Original Article

Synthesis and Herbicidal Activity of *N*-Alkyl-*N*-(substituted benzyl)-4-halo-2-alkenamides¹Kenji MATSUNARI, Hidetoshi SUGIYAMA,* Hideo SADOHARA[†] and Kenji MOTOJIMA[†]

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(Received January 16, 1998; Accepted July 27, 1998)

This paper reports the synthesis of novel *N*-alkyl-*N*-(substituted benzyl)-4-halo-2-alkenamides and their herbicidal activity against *Echinochloa oryzicola*. Their herbicidal activity was observed to be light-dependent. The study on the structure-activity relationships revealed that 4-chloro-2-pentenoyl is the best as the acyl skeleton, and the combinations of either isobutyl or isopentyl and either 4-cyano- or 4-chlorobenzyl substituents on the amide nitrogen atom are the most favorable to the activity.

Key words: 4-chloro-2-pentenoic acid, *N*-(chlorobenzyl)-*N*-isobutyl-4-chloro-2-penteamide, *Echinochloa oryzicola*, light-dependence, α -haloacetamide herbicide, nitrofen.

INTRODUCTION

Various structural types of amides possess herbicidal activity.^{1,2)} We have been interested in structural modifications of existing amide herbicides. In the course of trials starting from α -haloacetamide herbicides including the vinylogation and other derivatizations, we have disclosed that such vinylogous tertiary amides as *trans*-*N*-alkyl-*N*-(substituted benzyl)-4-halo-2-alkenamides exhibit a pronounced herbicidal activity especially against a barnyard grass species in the rice paddy field. Their herbicidal activity is light-dependent, and is similar to that of *ortho*-substituted diphenyl ether herbicides such as nitrofen,³⁻⁵⁾ and oxyfluorfen,⁶⁾ which cause a rapid necrosis. A number of light-dependent herbicides with various structural features have been known. Besides *ortho*-substituted diphenyl ethers, they are cyclic imides such as flumioxazin,⁷⁾ and nitrogen-heterocycles, to which substructures containing substituted phenyls are attached, such as oxadiazon,⁸⁾ sulfentrazone,⁹⁾ and pyraflufen-ethyl.¹⁰⁾

Because the structural features of *N*-alkyl-*N*-benzyl-4-halo-2-alkenamides are novel as light-dependent herbicides, we have examined the effect of structural modifications on the herbicidal activity with variations of substituents X, Y, R₁, and R₂ as shown in Fig. 1. This paper reports syntheses of *trans*-*N*-alkyl-*N*-benzyl-

4-halo-2-alkenamide derivatives and their structure-activity profiles against a barnyard grass species, *Echinochloa oryzicola*.

MATERIALS AND METHODS

1. Chemicals

N-Alkyl-*N*-(substituted benzyl)-4-bromo- and -4-chloro-2-alkenamides were synthesized, respectively, by the reaction of 4-bromo- and 4-chloro-2-alkenoyl chlorides with *N*-alkyl-*N*-benzylamines. 4-Bromo- and 4-chloro-2-alkenoyl chlorides were prepared by conventional methods from the corresponding alkenoic acids. 4-Bromo-2-alkenoic acids were prepared by the bromination of 2-alkenoic acid with *N*-bromosuccinimide.¹¹⁾ *N*-Alkylbenzylamines were obtained by refluxing a toluene solution of substituted benzyl halides with an excess amount of the corresponding alkylamines. All compounds listed in Tables 1-4 are those of the *RS-trans* form except for the compound 5 which is of the *trans*. The structure was confirmed by ¹H NMR and IR spectroscopic methods. All melting points are uncorrected. Synthetic examples of the 4-chloro- and 4-iodo-2-pentenamides are described below.

1.1 *N*-(Chlorobenzyl)-*N*-isobutyl-4-chloro-2-penteamide

To a mixture of *N*-(chlorobenzyl)-*N*-isobutylamine hydrochloride (0.5 g, 0.0022 mol) and triethylamine (0.5 g, 0.0049 mol) in 20 ml of dichloromethane was added

¹ Halopentenamides as Light-Dependent Herbicides (Part 1).

Fig. 1 *N*-Alkyl-*N*-substituted-benzyl-4-halo-2-alkenamides.

