Original Article

Quantitative Structure-Activity Relationships of the Herbicidal *N*-Benzyl-2-bromo-3,3-dimethylbutanamides*

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(Received January 17, 1983)

The growth inhibiting activity of 27 derivatives of *N*-benzyl-2-bromo-3,3-dimethylbutanamide having various substituents at the α -position and the benzene ring of the *N*-benzyl group against bulrush, *Scirpus juncoides*, was determined in the vial test. The structure-activity relationships were analyzed quantitatively by physicochemical substituent parameters and multiple regression analysis. The variation in the activity of *N*-(α -substituted benzyl) derivatives was shown to be related parabolically with variation in the steric dimension of the substituents. The greater the hydrophobicity of substituents is, the greater the activity is. The variation in the steric dimension of the benzene ring substituents was responsible for the activity of *N*-(1-methyl-1-substituted phenylethyl) derivatives.

INTRODUCTION

N-(1-Methyl-1-phenylethyl)-2-bromo-3,3-dimethylbutanamide (exp. code No. S-47) exhibits potent herbicidal activity.¹⁾ In our previous paper,²⁾ we examined the physicochemical roles of the substituents in the acid moiety of *N*-(1-methyl-1-phenylethyl)acylamides in the growth inhibiting activity against bulrush. We found that the hydrophobicity and steric bulkiness of the substituents are very important in determining the activity variation. In this paper, we have analyzed the relationship between the chemical structure of *N*-(α -substituted benzyl)- and *N*-(1-methyl-1-substituted phenylethyl)-2-bromo-3,3-dimethylbutanamides and the growth inhibiting activity against bulrush by the Hansch-Fujita method³⁾ in order to clarify the substituent effects in the amine moiety.

MATERIALS AND METHODS

1. Synthesis of Compounds

The structure of the compounds was confirmed by NMR and IR spectroscopy in addition to elementary analyses for C, H, N, and halogens. All melting points are uncorrected. The *N*-benzyl-2-bromo-3,3-dimethylbutanamides in Tables 1 and 3 were either the same as those in our previous paper¹⁾ or prepared by the reaction of 2-bromo-3,3-dimethylbutanoyl chloride⁴⁾ with appropriate benzylamines in the presence of a base. The benzylamines were obtained by the Hofmann reaction of corresponding carboxylic amides.^{5,6)}

2. Growth Inhibiting Activity

The I_{50} value (the molar concentration for 50% inhibition of shoot elongation) against bulrush, *Scirpus juncoides*, was determined by the vial test using the method reported previously.¹⁾ The activity was expressed as pI_{50} ($=\log 1/I_{50}$) and is listed in Tables 1 and 3.

* Herbicidal Activity of *N*-Benzylbutanamides (Part III). For Part II see Ref. 2).

RESULTS

1. Structure-activity Correlation of *N*-(α -Substituted Benzyl)-2-bromo-3,3-dimethylbutan-amides

As shown in Table 1, the activity varies considerably with variation of the substituent at the α -position of the *N*-benzyl group. In order to understand the factors governing the activity variation, the structure-activity relationship has been analyzed quantitatively by the Hansch-Fujita⁹⁾ method using physico-chemical substituent parameters and multiple regression analysis. In the preliminary analyses, we found that the steric effect of the substituent was important in determining the activity variation. However, no significant correlation was derived from the steric substituent parameters such as Hancock's corrected steric $E_s^{c,7)}$ molar refractivity MR ,⁸⁾ molecular weight MW , and van der Waals volume V_w ⁹⁾ singly or together with hydrophobic π ¹⁰⁾ and electronic $\sigma^{*11)}$ values. Finally we found that the STERIMOL parameters¹²⁾ are the best in correlating the activity variation. The STERIMOL parameters are the set

of values for each substituent developed by Verloop *et al.* representing a directional character of the steric effect. With the L^2 , L , and π values, we derived Eq. (1) for *N*-(α -substituted benzyl)-2-bromo-3,3-dimethylbutan-amides.

$$\begin{aligned} pI_{50} = & -0.981L^2 + 7.544L \\ & (0.713) \quad (5.725) \\ & + 0.816\pi - 10.421 \quad (1) \\ & (0.560) \quad (11.919) \\ n = & 10, s = 0.352, r = 0.852, \\ F_{3,6} = & 5.31 \end{aligned}$$

