3-(α-アルコキシイミノベンジル)イソオキサゾール誘導体の合成と殺菌活性

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Original Article

Synthesis and Fungicidal Activities of 3-(α-Alkoxyiminobenzyl)isoxazole Derivatives

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A series of 3-(α-alkoxyiminobenzyl)isoxazole derivatives were synthesized and their fungicidal activities against crop diseases were assessed. Studies of the structure-activity relationships revealed the strongest fungicidal activity when the alkoxyimino moiety was substituted with a methyl group. When the position-2 of the benzene ring on the benzyl moiety was substituted with a phenoxymethyl group, a good fungicidal activity was obtained. Among the compounds examined, 3-[2-(2,5-dimethylphenoxymethyl)-α-methoxyiminobenzyl]isoxazole (**27**) showed potent fungicidal activity against cucumber powdery mildew, wheat powdery mildew and wheat eye spot.

Key words: 3-(α-alkoxyiminobenzyl)isoxazole derivatives, alkoxyiminoacetamide derivatives, fungicidal activity, powdery mildew, eye spot.

INTRODUCTION

Alkoxyiminoacetamide derivatives are promising compounds for use as fungicidal agents with broad spectrum and a new mode of action, which do not show cross-resistance to any current fungicides.[1-4] In our previous paper, we reported the structure-activity relationships of fungicidal [2-(2,5-dimethylphenoxymethyl)-α-methoxyiminobenzyl]isoxazole derivatives, derived by replacing the methylcarbamoyl moiety of alkoxyiminoacetamide derivatives (SSF-129)[5,6] with an isoxazole ring.[7] In these derivatives, fungicidal activities against cucumber powdery mildew and wheat powdery mildew were the strongest with 4,5-dihydro-3-isoxazolyl, 3-isoxazolyl or 3-methyl-5-isoxazolyl groups as the isoxazole moiety.

In this study, we synthesized a series of 3-(α-alkoxyiminobenzyl)isoxazole derivatives (Fig. 1) and examined their fungicidal activities with reference to the effects of substituents on the α-alkoxyiminobenzyl moiety.

MATERIALS AND METHODS

1. *Instrumental Analysis*

Melting points were measured with a Büchi 535 melting point apparatus and are given uncorrected. Refractive indexes were measured with an Atago Abbe-refractometer. ^{1}H NMR spectra were measured on a JEOL JNM-GSX 270 spectrometer at 270 MHz using tetramethylsilane (TMS) as an internal standard.

2. *Synthesis of Compounds*

The methods used for synthesis of 3-(α-alkoxyiminobenzyl)isoxazole derivatives are shown in Fig. 2. The oximes were confirmed to be the *E*-isomers.[7] Typical synthetic procedures are described below.

2.1 *3-[2-(2,5-Dimethylphenoxymethyl)-α-hydroxyiminobenzyl]isoxazole (**32**)*

Hydroxylamine hydrochloride (2.29 g, 33 mmol) was added to a mixture of 3-[2-(2,5-dimethylphenoxymethyl)-benzoyl]isoxazole[7] (3.38 g, 11 mmol), pyridine (2.87 g, 36 mmol) and methanol (22 ml), and the mixture was stirred under reflux for 4 hr. The reaction mixture was poured into ice-water (100 ml), acidified with 36% hydrochloric acid and extracted with ether (150 ml). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 1.29 g (36.4%) of compound **32**. The product was recrystallized from ethyl acetate and hexane to give colorless crystals, mp 142–143°C. ^{1}H NMR($CDCl_3$) δ ppm : 2.11 (3H, s), 2.24 (3H, s), 4.99 (2H, s), 6.57 (1H, s), 6.63 (1H, d, J=7.3 Hz), 6.72 (1H, d, J=1.8 Hz), 6.97 (1H, d, J=7.3 Hz), 7.30–7.52 (3H, m), 7.61 (1H, s), 7.66 (1H, d, J=6.7 Hz), 8.40 (1H, d, J=1.8 Hz).

