Synthesis and Biological Activity of 1*H*-Pyrrolo[2,3-*b*]pyridine Derivatives: Correlation between Inhibitory Activity against the Fungus Causing Rice Blast and Ionization Potential

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Synthesis and biological activity of a variety of 3- and 6-substituted 1*H*-pyrrolo[2,3-*b*]pyridine (7-azaindole) derivatives are described. Many of the synthesized 7-azaindoles exhibited considerable fungicidal activity toward *Pyricularia oryzae*, a fungus which causes rice blast, in vivo. When quantum parameters of the tested 7-azaindoles were evaluated by semiempirical molecular orbital calculations, a relationship was observed between the activity and the calculated ionization potentials of the 7-azaindole derivatives.

Keywords: *1H-Pyrrolo[2,3-b]pyridine; fungicidal activity; ionization potential; rice blast*

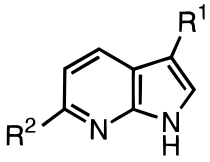
INTRODUCTION

Studies on the biological activities of 1*H*-pyrrolo[2,3-*b*]pyridine (7-azaindole) derivatives have attracted considerable interest in recent decades (Yakhontov and Prokopov, 1980), because they are aza-analogs of indoles whose skeletons are often found in alkaloids. Although the biological properties of some azaindoles in animals have been reported (Crooks et al., 1988), their activities with respect to plants have not been the subject of intensive study (Widholm, 1981). 7-Azaindole-3-acetic acid, for example, stimulates the vacuolation of protoplasm in the roots of *Allium cepa*. This effect parallels the growth-stimulating effect of the corresponding indole (Pilet, 1971). In contrast, 7-azatryptophan inhibits the growth of *Nicotiana tabacum* and *Daucus carota* cells (Widholm, 1972). These diverse biological activities of 7-azaindole derivatives prompted us to investigate 7-azaindoles as potential agrochemicals.

Structure−function relationships are of considerable interest in the fields of pharmacology and medicinal chemistry, as well as in agrochemistry. A number of physicochemical parameters, such as Hammett σ value and log *P* value, have been used for this purpose. In addition to these parameters, attempts have been made to correlate various quantum parameters with observed activities of some pharmaceuticals (Suter et al., 1995) and agrochemicals (Akagi et al., 1995).

From this point of view, we report herein the synthesis of a variety of 3- and 6-substituted 7-azaindole derivatives, which are similar in molecular size, as shown in Table 1, and a correlation of their quantum and physicochemical parameters with inhibitory activity against the fungus responsible for rice blast.

Table 1. List of Tested 7-Azaindole Derivatives



compd no.	R^1	R^2
1	H	H
2	Cl	H
3	Br	H
4	I	H
5	NO_2	H
6	NH_2	H
7	COMe	H
8	$CH{=}CH_2$	H
9	H	Cl
10	H	Br
11	H	I
12	H	NH_2
13	H	C≡CH
14	H	CN

Although 3-substituted 7-azaindoles can be easily and conveniently synthesized by electrophilic substitution reactions, procedures for direct functionalization at the 6-position of 7-azaindole are more difficult. We recently developed a method which allows the facile direct introduction of halogen atoms and cyano groups at the 6-position of 7-azaindole (Minakata et al., 1992b), and this has enabled us to prepare an extensive series of 6-functionalized analogs.

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EXPERIMENTAL PROCEDURES

Melting points were obtained using a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained on a HITACHI 270-30 infrared spectrometer. ^{1}H and ^{13}C NMR were recorded on a JEOL JMH-FX-90Q or a JEOL JMN-EX270 spectrometer with tetramethylsilane as the internal standard. Electron impact (EI) mass spectra were obtained on a Shimadzu GCMS-QP2000 or a JEOL JMS-DX303 mass spectrometer. Molecular orbital calculations were performed with the MOPAC program (PM3 method) on a CAChe Work System (SONY Tektronix). 7-Azaindole derivatives, **3** (Robison and Robison, 1956), **4** (Herbert and Wibberley, 1969), **5** and **6** (Robison et al., 1959), and **7** (Gálvez and Viladoms, 1982), were prepared using methods reported in the literature. Compounds **8**, **12**, and **13** (Minakata et al., 1992a) and **9** and **10** (Minakata et al., 1992b) were synthesized using procedures developed in Osaka University.