4-chloro-2-pentenoyl chloride (0.3 g, 0.0020 mol) with stirring at 10–15°C under ice-water cooling. After stirring for 2 hr at room temperature, the reaction mixture was washed successively with diluted HCl and water, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by column chromatography on silica gel (230–400 mesh) in *n*-hexane/ethyl acetate (5 : 1) to afford *N*-(4-chlorobenzyl)-*N*-isobutyl-4-chloro-2-pentenamide (0.5 g) as an oil. ^1H NMR (CCl_4) δ ppm : 0.85 (6H, d), 1.55 (3H, d), 1.90–2.30 (1H, m), 3.15 (2H, d), 4.30–4.75 (1H, m), 4.63 (2H, s), 6.20 (1H, d), 6.63–7.00 (1H, dd), 7.3 (4H, s), IR (NaCl) ν cm^{-1} : 1650 (CON), 1620 (HC=CH).

1.2 4-Chloro-2-pentenoic acid

To a mixture of NaCl (40 g, 0.68 mol) and trioctylmethylammonium chloride (1 g, 0.0024 mol) in 100 ml of water was added a solution of 4-bromo-2-pentenoic acid (10 g, 0.056 mol) in 4 ml of ethanol. After stirring at 80–90°C for 2 hr, the reaction mixture was poured into water, acidified with diluted HCl, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by distillation under reduced pressure to afford 4-chloro-2-pentenoic acid (4.5 g) as an oil, bp 85°C/0.1 mmHg, ^1H NMR (CCl_4) δ ppm : 1.70 (3H, d), 4.40–5.00 (1H, m), 6.05 (1H, d), 7.07 (1H, dd), 11.50 (1H, s), IR (NaCl) ν cm^{-1} : 1680 (COOH), 1630 (HC=CH).

1.3 *N*-(4-Chlorobenzyl)-*N*-isobutyl-4-iodo-2-pentenamide

To a solution of NaI (40 g, 0.27 mol) and benzyltriethylammonium chloride (0.3 g, 0.0014 mol) in 100 ml of water was added *N*-(4-chlorobenzyl)-*N*-isobutyl-4-bromo-2-pentenamide (5.0 g, 0.014 mol). After stirring at 80–90°C for 3 hr, the reaction mixture was poured into water, and extracted with toluene. The extract was dried over anhydrous sodium sulfate, and concentrated. The residue was purified by column chromatography on silica gel (230–400 mesh) in *n*-hexane/ethyl acetate (5 : 1) to afford *N*-(4-chlorobenzyl)-*N*-isobutyl-4-iodo-2-pentenamide (5.0 g) as an oil, ^1H NMR (CCl_4) δ ppm : 0.85 (6H, d), 1.95 (3H, d), 1.90–2.30 (1H, m), 3.15 (2H, d), 4.56 (2H, s), 4.5–5.2 (1H, m), 6.2–7.3 (2H, m), 7.3 (4H, s), IR (NaCl) ν cm^{-1} : 1640 (CON), 1605 (HC=CH).

2. Biological Test

Ten grams of each test compound was formulated as a wettable powder by mixing with 0.5 g of Emalgen 810, 0.5 g of Demol N, 18 g of Kunilite 250 (diatomaceous earth), 6 g of Carplex No/80 (White carbon) and 65 g of Zeeklite (clay). The wettable powder preparation was diluted with water to give various concentrations of the test emulsion.

To evaluate the herbicidal activity, ten barnyard grass seeds (*E. oryzicola*) were sown in a plastic pot in which paddy conditions were reproduced with rice plants on the 2.2–2.5 leaf stage, the lower stems and roots being submerged with vermiculite pads. Just after sowing, the test emulsion was added to the paddy water at several doses (usually 16–5000 g a.i./ha). The symptom of weed seedlings being kept at $25 \pm 2^\circ\text{C}$ was observed visually 3 weeks after the addition of the test emulsion (2 replications). The herbicidal activity was expressed as the ED_{90} , the dosage in terms of g a.i./ha required for the 90% damage of seedlings. The light-dependent effect was examined by comparing the shoot growth inhibitions under light and dark conditions.

Ten milliliters of the test emulsion diluted to 10 ppm was poured into each Petri dish ($\phi=9$ cm) lined with absorbent cotton and filter paper. Then, seeds of the barnyard grass (*E. oryzicola*) were placed on the cotton. The dishes were kept for 6 days in a greenhouse at $25 \pm 2^\circ\text{C}$ with daylight (12 hr) under the light conditions, whereas dishes were covered with aluminum foil under dark conditions (2 replications).