2.2 *3-[2-(2,5-Dimethylphenoxymethyl)-α-ethoxyiminobenzyl]isoxazole (**33**)*

A mixture of compound **32** (0.19 g, 0.6 mmol),

Fig. 1 Chemical structure of 3-(α-alkoxyiminobenzyl)isoxazoles.

iodoethane (0.12 g, 0.8 mmol), potassium carbonate (0.12 g, 0.9 mmol) and *N*,*N*-dimethylformamide (1.8 ml) was stirred at room temperature for 2 hr. The reaction mixture was poured into water (80 ml) and extracted with ether (100 ml). The organic layer was washed with brine (80 ml), dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 0.18 g (85.6%) of compound **33**. The product was recrystallized from ethyl acetate and hexane to give as colorless crystals, mp 90–91°C. ^{1}H NMR($CDCl_3$) δ ppm: 1.29 (3H, t, J=7.3 Hz), 2.13 (3H, s), 2.22 (3H, s), 4.27 (2H, q, J=7.3 Hz), 4.96 (2H, s), 6.53 (1H, s), 6.63 (1H, d, J=7.9 Hz), 6.75 (1H, d, J=1.8 Hz), 6.98 (1H, d, J=7.3 Hz), 7.26–7.49 (3H, m), 7.61–7.64 (1H, m), 8.38 (1H, d, J=1.8 Hz).

2.3 3-[2-(2,5-Dimethylphenoxymethyl)-α-methoxyiminobenzyl]isoxazole (27)

Methoxylamine hydrochloride (16.70 g, 0.20 mol) was added to a mixture of 3-[2-(3-methyl-2,4-dioxahexyl)-benzoyl]isoxazole[8] (27.53 g, 0.10 mol), pyridine (16.61 g, 0.21 mol) and methanol (200 ml), and the mixture was stirred under reflux for 1 hr. The reaction mixture was poured into ice-water (500 ml), acidified with 36% hydrochloric acid, and extracted with dichloromethane (300 ml×2). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 21.46 g (92.4%) of 3-(2-hydroxymethyl-α-methoxyiminobenzyl) isoxazole as a colorless oil. ^{1}H NMR($CDCl_3$) δ ppm: 2.25 (1H, t, J=6.7 Hz), 4.01 (3H, s), 4.48 (2H, d, J=6.7 Hz), 6.81 (1H, d, J=1.8 Hz), 7.20–7.61(4H, m), 8.41 (1H, d, J=1.8 Hz).

Carbon tetrabromide (23.21 g, 0.07 mol) was added to a mixture of 3-(2-hydroxymethyl-α-methoxyiminobenzyl)-isoxazole (11.61 g, 0.05 mol), triphenyl phosphine (15.74 g, 0.06 mol) and acetonitrile (100 ml) in an ice bath, and the mixture was stirred at 0 to 5°C for 15 min. The reaction mixture was poured into water (400 ml) and extracted with ether (400 ml). The organic layer was washed with brine (400 ml), dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 12.65 g (85.7%) of 3-(2-bromomethyl-α-methoxyiminobenzyl) isoxazole as deep blue crystals. ^{1}H NMR($CDCl_3$) δ ppm: 4.02 (3H, s), 4.38 (2H, s), 6.79 (1H, d, J=1.8 Hz), 7.21–7.56 (4H, m), 8.41(1H, d, J=1.2 Hz).

A mixture of 3-(2-bromomethyl-α-methoxyimino-benzyl)isoxazole (12.65 g, 43.0 mmol), 2,5-xylenol (7.88 g, 64.5 mmol), potassium carbonate (8.91 g, 64.5 mmol) and *N*,*N*-dimethylformamide (120 ml) was stirred at 70°C for 10 hr. The reaction mixture was poured into water (400 ml) and extracted with ether (400 ml). The organic layer was washed with brine (400 ml), dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 8.91 g (61.6%) of compound **27**. The product was recrystallized from ethyl acetate and hexane to give as colorless crystals, mp 95–96°C. ^{1}H NMR($CDCl_3$) δ ppm: 2.13 (3H, s), 2.23 (3H, s), 4.01 (3H, s), 4.95 (2H, s), 6.54 (1H, s), 6.64 (1H, d, J=7.3 Hz), 6.75 (aH, d, J=1.8 Hz), 6.98 (1H, d, J=7.9 Hz), 7.26–7.49 (3H, m), 7.62 (1H, d, J=9.2 Hz), 8.39 (1H, d, J=1.8 Hz).