3-Chloro-1*H*-pyrrolo[2,3-*b*]pyridine (2). A solution of 7-azaindole (**1**) purchased from Aldrich Chemical Co., Inc. (118 mg, 1 mmol) and *N*-chlorosuccinimide (150 mg, 1.1 mmol) in CCl_4 (20 mL) and $CHCl_3$ (10 mL) was stirred for 4 h at room temperature under an atmosphere of nitrogen. After the solvent was removed, 70 mL of ether was added and the solution was washed with saturated aqueous $NaHCO_3$ (20 mL × 2), dried ($MgSO_4$), and concentrated in vacuo to give **2** (152 mg, 99%) as a colorless powder: mp 169−170 °C; IR (KBr) ν 1592, 1292, 1002, and 764 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.18 (1H, dd, J = 5.0, 8.0 Hz, H-5), 7.36 (1H, s, H-2), 8.00 (1H, d, J = 8.0 Hz, H-4), 8.38 (1H, d, J = 5.0 Hz, H-6), 11.0−11.5 (1H, brs, H-1); ^{13}C NMR ($CDCl_3$) δ 104.3, 116.2, 118.6, 122.0, 127.2, 143.4, 147.2; MS (DEI) *m*/*z* (relative intensity) 154 (M^+ + 2, 33), 152 (M^+, 100). Anal. Calcd for $C_7H_5N_2Cl$: C, 55.10; H, 3.30; N, 18.36; Cl, 23.24. Found: C, 54.89; H, 3.22; N, 18.42; Cl, 23.08.

6-Iodo-1*H*-pyrrolo[2,3-*b*]pyridine (11). 6-Iodo-1-methoxycarbonyl-7-azaindole (302 mg, 1.0 mmol) (Minakata et al., 1992b) was dissolved in MeOH (30 mL) and 1 N NaOH (10 mL). After the solution was stirred for 20 h at room temperature, the solvent was removed and the residue was extracted with $CHCl_3$ (20 mL × 3), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography on a silica gel column using hexane/EtOAc (8:2) to give **11** (232 mg, 95%) as colorless needles: mp 196−197 °C; IR (KBr) ν 1594, 1564, 1402, 1086, and 754 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.51 (1H, dd, J = 1.6, 3.3 Hz, H-3), 7.41 (1H, dd, J = 3.3, 3.4 Hz, H-2), 7.46 (1H, d, J = 8.3 Hz, H-5), 7.66 (1H, d, J = 8.3 Hz, H-4), 10.0−11.0 (1H, brs, H-1); ^{13}C NMR ($CDCl_3$) δ 100.8, 107.8, 119.7, 125.6, 126.1, 130.7, 149.0; MS (EI) *m*/*z* (relative intensity) 244 (M^+, 100), 117 (M^+ − I, 80). Anal. Calcd for $C_7H_5N_2I$: C, 34.45; H, 2.07; N, 11.48; I, 52.0. Found: C, 34.69; H, 2.13; N, 11.37; I, 51.89.

6-Cyano-1*H*-pyrrolo[2,3-*b*]pyridine (14). 1-Benzoyl-6-cyano-7-azaindole (247 mg, 1.0 mmol) (Minakata et al., 1992b) was dissolved in MeOH (30 mL) and 1 N NaOH (10 mL). After the solution was stirred for 24 h at room temperature, MeOH was removed and the residue was extracted with $CHCl_3$ (20 mL × 3), dried ($MgSO_4$), and concentrated in vacuo. The crude product was separated by chromatography on a silica gel column using hexane/EtOAc (9:1) to give **14** (109 mg, 76%) as a colorless powder: mp 175−177 °C; IR (KBr) ν 2228 (CN), 1580, 1412, 1112, and 756 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.65 (1H, dd, J =1.9, 3.6 Hz, H-3), 7.51 (1H, d, J = 8.0 Hz, H-5), 7.66 (1H, dd, J = 3.6, 3.7 Hz, H-2), 8.08 (1H, d, J = 8.0 Hz, H-4), 11.0−12.0 (1H, brs, H-1); ^{13}C NMR ($CDCl_3$) δ 101.6, 118.7, 120.1, 123.8, 124.2, 129.5, 130.2, 148.2; MS (DEI) *m*/*z* (relative intensity) 143 (M^+, 100), 116 (M^+ − HCN, 43). Anal. Calcd for $C_8H_5N_3$: C, 67.12; H, 3.52; N, 29.36. Found: C, 67.18; H, 3.47; N, 29.45.

