benzoxazoles, when the above reaction was over, 200 ml of $CHCl_3$ was added to the reaction mixture instead of EtOH and the extract was concentrated, then chromatographed over 50 g of Al_2O_3 (300 mesh) with $CHCl_3$ as eluent. A crude crystalline mass was obtained from the first effluent fraction, and recrystallized to give an analytical sample.

Method C——Powdered anhyd. $AlCl_3$ (13.3 g, 0.1 mol) was gradually added to a solution of 0.1 mol of a substituted aniline and 0.1 mol of 3-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 CH_2Cl_2. 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. The new amidines were recrystallized from *n*-hexane–acetone and analyzed for C, H and N (Table II).

Each amidine was dissolved in 50 ml of 50% MeOH aq. soln. and adjusted with 10% HCl to pH 3. To this solution, 10 ml of 10% NaOCl aq. soln. was added dropwise during 5 min at 10—20°C, 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 h under reflux. When the reaction was over, the reaction solution was kept overnight below 10°C to separate the corresponding benzimidazole, which was purified by recrystallization.

Table II. 

Compd. No.	R_1	R_2	mp (°C)	Appearance	Formula	Analysis (%) Calcd (Found) C	H	N	Yield (%)
64	*p*-CH_3	3-Pyridyl	154—155	Colorless plates	$C_{13}H_{13}N_3$	73.91 (73.78)	6.20 (6.39)	19.89 (19.88)	70
65	*p*-CH_3	4-Pyridyl	108—109	Colorless needles	$C_{13}H_{13}N_3$	73.91 (74.03)	6.20 (6·42)	19.89 (20.11)	75
66	*o*-CH_3	3-Pyridyl	122—124	Colorless needles	$C_{13}H_{13}N_3$	73.91 (73.96)	6.20 (6.40)	19.89 (19.81)	50
67	*o*-CH_3	4-Pyridyl	175—176	Colorless needles	$C_{13}H_{13}N_3$	73.91 (73.88)	6.20 (6.50)	19.89 (19.74)	64
68	*p*-Cl	3-Pyridyl	186—188	Colorless needles	$C_{12}H_{10}ClN_3$	62.21 (62.38)	4.35 (4.21)	18.14 (17.97)	46
69	*p*-Cl	4-Pyridyl	113—114	Colorless needles	$C_{12}H_{10}ClN_3$	62.21 (62.29)	4.35 (4.58)	18.14 (18.42)	66
70	*o*-Cl	3-Pyridyl	86—88	Colorless needles	$C_{12}H_{10}ClN_3$	62.21 (62.37)	4.35 (4.48)	18.14 (17.93)	40
71	*o*-Cl	4-Pyridyl	115—117	Colorless prisms	$C_{12}H_{10}ClN_3$	62.21 (62.43)	4.35 (4.24)	18.14 (18.38)	58

Method D——1) A mixture of 0.03 mol of *o*-phenylenediamine, 0.035 mol of picolinic acid and 7 g of PPA was heated at 170—180°C for 3 h. 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. The crystalline mass was collected by suction, washed with H_2O, dried and recrystallized to give an analytical sample.

2) A mixture of 0.05 mol of alkoxyphenylenediamine, 0.05 mol of nicotinic acid and 50 g of PPE was heated at 120°C for 1 h with stirring. The reaction mixture was poured into 500 ml of ice-water and the resulting solution was cooled. The pH was adjusted to 8 by the addition of Na_2CO_3. The precipitate was collected by suction, washed with H_2O, dried and recrystallized to give an analytical sample.

Preparation of 2-(2-Pyridyl)-1-pyridylethylbenzimidazoles——A mixture of 0.005 mol of 2-(2-pyridyl)-benzimidazole and 0.005 mol of a vinylpyridine was treated with 0.01 mol of AcOH, and the whole was heated at 140°C for 6 h. After cooling, the reaction mixture was dissolved in 5 ml of $CHCl_3$ and the solution was chromatographed over 25 g of Al_2O_3 (300 mesh) with $CHCl_3$ as an eluent. The tarry residue from the first effluent fraction was triturated with a small amount of a mixture of ether and petr. ether and solidified. The resulting solid was collected by suction and recrystallized before use for the biological tests.