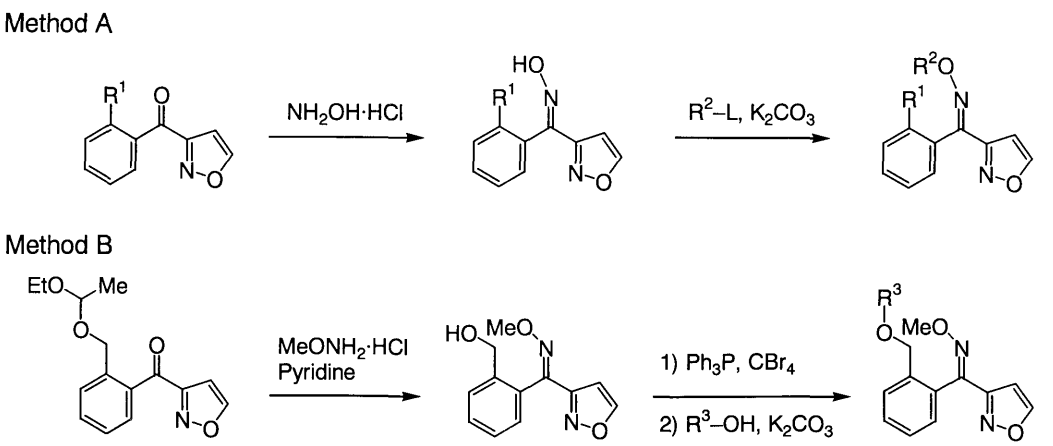


Fig. 2 Synthetic methods of 3-(α-alkoxyiminobenzyl)isoxazoles.

3. Biological Tests

3.1 Assay methods for fungicidal activity

3.1.1 Plant materials

Cucumber (*Cucumis sativus* L. cv. Sagamihanpaku) and wheat (*Triticum aestivum* L. cv. Nohrin-61) seedlings were used for the assay of disease controlling activity by foliar application. The seedlings were prepared as described previously.[7]

3.1.2 Methods for fungicidal activity assay

Disease controlling activity by foliar application on cucumber powdery mildew and wheat powdery mildew were assessed as described previously.[7]

The fungicidal activity by preventive application was expressed as an index of 4, 3, 2, 1 and 0, each corresponding to approximately 90% control at less than 7.8, 31.3, 125, 500 ppm and less than 90% control at 500 ppm, respectively.

3.2 Assay method for antifungal activity against Pseudocercosporella herpotrichoides in vitro

Mycelial growth inhibition tests were carried out by the agar dilution method. Each test compound dissolved and diluted in acetone was added to potato dextrose agar (PDA) medium which was kept at 50°C after autoclaving to give the adequate concentration (100 to 0.1 ppm, in 10-fold dilution). The final concentration of acetone in each medium was 1%. Three mycelial disks (4 mm in diameter) of *P. herpotrichoides*, precultured on potato sucrose agar (PSA) medium, were placed on PDA medium containing the given concentrations of the test compound using two replicates per concentration. The diameter of the mycelial mat was measured 18 days after incubation at 20°C. The effective concentration for 50% inhibition (EC_{50} value, ppm) of mycelial growth was calculated by the linear regression formula plotting the inhibition rate against the untreated control at each concentration against the logarithm of the concentration (ppm).

3.3 Field test

3.3.1 Wheat powdery mildew

Controlling activity of compound **27** on wheat powdery mildew was assessed by artificial inoculation in a greenhouse. The seeds of wheat (*T. aestivum* L. cv. Nohrin-61) were sown on 25th January 1995, and cultivated in a greenhouse. The conidia of the pathogen (*Erysiphe graminis* f. sp. *tritici*) were sprinkled over the wheat seedlings to inoculate them on 10th April at the tillers formed stage (Zadok's growth stage 25). The compounds dissolved in *N*,*N*-dimethylformamide (final concentration 1%) and diluted with water containing sticking agent were applied to the wheat seedlings with a hand sprayer at 7 days after inoculation (Zadok's growth stage 30–31), when the sign of powdery mildew was slightly recognizable on the lower leaves. The size of each plot was 3 m^2 (1×3 m) with three replications and the application volume was 150 ml/m^2. Assessment was carried out on 8th May (21 days after application) as percentage leaf area covered with sporulating lesion on the top three leaves of each hill, and the percent of control was calculated from percentage leaf area. Fifty hills were assessed in each plot.

