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Biological Activities of Benzimidazole Derivatives from Amino Acids

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The regression analysis was attempted as to biologically active compounds among the benzimidazole derivatives derived from amino acids. As a result, it seems to be necessary for the phytotoxic activity that side chains of amino acids contain nitrogen as a hetero atom and the number of carbon between a-carbon and the hetero atom is **two.**

Naturally occurring amino acids and some peptides were led to benzimidazole derivatives by incorporating their carboxyl groups into benzimidazole ring by the reaction with o-phenylenediamine (Maekawa and Ohtani, 1976, 1977).

These derivatives of amino acids and peptides had remarkable phytotoxicities. However, while benzimidazole derivatives from dipeptides showed generally only slight inhibition on the growth of plants at lower concentrations than 10 ppm, Z-Asp*-[B]# inhibited intensely the growth of radish and Glu*- [B] exhibited the remarkable activity on the root growth of rice (Table 1). Thus, the application for a lasting pesticide might be possible. That is to say, benzimidazole derivative from peptide will be decomposed in soil to give suitable amino acids*-[B], and thus, the resulting active compound may inhibit the growth of plants.

In the present paper, the regression analysis was attempted to the results of the examination carried out on the root growth of radish.

EXPERIMENTAL

Evaluation of phytotoxic effects on seedling growth

Compounds applied were synthesized by the authors. Since these preparations were not so soluble in water, they were adopted as an acetone solution. Namely, each 5 mg of the compound was dissolved in 50 ml of acetone, 10 ml of which (or further diluted solution with acetone) was poured into a Petri-dish (diameter 9 cm) placed beforehand a filter paper. After evaporating the solvent, 10 ml of water was added to the dish, followed by adding seeds.

Twenty seeds of rice or radish were used after immersing them in water

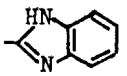
Abbreviations ; Z=Benzyloxycarbonyl; **e.g.** Ala*- = NH-CH(CH$_3$)- ; -[B]= 

Table 1. Inhibition on germianation and seeling growth of radish and rice by benzimidazole derivatives.

	Conc. (ppm)		Z-Asp-*[B]	Z-Glu-*[B]	Z-Thr-*[B]	Z-Trp-*[B]	H-Glu-*[B]
Radish	100	R	## Y	## Y	##	## Y	##
		S	## Y	##	##	##	##
	30	R	## Y	##	—	## Y	—
		S	## Y	##	—	##	—
	10	R	## Y	—	—	##	—
		S	##	—	—	##	—
	5	R	##			—	
		S	##			+	
	2	R	##			〃	
		S	##			〃	
	0.5	R	〃			—	
		S	—			—	
Rice	100	R	##	##	##	—	×
		S	—	##	##	—	+
	30	R	+	+	##	##	×
		S	+	+	##	##	##
	10	R	##	##	##	##	##
		S	+	##	##	##	##
	5	R	##	—	—	—	##
		S	+	—	+	—	+
	2	R	—	—	〃	—	—
		S	—	—	〃	—	—
	0.5	R	—	—	—	—	—
		S	—	—	—	—	—

R, Root; S, Stem; Y, Yellow.
×: Complete inhibition.
##: 60% or higher inhibition.
#: 30-60 % inhibition.
+: 30% or lower inhibition.
—: No inhibition on germination and seedling growth.
〃: Stimulation of germination.

for 1 day. These seeds were kept at 25°C for a certain time interval (4 days for radish, and 11 days for rice). The evaluation of activity was made by examining the rate of growth inhibition or stimulation on both of stem and root. The experiments with diluted solution were repeated twice.

Partition coefficients and substituent constant (β_0)

A mixture of 5 mg of the benzimidazole derivative, 10 ml of ethyl acetate, and 50ml of water was shaken in a separating funnel at room temperature

for 5 minutes, then was allowed to stand for 1 hour. After the ethyl acetate layer was concentrated *in vacuo*, the UV absorbance at 280 nm was measured to get the partition coefficient (P).

$$P = \frac{A_{280nm} \text{ of AcOEt solution}}{A_{280nm} \text{ of water solution}}$$

Substituent constant (β_0) was calculated as follows.

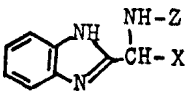
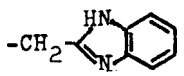
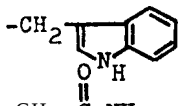
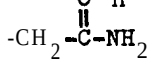
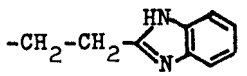
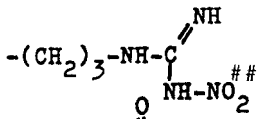
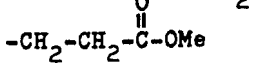
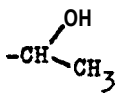
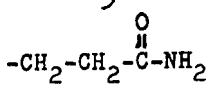
$$\beta_0 = \log P - \log P_{Gly}$$

P is a partition coefficient of Z-amino acid*-[B] and P_{Gly} is that of Z-Gly*-[B].

RESULTS

The substituent constants (β_0) obtained from ethyl acetate-water system and the concentrations (ppm) for 50 % inhibition are summarized in Table 2.

Table 2. Data for regression analysis.