Results and Discussion

Synthesis

The use of thioanilides for cycloaddition to thiazoles is of interest, because the Willgerodt–Kindler reaction can be used to generate thioamides.[1,8] In method A, when a mixture of 2- or 4-picolines and *m*-substituted anilines was heated with sulfur, both 5-substituted 2-pyridylbenzothiazoles and *N*-(*m*-substituted phenyl)-2-pyridinecarbothioamides were obtained. The latter *m*-substituted thioanilides were cyclized by potassium ferricyanide to 5- and 7- substituted 2-pyridylbenzothiazoles according to previous reports.[3,4] The cyclization to 7-substituted benzothiazole occurred preferentially in the course of this reaction.

In the ring closures of N^1-(*o*-, *m*- or *p*-substituted phenyl)pyridinecarboxamidines (method C), the reaction of 2-cyanopyridine and *m*-substituted anilines was employed to prepared N^1-(*m*-substituted phenyl)-2-pyridinecarboxamidines, and isomeric 5- and 7-substituted 2-(2-pyridyl)benzimidazoles were conveniently obtained. The other 3- and 4-pyridinecarboxamidines were obtained from the reactions of 3- or 4-picolines with *o*- or *p*-substituted anilines, respectively (Table II). Their IR spectra exhibited two secondary amine absorptions ($\nu_{C=NH}$ and ν_{-NH-}) at about 3300 and 3400 cm^{-1} and their NMR spectra in 4% dimethylsulfoxide (DMSO) also showed a broad single hydrogen peak at τ 3.00 to 4.00 due to two protons of the amidine group; this signal disappeared readily upon the addition of D_2O. These spectral assigments were based on the similarity of the signals to those of the previous N^1-(substituted phenyl)-2-pyridinecarboxamidines.[7,10,11]

Since reactions of alkoxyanilines with cyanopyridines in the presence of aluminum chloride hardly afforded the corresponding N^1-(alkoxyphenyl)pyridinecarboxamidines, the condensation of pyridinecarboxylic acids with alkoxy-*o*-phenylenediamines in the presence of PPE was

Table III. *In Vitro* Antimicrobial Activity [Incubation Time, 48 h; Minimum Inhibitory Concentration (MIC), μg/ml][a]

Compd. No.	*B. subtilis*[b]	*Ps. aeruginosa*[c]	*E. coli*[d]	*S. aureus*[e]	*Myco. ovicum*[f]
27	—	100	—	—	—
28	100	100	100	—	—
29	100	100	—	—	—
31	—	100	—	—	—
32	100	—	50	—	—
41	50	100	50	50	50
44	50	100	10	50	50

a) The bacteria were culturated at 37°C for 24 h in a peptone broth (1% Difco peptone, 0.2% yeast extract, pH 7.0). A portion of the bacterial culture was impregnated into PW-agar medium and into Sabouraud medium containing the test compounds which had previously been dissolved in dimethylformamide (DMF).
b) *Bacillus subtilis*.
c) *Pseudomonas aeruginosa*.
d) *Escherichia coli*.
e) *Staphylococcus aureus*.
f) *Mycobacterium ovicum*.

TABLE IV. Antifungal and Herbicidal Activities[a]

Compd. No.	Fungi[b]					Herbs[c]													
						Soil					Foliage					Water			
	R.B.[d]	D.M.C.[e]	G.M.C.[f]	C.C.[g]	B.D.R.[h]	Bnd.[i]	Crb.[j]	Swt.[k]	Amr.[l]	Lam.[m]	Bnd.	Crb.	Swt.	Amr.	Lam	Bnd.	Sdg.[n]	Kon.[o]	Rice.
1	×	×	×	×	×	×	×	×	×	×	×	×	×	○	△	×	⊙	○	×
2	×	×	×	×	×	×	×	×	○	×	×	×	×	⊙	⊙	⊙	⊙	⊙	×
3	×	×	×	×	×	×	×	×	×	×	×	×	×	△	×	×	○	○	△
4	×	×	×	×	×	×	×	×	×	×	×	×	×	△	○	△	△	○	×
13	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	○	○	×
14	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	⊙	⊙	×
19	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	△	×
23	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	○	×
24	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	○	△
25	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	△	○	×
26	×	×	△	×	○	×	×	×	×	×	×	×	×	×	×	△	×	×	×
29	×	⊙	○	○	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
32	○	○	×	△	×	×	×	×	×	×	×	×	×	△	○	×	×	×	×
37	⊙	△	○	○	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
41	○	⊙	⊙	○	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
44	○	×	×	△	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
46	△	×	○	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
50	⊙	×	⊙	○	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
53	△	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×