3.3.2 Wheat eye spot

Controlling activity of compound **27** on wheat eye spot was assessed under field conditions by artificial inoculation. Seeds of wheat (*T. aestivum* L. cv. Nohrin-61) were sown in the field on 14th November 1994. The inoculum was prepared by the following procedure. Oat seeds were inoculated in potato dextrose broth medium which was previously inoculated with *P. herpotrichoides* and incubated on a reciprocal shaker for 10 days at 25°C, and the inoculated oat seeds were incubated for further 14 days at 20°C. Then, the oat seeds were put on the foot of the wheat seedlings to inoculate them on 30th January and 16th February at tillering to tillers formed stage (Zadok's growth stage 21–25). The compounds dissolved in *N*,*N*-dimethylformamide (final concentration 1%) and diluted with water containing sticking agent were applied to the wheat seedlings with handy sprayer on 20th March and 3rd April at leaf sheath lengthening and leaf sheaths strongly erected stage (Zadok's growth stage 29–31). The size of each plot was 3 m^2 (1×3 m) with two replications and the application volume was 150 ml/m^2. Assessment was carried out on 5th June (63 days after the 2nd application) by observing the culm of all stalks of 10 randomly selected hills per plot, and degree of infection was calculated as follows:

Degree of infection = $\sum$(Number of culms belonging to each Disease Index × Disease Index) × 100 ÷ (Total numbers of culms assessed × 4)

The criteria of the disease incidence were as follows from degree of infection.

Disease Index	Degree of infected area of the culm
0	No symptoms on the culm (No incidence)
1	A small but typical symptom (eye spot) was observed on the culm surface of the 1st internode (Slight)
2	Less than half of the culm surface of the 1st internode was covered with the lesion (Moderate)
3	More than half of the culm surface of the 1st internode was covered with the lesion (Severe)
4	The lesion covered the culm surface of the 1st internode (Extreme)

RESULTS AND DISCUSSION

1. Fungicidal Activities of 3-(α-Alkoxyiminobenzyl)-isoxazole Derivatives

The physical properties of the synthesized compounds

and their fungicidal activities against cucumber powdery mildew and wheat powdery mildew are listed in Tables 1 through 5.

1.1 Effects of substituents (R^1) on the benzyl moiety

Table 1 shows the effects of substituents (R^1) on the benzyl moiety of 3-(α-methoxyiminobenzyl)isoxazoles on fungicidal activity. Among the isoxazole derivatives (**1**–**3**), phenoxymethyl derivative (**3**) was most active, followed by phenoxy derivative (**1**). Benzyloxy derivative (**2**) was less active. The results regarding substituents (R^1) on the benzene ring were the same as those of 2-alkoxyimino-2-phenylacetamide derivatives.[9]

1.2 Effects of substituents (X) on the phenoxymethyl moiety

Table 2 shows the effect of mono-substituent (X) on the phenoxymethyl moiety of 3-[α-methoxyimino-2-(phenoxymethyl)benzyl]isoxazoles on fungicidal activity. Substitution with a fluoro, chloro or methyl group at the 2-position on the benzene ring (**4**, **7** and **10**) seemed to be most favorable for fungicidal activity, followed by the 4-position (**6**, **9** and **12**) and 3-position (**5**, **8** and **11**). Among the compounds with a substituent at the 2-position on the benzene ring (**4**, **7**, **10**, **13**–**17**), the methyl derivative (**10**) was most active, followed by chloro (**7**) and bromo (**15**) derivatives. Methoxy (**14**) and nitro (**17**) derivatives showed decreased fungicidal activities. On the basis of these results, it seemed reasonable to assume that electron-withdrawing (NO_2) or electron-donating groups (MeO) on the phenoxymethyl moiety were involved in decreasing fungicidal activity. Among the mono-substituted derivatives, 2-methyl derivative (**10**) exhibited the strongest fungicidal activity against cucumber and wheat powdery mildew.

Table 3 shows the effects of poly-substituents (X) on the benzene ring of the phenoxymethyl moiety of 3-[2-(phenoxymethyl)-α-methoxyiminobenzyl]isoxazoles on fungicidal activity. Among the poly-substituted phenoxymethyl derivatives (**18**–**31**), 2,5-dimethyl (**27**) and 2,3,5-trimethyl (**30**) derivatives were most active, followed by 2,5-dichloro (**21**) and 4-chloro-2-methyl (**31**) derivatives. The 2,6-di-substituted derivatives (**22** and **28**) showed reduced activities relative to the 2,5-di-substituted derivatives (**21** and **27**). One possible explanation for this is that the favorable conformation of the benzene ring for the activity was transformed by the steric influence of substituents at the ortho position. Although the 2,3,5-trimethyl derivative (**30**) exhibited excellent activity, 2,3,5-trichloro derivative (**24**) was less active. This suggested that the presence of an electron-withdrawing group and the hydrophobic effect of tri-substituted chlorine atoms on the phenoxymethyl moiety were involved in decreasing fungicidal activity.

