Note

Structure-Activity Relationship in Herbicidal Activity of 5-Chloro-2,3-dicyanopyrazines against Barnyardgrass (*Echinochloa crus-galli*)[†]

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In the previous papers,^{1,2)} we reported the herbicidal activity of some series of 2,3-dicyanopyrazines against barnyardgrass, we found that the substituents at the 5- and 6-positions of the pyrazine ring play an important role in determining the activity variation. In order to obtain further information on the structure-activity relationships of this class of compounds, we examined the substituent effects of the 5-chloro-6-substituted derivatives on the herbicidal activity against barnyardgrass.

Compounds 1~7 were prepared according to the method previously reported.^{1,2)} The 5-chloro-6-(isopropyl)oxy derivative (**11**) was prepared as follows; A solution of 2,3-dicyano-5,6-dichloropyrazine (**21**)³⁾ (1.99 g, 10 mmol) in isopropyl alcohol (50 ml) was refluxed for 10 hr. After evaporation, the residue was chromatographed on silica gel (50 g, 100~200 mesh), with elution with benzene-hexane (1:1) to give 1.00 g (45%) of **11**. mp 48.5~50°C (hexane). IR cm^{-1} : 2230 ($\nu_{\text{C}\equiv\text{N}}$). Anal. Found: C, 48.51; H, 3.17; N, 25.20. Calcd. for $\text{C}_9\text{H}_7\text{N}_4\text{OCl}$: C, 48.55; H, 3.17; N, 25.17%. Similarly compounds 8~10 were prepared. The 5-chloro-6-phenoxy derivative (**12**) was prepared as follows; A solution of phenol (0.47 g, 5 mmol) and sodium hydroxide (0.21 g, 5 mmol) in water (10 ml) was added to a stirred solution of **21** (1.00 g, 5 mmol) in tetrahydrofuran (50 ml). The reaction mixture was stirred at -20°C for 1 hr. After evaporation, the residue was extracted with benzene, washed with water, and chromatographed on silica gel (50 g, 100~200 mesh), with elution with benzene to give 0.65 g (50%) of **12**. mp 115~118°C (hexane). IR cm^{-1} :

2240 ($\nu_{\text{C}\equiv\text{N}}$). Anal. Found: C, 56.12; H, 1.97; N, 21.86. Calcd. for $\text{C}_{12}\text{H}_5\text{N}_4\text{OCl}$: C, 56.16; H, 1.96; N, 21.83%. Similarly compounds 13~15 were prepared.

Submerged pot tests were carried out and the herbicidal activity was expressed as the pI_{50} value (negative logarithm of I_{50} value defined as the molar extracellular concentration in mol/10a required for 50% growth-inhibition) according to the method previously reported.¹⁾ The structure-activity relationship was analyzed by means of physicochemical substituent parameters and regression analysis.⁴⁾ The substituent parameters (hydrophobic π and electronic σ_p) listed in Table I were taken from the literature.^{5,6)}

$$\text{pI}_{50} = -0.317\pi^2 + 0.828\pi - 0.896\sigma_p - 0.584 \quad (1)$$

$$(\pm 0.080) (\pm 0.182) (\pm 0.196) (\pm 0.118)$$

$$n=21, \quad s=0.104, \quad r=0.944, \quad F=46.06.$$

The structure-activity relationship in these compounds is expressed by Eq. (1). The squared correlation matrix of the variables used in Eq. (1) is shown in Table II. In Eq. (1), n is the number of compounds, s is the standard deviation, r is the correlation coefficient, F is the F -value of the correlation and the figures in parentheses are the 95% confidence intervals of the corresponding constants.

The significance of the π^2 and π terms indicates that the hydrophobicity of the molecule plays a role in the translocation process of these compounds to a target site in the plant body. The negative sign of the σ_p term means the activity decreases with increasing electron-withdrawing property of the 6-substituent. The electron-withdrawing effect may facilitate an interaction with hydrolytic enzymes which participate in a detoxication process in the plant body.

Although the activity of the 5-chloro-2,3-dicyanopyrazines varies parabolically with the change of the π value, the parabolic relationships between hydrophobicity and herbicidal activity of these compounds and the other two series of 2,3-dicyanopyrazines^{1,2)} against barnyardgrass are different from each other. This indicates that the mode of penetration of 2,3-dicyanopyrazines to a target site in the plant body varies according to the structure of the 5-substituent group or atom which may be an essential moiety for exhibiting the herbicidal activity.

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[†] Studies on Herbicidal 2,3-Dicyanopyrazines. Part III. For Part II, see ref. 2.

TABLE I. HERBICIDAL ACTIVITY OF 2,3-DICYANO-5-CHLORO-6-SUBSTITUTED PYRAZINES

No.	R	mp (°C) or n_D^{25}	π^c	σ_p^c	Activity (pI_{50}) ^d	
					Obsd.	Calcd.
1	H	89~90	0.00	0.00	-0.59	-0.58
2	Me	172~173	0.56	-0.17	-0.03	-0.07
3	Et	87~88	1.02	-0.15	0.06	0.06
4	<i>n</i> -Pr	1.5494	1.55	-0.13	-0.01	0.05
5	<i>n</i> -Bu	1.5400	2.13	-0.16	-0.13	-0.12
6	CH ₂ Ph	73~75	2.01	-0.09	-0.20	-0.12
7	Ph	139~141	1.96	-0.01	-0.10	-0.17
8	OMe	116~117	-0.02	-0.27	-0.44	-0.36
9	OEt	58~59	0.38	-0.24	-0.10	-0.10
10	O- <i>n</i> -Pr	34~42	1.05	-0.25	0.24	0.16
11	O- <i>iso</i> -Pr	48.5~50	0.85	-0.45	0.30	0.29
12	OPh	115~118	2.08	-0.03	-0.07	-0.21
13	SMe	86~90	0.61	0.00	-0.02	-0.20
14	SEt	55~58.5	1.07	0.03	0.01	-0.09
15	SPh	136~138.5 ^a	2.32	0.18	-0.60	-0.53
16	NHMe	185~186	-0.47	-0.84	-0.22	-0.29
17	NHEt	146~147	0.08	-0.61	-0.01	0.03
18	NH- <i>n</i> -Bu	114~115	1.45	-0.51	0.50	0.41
19	NMe ₂	47~48	0.18	-0.83	0.24	0.30
20	NHPh	175~176	1.38	-0.40	0.11	0.31
21	Cl	179~180 ^b	0.71	0.23	-0.53	-0.36

^a Reported mp 131~133°C.⁷⁾^b Reported mp 179~180°C.³⁾^c Taken from refs. 5 and 6.^d Negative logarithm of the I_{50} value (mol/10a) required for 50% inhibition.TABLE II. SQUARED CORRELATION MATRIX (r^2) OF VARIABLES USED IN EQ. (1)

	π^2	π	σ_p
π^2	1.000	0.846	0.169
π		1.000	0.254
σ_p			1.000

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