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Original Article

Synthesis and Herbicidal Activity of New Oxazolidinedione Derivatives

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A series of new 3-(substituted phenyl)-5-alkylidene-1,3-oxazolidine-2,4-dione derivatives was synthesized by reacting substituted phenyl isocyanates with 2-hydroxy-3-alkenoates prepared through an acid-catalyzed isomerization of 3,3-disubstituted glycidates, and their herbicidal activities against various weeds as well as the crop safeties were examined.[1,2] The herbicidal activities of these oxazolidinedione derivatives were primarily influenced by the substituents on the phenyl group and by the structure of the alkylidene moiety. The compounds having a 2,4-dihalo-5-alkoxyphenyl moiety exhibited relatively higher herbicidal activities while the introduction of a long chain alkylidene group at the 5-position of the oxazolidine ring reduced the activity. The crop safety was found to be markedly affected by the substituent at the 5-position of the phenyl group and a cyclopentyloxy group seemed to be the most preferable one. Among the compounds synthesized, 3-(4-chloro-5-cyclopentyloxy-2-fluorophenyl)-5-isopropylidene-1,3-oxazolidine-2,4-dione (KPP-314) was selected as a promising paddy rice herbicide. In greenhouse pot tests, KPP-314 exhibited an excellent activity against annual lowland weeds by pre- and post-emergence soil treatments at 150 to 450 g a.i./ha with a wide safety margin between rice plant and *Echinochloa oryzicola.*

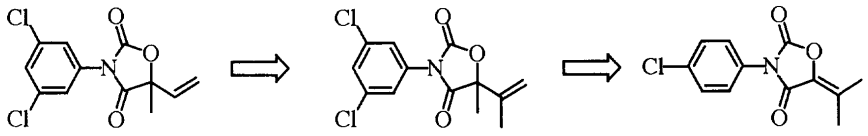
Key words: KPP-314, cyclic imide, Protox inhibitor, peroxidizing herbicide, rice, *Echinochloa oryzicola.*

INTRODUCTION

Various cyclic imide-type compounds with high herbicidal activities and excellent crop selectivities have been synthesized and some of them are being used practically as herbicides in Japan and other countries. Their biochemical mode of action has been known to be the inhibition of protoporphyrinogen-IX oxidase (Protox) in the plant chlorophyll biosynthesis.[3,4]

In the course of our synthetic studies on the structural modification of oxazolidinedione fungicides such as vinchlozolin[6] through a prototype lead compound (**15**), we found that 3-(4-chlorophenyl)-1,3-oxazolidine-2,4-dione derivative (**3**) bearing an isopropylidene group at the 5-position of the oxazolidine ring exhibited a good herbicidal activity against several lowland weeds (Fig. 1). A few 5-(substituted alkylidene)-1,3-oxazolidine-2,4-dione derivatives have already been known, but their herbicidal activities have not been reported so far.[5–8] Therefore, a large number of new oxazolidinedione derivatives carrying various substituents on the phenyl group at the 3-position of the oxazolidine ring were synthesized and their herbicidal activities and crop safeties were evaluated to discover novel cyclic imide-type herbicides. As a result of the skeletal modifications, a series of 3-(5-alkoxy-2-fluoro-4-chlorophenyl)-5-isopropylidene-1,3-oxazolidine-2,4-dione derivatives was found to be highly active against many broadleaf and several grass weeds examined. Through the subsequent extensive evaluations, 3-[5-(1-butyn-3-yl) oxy-4-chloro-2-fluorophenyl]-5-isopropylidene-1,3-oxazolidine-2,4-dione (**31**; KPP-300) and 3-[4-chloro-5-cyclopentyloxy-2-fluorophenyl]-5-isopropylidene-1,3-oxazolidine-2,4-dione (**25**; KPP-314) were selected as the two most active ones among the synthesized derivatives.

The herbicidal spectrum of these oxazolidinedione derivatives was similar to that of other cyclic imide-type herbicides and light was essential for the herbicidal activity. Furthermore, the compounds **25** and **31** severely inhibited the growth of *Senedesmus acutus* cells at 10^{-5} M with degrading the chlorophyll of the cells and causing a high ethane formation.[9] Consequently, these new oxazolidinedione derivatives were thought to be classified into the peroxidizing herbicides including tetra-



vinchlozolin Prototype lead compound (**15**) Lead compound (**3**)

Fig. 1 Generation of new oxazolidinedione derivatives.

hydrophthalimides and diphenyl ethers. KPP-314 thus obtained has been developed collaboratively Sagami Chemical Research Center and Kaken Pharmaceutical Co. Ltd., and various products containing KPP-314 as an active ingredient have been registered and marketed in Japan.