The L parameter in Eq. (1) expresses the length of substituents (R_1R_2C shown in Fig. 1, in Å) along the axis connecting the aromatic carbon. The π values were estimated from the observed $\log P$ ¹³⁾ values for aliphatic moiety by means of additivity principle.¹⁴⁾ In this and the following equations, n is the number of compounds included in the correlation, s is the standard deviation, r is the correlation coefficient, and F_{ν_1, ν_2} is the F ratio of the correlation where $\nu_1 = m$ and $\nu_2 = n - m - 1$; m is the number of independent variables used in the correlation. The figures in parentheses are the 95% confidence inter-

Table 1 *N*-(α -Substituted benzyl)-2-bromo-3,3-dimethylbutan-amides and their growth inhibiting activity against bulrush.

R ₁	R ₂	mp (°C)	L(CR ₁ R ₂) ^{a)}	π (CR ₁ R ₂ Ph) ^{b)}	pI_{50}	
					Obsd.	Calcd. ^{c)}
H	H	108 -110	3.00	2.22	5.25	5.23
Me	H	141 -143	4.11	2.54	5.81	6.13
Et	H	121.5-123	5.05	3.08	5.30	5.23
<i>i</i> -Pr	H	160.5-163	5.05	3.49	4.97	5.57
Me	Me	182 -183	4.11	2.86	6.47	6.40
Et	Me	159 -160	5.05	3.40	5.91	5.49
CN	Me	205 -206	3.99	0.85	4.71	4.80
Et	Et	172 -173	4.73	3.94	<3.5 ^{d)}	6.59
	-(CH ₂) ₂ -	161 -162.5	4.14	2.22	6.11	5.86
	-(CH ₂) ₃ -	196 -197.5	4.69	2.87	5.93	5.78
	-(CH ₂) ₄ -	212 -214	4.97	3.55	5.83	5.80
	-(CH ₂) ₅ -	212.5-213.5	6.17	3.99	<2.9 ^{d)}	2.11

^{a)} STERIMOL parameter, taken from Ref. 12). ^{b)} Estimated from π values for aliphatic moiety based on $\log P$ by means of the additivity principle. ^{c)} Calculated by Eq. (1). ^{d)} Not included in the correlation.

Fig. 1 Projection of substituents along the L axis showing the parameter L .

Table 2 The squared correlation matrix of the variables used in Eq. (1).

	L^2	L	π
L^2	1.000	0.993	0.496
L		1.000	0.455
π			1.000

vals of the corresponding constants. In Eq. (1), the L^2 term and the intercept are justified respectively at levels more than 99.5% and

75%, by t test. The other terms are justified at levels better than 95%. The squared correlation matrix of the variables is shown in Table 2.

2. Structure-activity Correlation of *N*-(1-Methyl-1-substituted Phenylethyl)-2-bromo-3,3-dimethylbutanamides

Table 3 shows the activity of *N*-(1-methyl-1-phenylethyl)-2-bromo-3,3-dimethylbutanamides having various substituents at the benzene ring. We have analyzed the benzene ring substituents and found that the activity is represented by Eq. (2) with STERIMOL parameter, L .

$$pI_{50} = -0.587L_o - 0.700L_m \quad (0.332) \quad (0.537) \\ - 0.777L_p + 6.168 \quad (0.248) \quad (0.408) \quad (2)$$

$$n=16, s=0.332, r=0.894,$$

$$F_{3,12}=15.87$$

o , m , and p refer to the *ortho*, *meta*, and *para* substituents respectively. The L_m term is jus-

Table 3 *N*-(1-Methyl-1-substituted phenylethyl)-2-bromo-3,3-dimethylbutanamides and their growth inhibiting activity against bulrush.