Fungicidal Tests against Rice Blast. For these experiments, the above compounds were formulated into a 20% wettable powder and then made up in an aqueous suspension at a concentration of 250 ppm. [Formulation: 20% azaindole derivative, 4% α-(*p*-nonylphenyl)-ω-hydroxypoly(oxyethylene) (Matsumoto Yushi-Seiyaku Co. Ltd.), 8% hydrated silica (Shionogi & Co., Ltd.), and 68% bentonite.] They were then sprayed on six rice seedlings (*Oryza sativa* L. variety Aichiasahi) at the fourth-leaf stage. The rice plants were inoculated by spraying a spore suspension of *Pyricularia oryzae* containing ca. 10^5 spores/mL. The inoculated plants were kept in a humid chamber at 25 °C for one day and then transferred to a greenhouse. One week after inoculation, the number of rice blast lesions on the fourth leaves was counted and the protective value of the test compound was calculated using the following formula:

$$\text{protective value (\%)} = \frac{(1 - \text{av no. of lesions in treated plants})}{(\text{av no. of lesions in untreated plants})} \times 100$$

RESULTS AND DISCUSSION

There are no examples of the synthetic procedures for the tested 7-azaindole derivatives except for compounds **3** (Robison and Robison, 1956), **4** (Herbert and Wibberley, 1969), **5** and **6** (Robison et al., 1959), and **7** (Gálves and Viladoms, 1982). Although bromine can be used in the 3-bromination of 7-azaindole (Robison and Robison, 1956), we employed *N*-chlorosuccinimide in the 3-chlorination of 7-azaindole, a procedure which gives 3-chloro-7-azaindole **2** in excellent yield. The introduction of a vinyl group to 7-azaindole at the 3-position proceeded from the 3-formyl derivative via a two-step reaction (Minakata et al., 1992a). For other derivatives, however, we were able to achieve the facile and direct introduction of functional groups such as halogeno and cyano groups onto 6-position of 7-azaindole (Minakata et al., 1992b). In addition, 6-bromo-7-azaindole was conveniently converted into the 6-amino- or ethynyl-substituted analogs by a substitution reaction using aqueous ammonia or by a cross-coupling reaction with (trimethylsilyl)acetylene, using palladium as the catalyst, respectively.

Some of the synthesized 7-azaindoles exhibited considerable fungicidal activity in vivo toward *P. oryzae*, a fungus which causes rice blast. In order to correlate structure with activity, several physicochemical parameters of the tested 7-azaindoles were evaluated. The hydrophobic parameter π for each substituent is defined as follows:

$$\pi = \log P_X - \log P_H$$

P_H is the partition coefficient of benzene between 1-octanol and water, and P_X is that for monosubstituted benzene (Fujita et al., 1964). Dipole moments and ionization potentials were calculated using a semiempirical molecular orbital calculation with the MOPAC-PM3 method. The parameters and the protective values against rice blast are summarized in Table 2.

The following equations (eqs 1−3) and r^2 values are calculated using least squares without the compounds **1**, **9**, and **11**, which did not exhibit the activity.

$$Y = 4.06X + 37.7 \qquad r^2 = 0.019 \qquad (1)$$

$$Y = -10.3X + 61.1 \qquad r^2 = 0.384 \qquad (2)$$

$$Y = -46.3X + 443.7 \qquad r^2 = 0.629 \qquad (3)$$

Figure 1 shows the relation between the π value and the protective value of 7-azaindole derivatives, where no clear correlation is observed.