MATERIALS AND METHODS

1. Synthesis of Compounds

1.1 General procedure

On the typical synthetic routes [Route-A and B] *via* alkyl (2,4-dihalophenyl) carbonates (**ii**) or bis(2,4-dihalophenyl) carbonates (**xii**) to 3-(5-alkoxy-2,4-dihalophenyl)-5-alkylidene-1,3-oxazolidine-2,4-dione derivatives (**xi**) as outlined in Fig. 2, the substituted phenyl isocyanates (**ix**), the most important intermediates, were easily prepared by phosgenation of the corresponding aniline derivatives (**viii**). In both routes for the synthesis of aniline derivatives (**viii**) from 2,4-dihalophenols (**i**), the hydroxy group of **i** had to be protected by an electron-withdrawing group such as an alkoxycarbonyl group for regio-selective nitration at the *meta* position.

By Route-A, the alkyl phenyl carbonates (**ii**) were nitrated regio-selectively according to the conventional method,[10] and the nitro compounds (**iii**) obtained were hydrogenated with transition metal catalysts such as palladium on charcoal or platinum oxide, yielding 2,4-dihalo-5-alkoxycarbonyloxyanilines (**iv**). Alkylation of *N*-protected phenols (**vi**) prepared by carbamation of **iv** and subsequent hydrolysis of **v** gave the desired 5-alkoxy-2,4-dihaloanilines (**viii**) after deprotection of *O*-alkylated carbamates (**vii**).

In addition, since it has been known that a phenoxycarbonyl group as a protective group of the hydroxy group is also effective for regio-selective nitration, we have developed another route [Route-B] *via* bis(2,4-dihalophenyl) carbonates (**xii**) which were prepared by carbonation of two equivalents of 2,4-dihalophenols (**i**) with phosgene gas or its dimer in aqueous alkaline solution. The bisphenyl carbonates (**xii**) thus obtained were readily nitrated regio-selectively at the *meta* positions according to a common nitration method. Then, the nitro compounds (**xiii**) were hydrogenated to the aniline derivatives (**xiv**).[11] Although direct alkylation of **xiv** with several alkylating reagents in a two-phase system consisting of organic solvent and aqueous alkaline solution gave the desired 5-alkoxy-2,4-dihaloanilines (**viii**) through one-pot reactions,[12,13] better overall yields were observed when, after finishing the protection of a pair of amino groups by alkoxycarbonyl groups, the hydrolysis of the carbonate bond and alkylation of the phenoxide produced were carried out stepwise or simultaneously to give alkyl *N*-(2,4-dihalo-5-alkoxyphenyl)carbamates (**vii**). Then, the carbamates (**vii**) were deprotected in alkaline solution affording 5-alkoxy-2,4-dihaloanilines (**viii**).

5-Alkoxy-2,4-dihaloanilines (**viii**) were converted to the key intermediates, 5-alkoxy-2,4-dihalophenyl isocyanates (**ix**), by phosgenation using phosgene or its dimer. Finally, the substituted phenyl isocyanates (**ix**) reacted with 2-hydroxy-3-alkenoate (**x**) under basic conditions to give the final 3-(2,4-dihalo-5-alkoxyphenyl)-5-alkylidene-1,3-oxazolidine-2,4-dione derivatives (**xi**).

On the other hand, 5-alkoxycarbonyloxy-2,4-dihalophenyl isocyanates (**xvi**) prepared from the corresponding anilines (**iv**) could be used as different key intermediates for the synthesis of oxazolidinedione derivatives (**xi**) through Route-C in Fig. 2. The condensation of **xvi** with 2-hydroxy-3-alkenoates (**x**) gave 5-alkylidene-1,3-oxazolidine-2,4-diones (**xvii**), which were converted into the final products (**xi**) by selective hydrolysis of the carbonate group and subsequent alkylation at the 5-position of the phenyl group. By employing this route, 3-(substituted phenyl)-5-alkylidene-1,3-oxazolidine-2,4-dione derivatives with a variety of substituent at the 5-potion of the phenyl group could easily be synthesized.