X	mp(°C)	L_o^a	L_m^a	L_p^a	pI_{50}	
					Obsd.	Calcd. ^{b)}
H	182 –183	0.00	0.00	0.00	6.43	6.17
<i>o</i> -Me	160.5–163	0.94	0.00	0.00	5.51	5.62
<i>o</i> -Et	163 –164	2.05	0.00	0.00	4.70	4.97
<i>o</i> -F	168 –169	0.59	0.00	0.00	6.26	5.82
<i>o</i> -Cl	155.5–157	1.46	0.00	0.00	5.84	5.31
<i>o</i> -OMe	143 –145	1.92	0.00	0.00	4.84	5.04
<i>m</i> -Me	156.5–157.5	0.00	0.94	0.00	5.51	5.51
<i>m</i> -F	181 –182	0.00	0.59	0.00	5.52	5.75
<i>m</i> -Cl	172.5–174	0.00	1.46	0.00	5.24	5.15
<i>p</i> -Me	199 –200	0.00	0.00	0.94	5.57	5.44
<i>p</i> -Et	190 –191	0.00	0.00	2.05	4.53	4.57
<i>p</i> -Pr(<i>n</i>)	147 –149	0.00	0.00	2.99	4.29	3.84
<i>p</i> -Pr(<i>i</i>)	180.5–182	0.00	0.00	2.05	4.25	4.57
<i>p</i> -F	183.5–184.5	0.00	0.00	0.59	5.22	5.71
<i>p</i> -Cl	198 –199	0.00	0.00	1.46	4.94	5.03
<i>p</i> -OMe	170.5–171.5	0.00	0.00	1.92	4.53	4.68

^{a)} STERIMOL parameter, taken from Ref. 12). The value of the reference is shifted to $L(H)=0$.

^{b)} Calculated by Eq. (2).

Table 4 The squared correlation matrix of variables used in Eq. (2).

	L_o	L_m	L_p
L_o	1.000	0.073	0.215
L_m		1.000	0.116
L_p			1.000

tified at a level more than 90% and the other terms are justified at levels better than 99.5%. For the sake of simplicity, the scale of L value in this case was shifted so as to make $L(H)=0$. The squared correlation matrix of the variables is shown in Table 4. The use of other steric parameters, E_s , MR , MW , and V_w instead of L or addition of π and σ singly or together to Eq. (2) did not afford any significant improvement.

DISCUSSION

The steric effect of the substituent in the acid moiety of this type of amides was shown in our previous paper²³ to be represented by E_s^* . The E_s^* is taken as a parameter emphasizing the effect of branching besides steric bulk.¹⁵⁾ However, E_s^* is not responsible at all for the steric effect of the substituent in the amine moiety. The use of STERIMOL width parameters,¹²⁾ B_1 and B_4 , instead of L does not give a significant correlation. The L parameter well represents the length of substituents. According to Eq. (1), the activity is related parabolically to the L value, the optimum L value being 3.71 Å. The negative sign of the L_o , L_m , and L_p terms in Eq. (2) means that the activity decreases with increasing length of the benzene ring substituent. These seem to indicate that the smooth shape without extreme projection or hollow around the amine moiety is necessary for the high activity. The suitable fit of the molecule around the amine moiety with the target site may be important in determining the activity variation. Comparing the magnitude of the coefficient in Eq. (2), the substituent effect at the *meta*- or *para*-position of the phenyl group is more critical than that at the *ortho*-position. The hypothetical cavity of the target site corresponding to the *meta*- or *para*-position

seems to be considerably smaller than that corresponding to the *ortho*-position. The positive sign of the π term in Eq. (1) means that the activity increases with increasing hydrophobicity of the substituent.

ACKNOWLEDGMENTS

We wish to express our thanks to Prof. Toshio Fujita of Kyoto University for his invaluable suggestions. We also thank Dr. Kenzo Ueda, Dr. Akira Fujinami, and Mr. Naganori Hino for their fruitful discussions. We are indebted to Messrs. Masaharu Ishiwatari and Yoshihisa Nagano for their skilful technical assistance.

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要 約

除草活性を有する *N*-benzyl-2-bromo-3,3-dimethylbutanamides の定量的構造活性相関*桐野 修, 古沢久仁彦, 高山千代蔵
松本啓志, 嶺 昭彦

N-ベンジル基の α -位あるいはベンゼン環に種々の置換基を有する 27 個の *N*-benzyl-2-bromo-3,3-dimethylbutanamide 誘導体の, イヌホタルイ (*Scirpus juncoides*)

生育阻害活性をバイアル試験により求めた。そして, 構造と活性との関係を物理化学的パラメータを用いて重回帰分析により解析した。その結果, 活性は置換基の立体的な長さに対して放物線的な関係にあることがわかった。また, 疎水性が大きいほど活性は高い。*N*-(1-メチル-1-置換フェニルエチル) ブタンアミド誘導体の活性においても, ベンゼン環置換基の立体的な長さが重要であった。

* *N*-Benzylbutanamides の除草活性 (第 3 報)