RESULTS

1. Light-Dependence

Figure 2 clearly indicates that the light is required for the inhibitory action of *N*-(4-chlorobenzyl)-*N*-isobutyl-4-chloro-2-pentenamide against the growth of the barnyard grass seedlings. The light-dependent symptom is

Fig. 2 Herbicidal activity of *N*-(4-chlorobenzyl)-*N*-isobutyl-4-chloro-2-pentenamide (CPA), oxyfluorfen (OXF), and pretilachlor (PRC) under light (L) and dark (D) conditions.

similar to that caused by oxyfluorfen. Pretilachlor used as a reference inhibits the growth of the barnyard grass under dark conditions significantly. Its inhibitory activity under light conditions seems greater, but the light-dependent inhibition of the 4-chloropentenamide and oxyfluorfen is much clearer than that of pretilachlor. The light-dependency of the herbicidal action was observed for other *N,N*-disubstituted 4-halo-2-pentenamides with a measurable potency.

2. Effect of Substituents at the 4-Position of the Acyl Moiety

Since the initial stage of the synthetic project, we noticed that either Cl or Br is required as the substituent at the 4-position at least for moderately or highly potent compounds. Thus, the range of substituent variations was rather limited. For only four compounds in which other variable, R_1 , R_2 , and Y are fixed, the effect of the substituent at this position can be compared directly as shown in Table 1. The Cl substituent was selected as being the most favorable. The hydroxy compound (**1**) is almost inactive. It seems to be that the electron-withdrawing property with an appropriate hydrophobicity is important for the substituents at the 4-position of the acyl moiety.

3. Effect of the Length of the Acyl Moiety

The X, Y, and R_2 substituents being fixed as Br or Cl, 4-Cl, and isobutyl, respectively, the effect of the length of the acyl moiety, i.e., that of the R_1 substituent was examined as shown in Table 2. In the series of the X = Br as well as X = Cl, the methyl and ethyl compounds (**3**, **6**, **2**, **12**) showed the highest activity. The activity in the 4-bromoalkenamides decreased with lengthening as well as shortening the alkyl group. Thus, the methyl and ethyl groups were suggested to be optimum in terms of hydrophobicity and/or bulkiness.

Table 1 Structure and herbicidal activity of *N*-(4-chlorobenzyl)-*N*-isobutyl-4-halo (or hydroxy)-2-pentenamides.

No.	X	n_D^{20}	Herbicidal activity ^{a)} ED ₉₀ (g a.i./ha)
1	OH	1.5362	> 5000
2	Cl	1.5418	16
3	Br	1.5632	125
4	I	1.5879	250

^{a)} The ED₉₀ value is the dosage in terms of g a.i./ha required for the 90% damage of barnyard grass seedlings.

Table 2 Structure and herbicidal activity of *N*-(4-chlorobenzyl)-*N*-isobutyl-4-bromo (or chloro)-2-alkenamides.

No.	R_1	X	n_D^{20}	Herbicidal activity ^{a)} ED ₉₀ (g a.i./ha)
5	H	Br	1.5587	> 4000
3	Me	Br	1.5632	125
6	Et	Br	1.5546	125
7	<i>n</i> -Pr	Br	1.5462	250
8	<i>i</i> -Pr	Br	1.5470	250
9	<i>n</i> -Bu	Br	1.5261	2500
10	<i>n</i> -Hex	Br	1.5537	5000
11	<i>n</i> -Oct	Br	1.5296	> 5000
2	Me	Cl	1.5445	16
12	Et	Cl	1.5402	16
13	<i>n</i> -Pr	Cl	1.5385	500-1000

^{a)} The ED₉₀ value is the dosage in terms of g a.i./ha required for the 90% damage of barnyard grass seedlings.

An hydrophobic interaction with possible receptor sites would occur at the R_1 position, but the bulkiness of hydrophobic alkyl groups should be between Me and Pr. The activity of the Cl analogs seems to decrease more sharply than that of the Br series with increasing the length of the alkyl groups. The pentenamide (R_1 = Me) skeleton with X = Cl was selected as the most favorable structural pattern.