1.2 Typical procedure

Typical synthetic procedures employed are described as follows with examples. All melting points were measured by Yanagimoto or Büchi B-530 melting point apparatus. The chemical structures were confirmed by NMR spectrometers (Bruker AM-400 NMR, DPX-250 NMR or EM-390 NMR, Internal standard: tetramethylsilane) and IR spectrophotometers (Jasco A-202 and FT/IR-5300, Method: potassium bromide disk and sodium chloride liquid film cell).

1.2.1 Synthesis of alkyl N-(2-chloro-4-fluoro-5-hydroxyphenyl)carbamate

(1) Synthesis of ethyl (2-chloro-4-fluoro-5-hydroxyphenyl)carbamate via the methyl carbonate [Route-A]

a) Synthesis of 4-chloro-2-fluoro-5-(methoxycarbonyloxy)aniline

To an ethanol (600 ml) solution of methyl (2-chloro-4-

fluoro-5-nitrophenyl) carbonate (52.1 g, 0.24 mol) was added platinum dioxide (1.5 g) and the mixture was stirred under hydrogen atmosphere until no hydrogen gas was absorbed. After removal of the catalyst by filtration, the solvent and water in the filtrate was azeotropically evaporated under reduced pressure to give

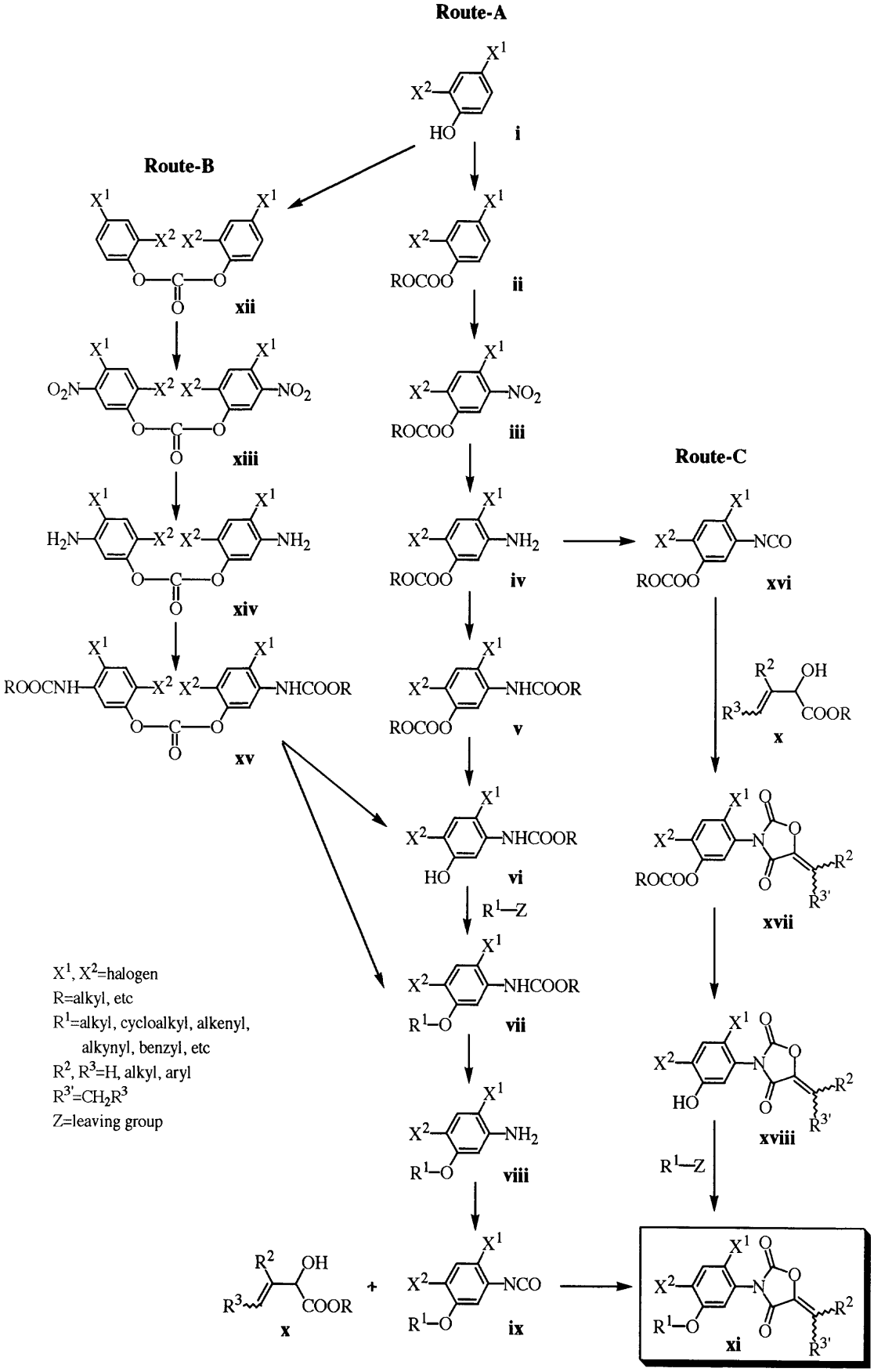


Fig. 2 Synthetic routes for 3-(2,4-dihalo-5-alkoxyphenyl)-5-alkylidene-1,3-oxazolidine-2,4-dione derivatives.

a slightly reddish brown oil of 4-chloro-2-fluoro-5-(methoxycarbonyloxy)aniline quantitatively. ^{1}H-NMR($CDCl_3$, TMS, ppm): δ 3.86 (3H, s), 4.13 (2H, br s), 6.48 (1H, d, J_{HF}=8.0 Hz), 6.92 (1H, d, J_{HF}=10.0 Hz).

b) Synthesis of ethyl N-[4-chloro-2-fluoro-5-(methoxycarbonyloxy)phenyl]carbamate