 X =	Conc. (ppm) for 50% inhibition (I_{50})	β_0	β_c
	2	0.53	1.70
	a	1.10	2.75
	20	-0.82	-1.17
	30	0.55	2.20
	70	−0.38	
	75	0.50	0.68
	140	-- 0.15	—0.32
	300	—1.35	**-0.67**

refer to Z-Arg@-[B]

The relationship between log $1/I_{50}$ and β_0 is shown in Eq. (1) and Fig. l-a. In Fig. l-a, both Z-Asp*-[B] and Z-Asn*- [B] which are far distant from Eq. (1) possess two carbons between the a-carbon and the herero atom.

$$\log 1/I_{50} = 0.53\ \beta_0 - 1.54 \quad \cdots\cdots\cdots\cdots (1)$$

n	r
8	0.624

On the other hand, both of Z-Thr*-[B] and Z-Glu*(γ-OMe)- [B] have not nitrogen, but oxygen as a hetero atom. It was assumed that two as to the number of carbon was favorable for the activity and oxygen as a hetero atom was not good for it. So, +1.4 was added to β_0 in the former case and the contribution of -1 was considered in the latter case. Thus, an altered parameter was named β_0* and then Eq. (2) and Fig. l-b was obtained.

$$\log 1/I_{50} = 0.62\ \beta_0^* - 1.60 \quad \cdots\cdots\cdots (2)$$

n	r
8	0.993

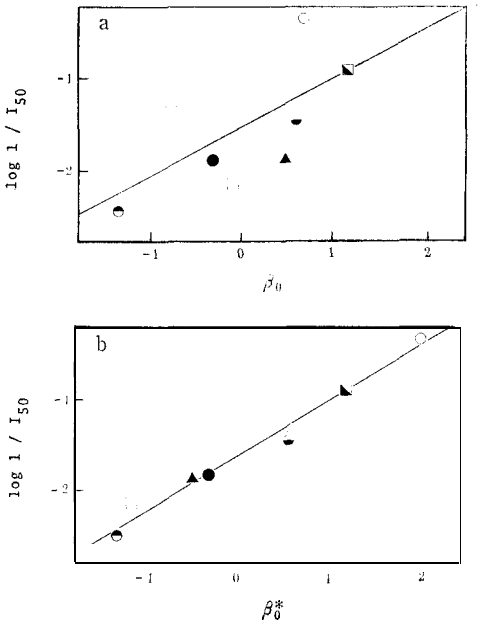


Fig. 1. The relationship between chemical structure and herbicidal activity on radish (refer to Eqs. 1 and 2).

● Z-Arg*-[B] △ Z-Asn*- [B] ○ Z-Asp"- [B]
◓ Z-Gln*- [B] ◒ Z-Glu*- [B] ▲ Z-Glu*(γ-OMe)-[B]
□ Z-Thr*- [B] ◪ Z-Trp*- [B]

Then, the relationship between the substituent constants (β_c) calculated from the data of Hansch-Fujita (Leo *et al.,* 1971) in octanol-water system and log $1/I_{50}$ was illustrated in Eq. (3) and Fig. 2-a.

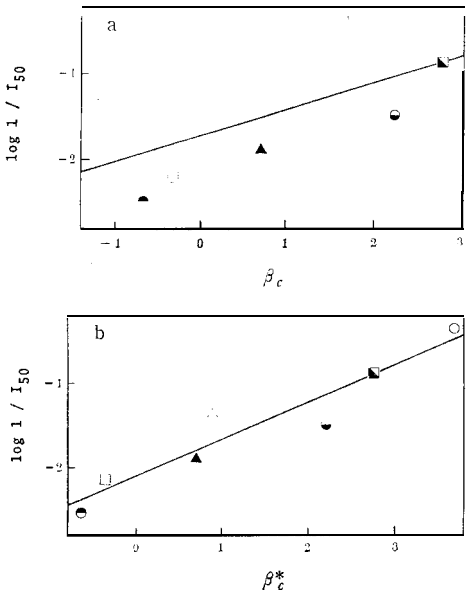


Fig. 2. The relationship between chemical structure and herbicidal activity on radish (refer to Eqs. 3 and 4).

$$\log 1/I_{,,} = 0.30\ \beta_c - 1.72 \qquad \text{.....*....} \quad (3)$$

n	r
7	0.600

In the similar manner described above, if $+2$ was added to β_c in the case that the number of carbon was two, so Eq. (4) and Fig. 2-b was given from $\log 1/I_{50}$ and β_c* (new parameter).

$$\log 1/I_{50} = 0.43\ \beta_c^* - 2.06 \qquad \text{.....} \quad (4)$$

n	r
7	0.923

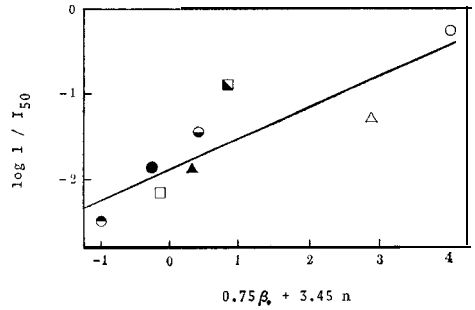
The function was determined using three kinds of parameters, $I_{,,}$, β_0, and n (Eq. (5)). Here, n was defined as $+1$ when the number of carbon was two and as 0 in the other cases.

$$\log 1/I_{50} = 0.75\ \beta_0 + 3.45\ n - 2.40 \qquad \text{..*.....} \quad (5)$$

n	r
8	0.864

The relationship between $\log 1/I_{50}$ and $0.75\ \beta_0 + 3.45\ n$ is plotted in Fig. 3. The coefficient of a parameter for the number of carbon is 3.45 and it is very high.

From the results described above, it seems to be necessary for higher activities that side chains of amino acids contain nitrogen as a hetero atom and the number of carbon between α-carbon and a hetero atom is two.



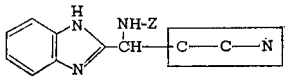


Fig. 3. The relationship between chemical structure and herbicidal activity on radish (refer to Eq. 5) and a proposed structure for higher activity.

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