Table 2. Protective Activity against Rice Blast and Parameters of 3- and 6-Substituted 7-Azaindoles

compd no.	protective value[a] (%)	π	dipole moment[b] (debye)	ionization potential[b] (eV)
1	0	0	1.35	8.76
2	29	0.71	0.97	8.59
3	24	0.86	0.97	8.86
4	92	1.22	1.10	8.49
5	1	−0.28	5.14	9.71
6	72	−1.23	1.82	8.06
7	15	−0.55	3.14	9.01
8	47	0.82	1.05	8.43
9	0	0.71	2.29	8.58
10	26	0.86	2.67	8.98
11	0	1.22	2.21	8.78
12	45	−1.23	1.20	8.33
13	49	0.47	1.38	8.75
14	19	−0.57	5.06	9.14

[a] Methods used for estimating these data are cited in Experimental Procedures. [b] Calculated by the PM3 method.

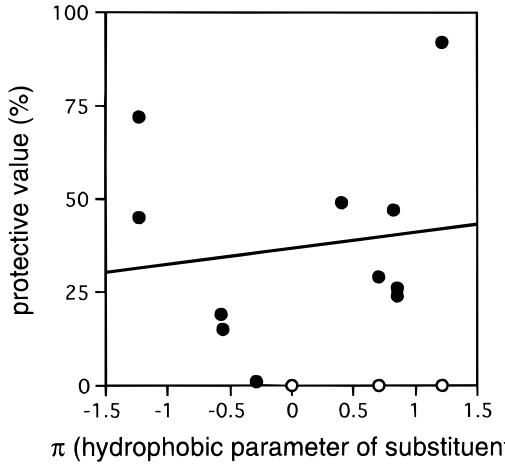

Figure 1. π value of 7-azaindole versus protective activity against rice blast.

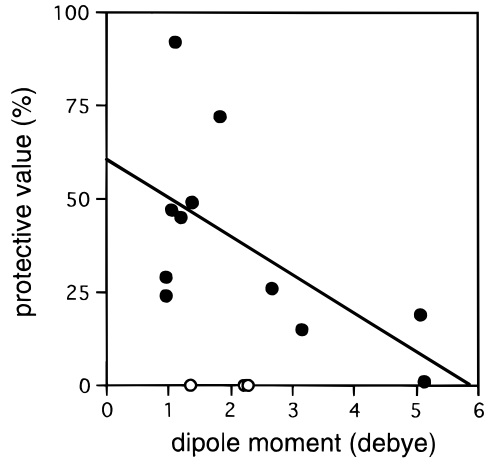

Figure 2. Dipole moment of 7-azaindole versus protective activity against rice blast.

The relation between the calculated dipole moment and activity is illustrated in Figure 2, which also shows that there is little correlation between them.

On the other hand, a more clear relationship was observed between activity and the calculated ionization potentials. These results show that higher activity is correlated with a decrease in the value of the ionization potential in the range 8−10 eV (Figure 3). Based on our experience, this type of relationship between biological activity and ionization potential has rarely been reported for agrochemicals (Nakayama et al., 1993).

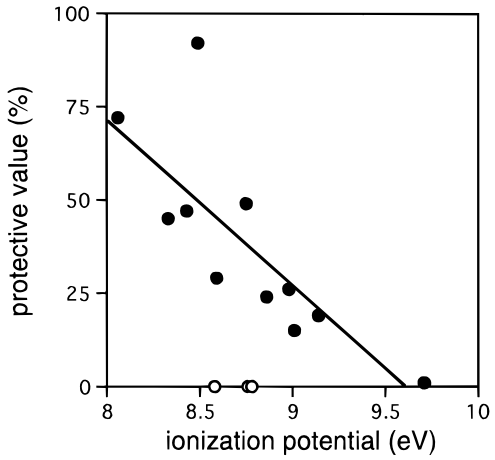

Figure 3. Ionization potential of 7-azaindole versus protective activity against rice blast.

These results suggest that 7-azaindole derivatives may be involved in one of the electron transfer processes in *P. oryzae* (rice blast fungus), although it cannot be concluded that these fungicidal compounds act in this fashion in a complex organism. The data are of interest because it provides fundamental information which may be useful for the design of agricultural fungicides for rice blast by using 7-azaindole as the basic core structure.

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