To an acetone (300 ml) solution of 4-chloro-2-fluoro-5-(methoxycarbonyloxy)aniline (22.0 g, 100 mmol) and potassium carbonate (13.8 g, 100 mmol) was added ethyl chloroformate (16.3 g, 150 mmol) at room temperature and the mixture was heated at 60°C with stirring for 5 hr. After the completion of the reaction, the solvent was removed under reduced pressure. To the residue obtained was added 1 N hydrochloric acid (100 ml) and then extracted with ethyl acetate (100 ml×3). The organic layers combined were washed with water and dried over anhydrous magnesium sulfate. The white solid obtained by removal of the solvent was recrystallized from toluene/hexane to give ethyl *N*-[4-chloro-2-fluoro-5-(methoxycarbonyloxy)phenyl]carbamate (23.3 g, 80 mmol) in 80% yield as white crystals. Mp: 143.8–147.2°C; ^{1}H-NMR ($CDCl_3$, TMS, ppm): δ 1.13 (3H, t, J=6.5 Hz), 3.92 (3H, s), 4.23 (2H, q, J=6.5 Hz), 6.80 (1H, br s), 7.15 (1H, d, J_{HF}=10.5 Hz), 8.12 (1H, d, J_{HF}=8.0 Hz).

c) Synthesis of ethyl N-(4-chloro-2-fluoro-5-hydroxyphenyl)carbamate

A mixture of ethanol (200 ml), water (100 ml), ethyl *N*-[4-chloro-2-fluoro-5-(methoxycarbonyloxy)phenyl]carbamate (45.2 g, 155 mmol) and potassium carbonate (21.4 g, 155 mmol) was refluxed for 2 hr. After the completion of the reaction, the solvent was removed under reduced pressure. To the residue obtained was added 1 N hydrochloric acid (300 ml) and then extracted with ethyl acetate (100 ml×3). The organic layers combined were washed with water and dried over anhydrous magnesium sulfate. The white solid obtained by removal of the solvent was recrystallized from chloroform/hexane to give ethyl *N*-(4-chloro-2-fluoro-5-hydroxyphenyl)carbamate (35.2 g, 151 mmol) in 97% yield as a white solid. Mp: 143.8–147.2°C; ^{1}H-NMR ($CDCl_3$, TMS, ppm): δ 1.32 (3H, t, J=7.2 Hz), 4.23 (2H, q, J=7.2 Hz), 6.80 (1H, br s), 7.04 (1H, d, J_{HF}=10.5 Hz), 7.85 (1H, d, J_{HF}=7.5 Hz).