4. Effect of Substituents on the Benzyl-Benzene Ring in the Amide Moiety

Originally, various combinations of alkyl groups as two substituents on the amide nitrogen atom were examined for the 4-Cl- and 4-Br-pentenamides. Simple *N,N*-dialkyl combinations did not exceed an expected standard of the herbicidal potency. Combinations of (un)substituted benzyls and appropriate alkyls were required at least for the moderate activity. In Table 3, the herbicidal activity of *N,N*-disubstituted 4-Cl-2-pentenamides in which one of the *N*-substituents, R_2 , is fixed as isobutyl and the other is variously substituted benzyls are listed to show the effect of aromatic substituents. Because the *para* isomer (**17**) was the most potent among the CN-substituted isomers (**15**–**17**), the *para*-substitution was thought to be most favorable for the activity in general.

A number of *para*-substituted derivatives were synthesized. The activity of the compounds with electron-withdrawing substituents, 4-Cl (**2**), 4-CN (**17**), and 4-CF₃ (**18**) was higher, whereas that of the others was lower than that of the unsubstituted one (**14**). The activity did

Table 3 Structure and herbicidal activity of *N*-benzyl-*N*-isobutyl-4-chloro-2-pentenamides.

No.	Y	n_D^{20} (or mp)	Herbicidal activity ^{b)}
			ED ₉₀ (g a.i./ha)
14	H	1.5430	125
15	2-CN	1.5431	250-500
16	3-CN	1.5455	500
17	4-CN	1.5500	16
2	4-Cl	1.5455	16
18	4-CF ₃	1.4994	31-62
19	4-Me	1.5357	125
20	4-NO ₂	1.5529	250
21	4-SO ₂ Me	1.5503	>1000
22	4-CHO	1.5545	1000
23	4-CO ₂ H	191-193°C	>5000
24	4-CO ₂ Et	1.5312	1000
25	4-SMe	1.5679	250-500
26	4-CONH ₂	138-139°C	500
27	4-NHAc	1.5565	>5000
28	2,4-Cl ₂	1.5540	125
29	2-OMe, 4-Cl	1.5452	500-1000
30	2-OSO ₂ Me, 4-Cl	1.5406	500-1000
31	3-NO ₂ , 4-Cl	1.5582	31
32	3-OMe, 4-Cl	1.5462	16
33	3-OPr, 4-Cl	1.5349	31
34	3-OSO ₂ Me, 4-Cl	1.5342	31
35	3-CO ₂ Et, 4-Cl	1.5360	<16
36	2-Cl, 4-CN	— ^{a)}	<16
37	3-OMe, 4-CN	1.5479	16
38	2-Br, 4-CN, 5-Cl	— ^{a)}	<16
39	2-OMe, 5-Cl	84-85°C	>1000
40	2-OSO ₂ Me, 5-Cl	1.5430	>1000
41	2-Cl, 5-OMe	88-89°C	31
42	2-Cl, 5-OPr	— ^{a)}	62
43	2-Cl, 5-OSO ₂ Me	1.5398	31

^{a)} Not measured due to the strong viscosity. ^{b)} The ED₉₀ value is the dosage in terms of g a.i./ha required for the 90% damage of barnyard grass seedlings.

not seem to depend only on the electron-withdrawing nature of substituents, because electron-withdrawing substituents, such as SO₂Me (**21**), CO₂Et (**24**), and NO₂ (**20**), did not potentiate the activity. The effect of multiple substitutions is more complicated. The introduction of various substituents into the 2-position of the 4-Cl compound (**2**) decreased the activity markedly as observed for compounds **28-30**, whereas that into the 3-position as in the compounds **31-35** affected the activity only to a lesser extent. The introduction of substituents into the 4-CN compounds (**36, 37**) did not show positional effects such as observed in the 4-Cl compound. 2,5-Di- and 2,4,5-tri-substituted compounds generally exhibited a high activity only when they have the 2-Cl and 2-Br substitution patterns (**41-43, 38**). The multiple substitutions

showed no practical advantage over the single substitutions such as 4-Cl and 4-CN. Accordingly the 4-Cl substitution was selected as the most favorable one.

5. Effect of the *N*-Alkyl Substituents (*R*₂) in the Amide Moiety

Table 4 lists the herbicidal activity of *N*-alkyl-*N*-(4-chlorobenzyl)-4-chloro-2-pentenamides. The *i*-Bu (**2**) and *i*-Pent (**52**) derivatives exhibited an excellent activity. Among the straight chain alkyl groups, *n*-Bu was most favorable to the activity. The effects of branching were such that the potency sequence are *n*-Pr (**46**) > *i*-Pr (**47**), and *i*-Bu (**2**) > *n*-Bu (**48**) > *s*-Bu (**49**) >> *t*-Bu (**50**). The branching at the α -position of alkyl groups worked to reduce the activity here. Especially, the double-

Table 4 Structure and herbicidal activity of *N*-(4-chlorobenzyl)-*N*-alkyl-4-chloro-2-pentenamides.