a) Assessment method: 5 to 20 plants of 10 cm height in a pot (100 cm^2) were used as a group. Preventive value at a dosage of 1000 ppm by spraying (% of disease control): ⊙, more than 80; ○, from 60 to79; △, from 40 to 59; ×, below 39.
b) Antifungal activities were observed during 7 d.
c) All compounds were examined by applications to soil, foliage and paddy field (water) during a period of 15 to 20 d. Abbreviations: ⊙, the growth of tested plants was greatly inhibited; ○, inhibited; △, the foliage of tested plants was wilted or etiolated.
d) Rice blast.
e) Downy mildew of cucumber.
f) Gray mold of cucumber.
g) Citrus canker.
h) Bakanae disease of rice.
i) Barnyardgrass.
j) Crabgrass.
k) Swartweed.
l) Green amaranth.
m) Lambsquartes.
n) Annual sedge.
o) Konag.

carried out by heating at 120°C to give the corresponding alkoxybenzimidazoles (method D). However, on the addition of PPA, the reaction mixture tended to resinify.

In order to investigate the structure-activity relationship of benzimidazoles, protection of the N–H bond of the benzimidazole nucleus was performed by reacting benzimidazoles with 2- or 4-vinylpyridines in the presence of glacial acetic acid as described in the previous report,[9] and the 1-pyridylethylbenzimidazoles were subjected to biological screening tests as follows.

Antimicrobial, Insecticidal and Herbicidal Activities

The organisms selected from the initial screening results for the estimation of antimicrobial activity and the compounds which were found to have antibacterial activity [minimum inhibitory concentration (MIC)$<$100 μg/ml] are given in Table III. Neither benzoxazoles nor benzothiazoles had antibacterial activity. Most of the benzimidazoles showed weak or limited activity against the microorganisms except for 5-nitro-2-(2-pyridyl)benzimidazoles (**44**), which had activity against *Escherichia coli*. Nitro and chloro groups at the 5 position appear to be more effective. As regards the substituent on the imidazole nucleus, the 2-pyridyl group is better than other substituents. Antifungal, insecticidal and herbicidal activities were also examined; ethanolic solutions of the test compounds were diluted with water and dosed by spraying at a concentration of 1000 ppm. The results in Table IV indicate that the imidazole nucleus may be effective for fungicidal activity and the thiazole nucleus for herbicidal acitivity. Methoxy, ethoxy, trifluoromethyl and chloro groups at the 5 position are potent substituents, and the 2-pyridyl group at the 2 position is a common structural unit. All the 1-substituted 2-(2-pyridyl)benzimidazoles are inactive. The imidazole NH proton appears to play an important role in the activity.

From these results, 2-(2-pyridyl)-5-trifluoromethylbenzothiazole (**2**), 5-chloro-2-(2-pyridyl)benzimidazole (**41**) and 7-chloro-2-(2-pyridyl)benzimidazole (**50**) were selected for further examination, *i.e.*, by testing their growth-inhibitory activity against Panonycus citri in comparison with that of 1,1-bis(*p*-chlorophenyl)-2,2,2-trichloroethanol as the reference compound for insecticidal activity. Among them, 7-chloro-2-(2-pyridyl)benzimidazole exhibited 91.5% inhibition during 21 days at a dosage of 500 ppm: the action developed slowly for two days after administration and then the apparent effectiveness was maintained throughout, being comparable to that of the reference compound (98.3% inhibition at a dosage of 200 ppm). 2-(2-Pyridyl)-5-trifluoromethylbenzimidazole gave 81.3% inhibition at 500 ppm, but the action of 5-chloro-2-(2-pyridyl)benzimidazole was unexpectedly weak (32.5% inhibition).

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