1.3 Effects of O-substituents (R^2) of the alkoxyimino moiety

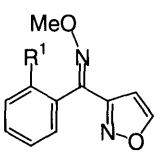
The effects of *O*-substituents (R^2) of the alkoxyimino moiety on the fungicidal activity were examined with a 2,5-dimethyl group on the benzene ring of the phenoxymethyl moiety (Table 4). All of the compounds except methyl derivative (**27**) were less active or inactive against cucumber and wheat powdery mildews, suggesting that the methoxyimino moiety was essential for the activity.

To increase fungicidal activity, we synthesized 3-[2-(heteroaryloxymethyl)-α-methoxyiminobenzyl]isoxazoles with pyridine,[10] benzoxazole, benzothiazole, quinoline and isoxazole rings instead of the benzene ring of the phenoxymethyl moiety of compound **27**. However, the fungicidal activity was reduced (unpublished).

2. Antifungal Activity against Pseudocercosporella herpotrichoides In Vitro

The antifungal activities of compounds **10**, **27** and **30** against *Pseudocercosporella herpotrichoides*, which

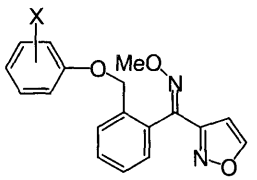
Table 1 3-(2-Substituted-α-methoxyiminobeazyl)isoxazoles and their fungicidal activities against cucumber and wheat powdery mildews by preventive application.



Compound No.	R^1	n_D(°C)	Fungicidal activity[a] Sf	Eg
1	PhO	1.5930(22.5)[b]	3	0
2	$PhCH_2O$	1.5861(23)	2	0
3	$PhOCH_2$	1.5867(25)	3	1

Sf: cucumber powdery mildew, Eg: wheat powdery mildew. [a] Fungicidal activities are expressed as an index of 4, 3, 2, 1 or 0, corresponding to approximately 90% of the control at 7.8, 31.3, 125, 500 ppm or less than 90% control at 500 ppm, respectively. [b] *E*/*Z* mixture (approximately 8 : 2 from ^{1}H NMR spectra).

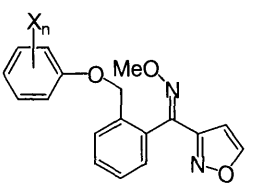
Table 2 3-[2-(Substituted phenoxymethyl)-α-methoxyiminobenzyl] isoxazoles and their fungicidal activities against cucumber and wheat powdery mildews by preventive application.



Compound No.	X	mp (°C) or n_D(°C)	Fungicidal activity[a] Sf	Eg
3	H	1.5867(25)	3	1
4	2-F	76–77	3	2
5	3-F	1.5740(22.5)	2	1
6	4-F	1.5743(22)	3	1
7	2-Cl	1.5930(26)	4	2
8	3-Cl	1.5903(26)	3	1
9	4-Cl	96.5–97.5	4	1
10	2-Me	39–42	4	4
11	3-Me	1.5810(26)	3	2
12	4-Me	82–84	4	2
13	2-Et	1.5762(26)	3	2
14	2-MeO	1.5892(22)	2	0
15	2-Br	1.6053(23)	4	2
16	2-CF_3	1.5480(26)	3	1
17	2-NO_2	109–110	0	0

[a] Fungicidal activities are expressed as in Table 1. Abbreviation, see Table 1.

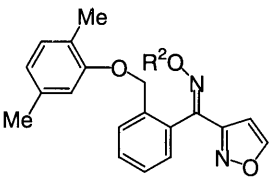
Table 3 3-[2-(Polysubstituted phenoxymethyl)-α-methoxyiminobenzyl]-isoxazoles and their fungicidal activities against cucumber and wheat powdery mildews by preventive application.