No.	R ₂	<i>n</i> _D ²⁰ (mp)	Herbicidal activity ^{a)}
			ED ₉₀ (g a.i./ha)
44	Me	1.5527	2000
45	Et	1.5399	250
46	<i>n</i> -Pr	1.5388	125
47	<i>i</i> -Pr	1.5387	250
48	<i>n</i> -Bu	1.5433	31
2	<i>i</i> -Bu	1.5455	16
49	<i>s</i> -Bu	1.5433	375
50	<i>t</i> -Bu	94–95°C	> 5000
51	Allyl	1.5605	375
52	<i>i</i> -Pent	1.5426	< 16
53	<i>c</i> -Hex	1.5633	31
54	<i>c</i> -Hep	1.5632	62
55	<i>n</i> -Oct	1.5301	> 5000

^{a)} The ED₉₀ value is the dosage in terms of g a.i./ha required for the 90% damage of barnyard grass seedlings.

branched *t*-Bu group in the compound **50** was unfavorable to the activity. It was somewhat curious that the *c*-Hex (**53**) and *c*-Hep (**54**) derivatives retained the high activity in spite of the α -branching. Thus, not the branching itself but other factors such as conformational flexibilities may be significant in determining the activity. Therefore isobutyl group was selected as the most favorable R₂ substituent in any case.

DISCUSSION

Light-dependency of the herbicidal symptom of the 4-chloropentenamides is more conspicuous than that of the α -haloacetamide herbicides such as pretilachlor.

The activity of α -haloacetamide has not been reported to be light-dependent and the primary mode of action has been considered to inhibit the cell division probably by attacking SH groups of some protease systems as alkylating agents.¹²⁾ Recently, Böger reported a new target site of chloroacetamides, which is related to lipid metabolism, particularly the processing of fatty acids.¹³⁾ Although the principal mode of action seems to differ between 4-chloro-pentenamides and α -haloacetamides, our expectation for the vinylogated haloacetamides to be herbicidally active was really the case. The range of the substituent variations tolerable to the activity was not so wide at the 4-position of the acyl moiety. The structure-activity relationship was examined most extensively for the aromatic substituents on the *N*-benzyl-benzene ring. From practical evaluations, the compound having the combination of the best substituents at each position, R₁, R₂, X, and Y, *RS-trans-N*-isobutyl-*N*-(4-chlorobenzyl)-4-chloro-2-pentenamide (**2**) was selected as a candidate for detailed field trials.

In Table 5, the herbicidal activity of the candidate (**2**) is compared with that of chlomethoxyfen, a typical light-dependent diphenyl ether. The potency of the compound **2** is 10 times higher than that of chlomethoxyfen in the pot test. This could be regarded as a promising sign.

To understand the physicochemical background of the substituent effects and to justify the selection of this candidate compound (**2**), the quantitative structure-activity analyses have been done, which will be published elsewhere.

ACKNOWLEDGMENTS

We wish to thank Professor Toshio Fujita of Department of Agricultural Chemistry, Kyoto University for his valuable advices and discussions.

Table 5 ED₉₀ values of chlomethoxyfen and compound **2**.

Compound	Structure	Herbicidal activity ^{a)}
		ED ₉₀ (g a.i./ha)
Chlomethoxyfen		250
2		16

^{a)} The ED₉₀ value is the dosage in terms of g a.i./ha required for the 90% damage of barnyard grass seedlings.

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要 約

***N*-アルキル-*N*-置換ベンジル-4-ハロ-2-アルケンアミドの合成と除草活性**

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N-アルキル-*N*-置換ベンジル-4-ハロ-2-アルケンアミドの合成を行い, それらのタイヌビエ (*Echinochloa oryzicola*) に対する除草活性を評価した。アシル部位とアミド部位に於ける置換基を種々変化させ除草活性との関係について検討を行った。それらの除草活性は光要求型であることが観察された。その構造と活性の関係に於いて, アシル部位としては 4-クロロ-2-ペンテノイル基が最も良好であり, アミド部位に於ける置換基についてはイソブチル基または, イソペンチル基の何れかと 4-シアノもしくは 4-クロロベンジル置換基との組合せが除草活性に対し最も好ましいことが判明した。