Compound No.	X	mp (°C) or n_D(°C)	Fungicidal activity[a] Sf	Eg
18	2,4-F_2	75.5–76.5	4	2
19	2,5-F_2	67–68	3	2
20	2,4-Cl_2	107–108	4	0
21	2,5-Cl_2	93–94	4	3
22	2,6-Cl_2	102.5–103.5	3	0
23	3,4-Cl_2	1.5971(26)	3	2
24	2,3,5-Cl_3	137–138.5	1	0
25	2,3-Me_2	106.5–108	4	2
26	2,4-Me_2	1.5782(23)	4	2
27	2,5-Me_2	95–96	4	4
28	2,6-Me_2	1.5744(26)	2	2
29	3,4-Me_2	1.5805(22)	3	2
30	2,3,5-Me_3	110.5–111.5	4	4
31	4-Cl-2-Me	85–86	4	3

[a] Fungicidal activities are expressed as in Table 1. Abbreviation, see Table 1.

Table 4 3-[2-(2,5-Dimethylphenoxymethyl)-α-alkoxyiminobenzyl] isoxazoles and their fungicidal activities against cucumber and wheat powdery mildews by preventive application.



Compound No.	R^2	mp (°C) or n_D (°C)	Fungicidal activity[a] Sf	Eg
32	H	142–143	2	0
27	Me	95–96	4	4
33	Et	90–91	0	0
34	Pr	81–83	0	0
35	*i*-Pr	101–103	0	0
36	Allyl	87–88	0	0

[a] Fungicidal activities are expressed as in Table 1. Abbreviation, see Table 1.

Table 5 Antifungal activities of selected compounds **10**, **27** and **30** against *Pseudocercos orella her otrichoides*.

Antifungal activity	Test compound				
	10	**27**	**30**	SSF-129[a]	Prochloraz
EC_{50} (ppm)	1.42	1.05	3.90	1.09	0.04

[a] (*E*)-2-[2-(2,5-Dimethylphenoxymethyl)phenyl]-2-methoxyimino-*N*-methylacetamide.

Table 6 Disease control activities of selected compound **27** against wheat eye spot and wheat powdery mildew (field test).

Test compound	Treatment (ppm)	Eye spot		Powdery mildew	
		Degree of infection (%)	Disease control (%)	Infected leaf area (%)	Disease control (%)
27	400	19.8	76	5.8	86
	100	36.9	56	9.3	78
SSF-129	400	36.7	56	15.5	63
	100	66.5	20	13.0	69
Prochloraz[a]	400	28.3	66	—	—
	100	63.5	23	—	—
Triadimefon[b]	125	—	—	1.4	97
Untreated	—	82.9	—	37.8	—

[a] Sportak® 25% EC (Nissan Chemical Ind., Ltd.) [b] Bayleton® 25% WP (Nihon Bayer Agrochem K.K.).

causes wheat eye spot, were assessed (Table 5). Compound **27** showed almost the same antifungal activity as SSF-129, but was inferior to commercially available fungicide, prochloraz.

3. *Field Test of Compound 27*

Controlling activity of compound **27** against wheat powdery mildew and wheat eye spot was assessed under field conditions (Table 6).

Compound **27** showed better control at 100 ppm by preventive application against wheat eye spot than SSF-129 and prochloraz regardless of the *in vitro* EC_{50} values. However, the activity of this compound against wheat powdery mildew was inferior to that of commercially available fungicide, triadimefon. The reasons were not clear from our experiments why the controlling activity of prochloraz against wheat eye spot under field condition was inferior to that of compound **27**, in spite of superior activity on mycelial growth inhibitory activity in vitro.

Our studies indicated that the 3-[2-(substituted phenoxymethyl)-α-methoxyiminobenzyl]isoxazole derivatives, a new class of fungicides, are highly effective against cucumber powdery mildew, wheat powdery mildew and wheat eye spot. Modification of the isoxazole ring of 3-[2-(substituted phenoxymethyl)-α-methoxyiminobenzyl]isoxazoles will be reported elsewhere.

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要　　約

3-(α-アルコキシイミノベンジル)イソオキサゾール誘導体の合成と殺菌活性

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種々の3-(α-アルコキシイミノベンジル)イソオキサゾール誘導体を合成し，アルコキシイミノ部分およびベンゼン環2位の置換基と殺菌活性における構造と活性相関を調べた．その結果，アルコキシイミノ部分はメトキシイミノ基，ベンゼン環の2位はフェノキシメチル基を導入した化合物がキュウリうどんこ病とコムギうどんこ病に対して優れた殺菌活性を示した．中でも，3-[2-(2,5-ジメチルフェノキシメチル)-α-メトキシイミノベンジル]イソオキサゾール(**27**)は，圃場試験においてコムギうどんこ病およびコムギ眼紋病に対して高い防除活性を示した．