(2) Synthesis of methyl (2-chloro-4-fluoro-5-hydroxyphenyl)carbamate via diphenyl carbonate [Route-B]

a) Synthesis of bis(2-chloro-4-fluoro-5-nitrophenyl) carbonate

To a methylene chloride (2.5 *l*) solution of 2-chloro-4-fluorophenol (733 g, 5.0 mol) in a three-necked flask equipped with a mechanical stirrer, 4 N sodium hydroxide solution (1.35 *l*) was added with cooling in an ice-cold water bath. To the solution was introduced phosgene gas generated by decomposing trichloromethyl chloroformate (243 g, 1.23 mol) on an active charcoal (3.8 g) at 40–50°C. After introduction of phosgene gas, the reaction solution was further stirred overnight at room temperature. Then, the organic layer was separated, and the aqueous layer was extracted with methylene chloride (500 ml×2). The organic layers combined were washed with 1 N sodium hydroxide solution (1.0 *l*) and water, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give a white solid of bis(2-chloro-4-fluorophenyl) carbonate (801 g, 2.5 mol) quantitatively. Mp: 91.0–92.0°C; ^{1}H-NMR ($CDCl_3$, TMS, ppm): δ 6.87–7.0 (6H, m). Thus obtained bis(2-chloro-4-fluorophenyl) carbonate (801 g, 2.5 mol) was put in a three-necked flask equipped with a mechanical stirrer and a dropping funnel, and sulfuric acid (98%, 2.0 *l*) was added with stirring well. To the suspension, a mixed acid prepared from nitric acid (60%, 400 ml) and sulfuric acid (98%, 400 ml) was added dropwise with vigorous stirring over a period of 7 hr. After addition, the mixture was stirred vigorously for further 1 hr and then poured into cold water (5.0 *l*). The white solid precipitated was filtrated, washed with water and well dried to give bis(2-chloro-4-fluoro-5-nitrophenyl) carbonate (1026 g, 2.5 mol) quantitatively. Mp: 165.0–165.5°C (recrystallized from toluene); ^{1}H-NMR ($CDCl_3$, TMS, ppm): δ 7.58 (2H, d, J_{HF}=9.9 Hz), 8.25 (2H, d, J_{HF}=8.3 Hz).

b) Synthesis of bis(5-amino-2-chloro-4-fluorophenyl) carbonate

Bis(2-chloro-4-fluoro-5-nitrophenyl) carbonate (233 g, 0.57 mol), toluene (2.3 *l*) and 5% Pd on charcoal (17.4 g) were put in a three-necked flask equipped with a mechanical stirrer, and hydrogen gas was introduced thereinto with vigorous stirring. By controlling a rate of introduction of hydrogen gas, the reaction temperature was maintained at 50–60°C. After the completion of the reaction, the mixture was heated at about 80°C, and the catalyst was recovered by filtration. The toluene layer separated from the filtrate was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give a white solid of bis(5-amino-2-chloro-4-fluorophenyl) carbonate (143 g, 0.41 mol) in 72% yield. Mp: 136.0–137.0°C; ^{1}H-NMR ($CDCl_3$, TMS, ppm): δ 3.83 (4H, br s), 6.71 (2H, d, J_{HF}=8.5 Hz), 7.08 (2H, d, J_{HF}=10.5 Hz).

c) Synthesis of methyl N-(4-chloro-2-fluoro-5-hydroxyphenyl)carbamate

To an acetone (1.5 *l*) solution of bis(5-amino-2-chloro-4-fluorophenyl) carbonate (233 g, 0.68 mol) and potassium carbonate (188 g, 1.36 mol), methyl chloroformate (126 g, 1.33 mol) was added dropwise at room temperature, and the mixture was stirred for 4 hr at 60°C. The resulting mixture was condensed by evaporation, acidified with acetic acid and poured into cold water. The solid deposited was filtrated, washed with water and

well dried to give bis[2-chloro-4-fluoro-5-(methoxycarbonylamino)phenyl] carbonate (279 g, 0.60 mol) in 88% yield as a white solid. Mp: 212.0–214.0°C; ^{1}H-NMR ($CDCl_3$, TMS, ppm): δ 3.80 (6H, s), 6.87 (2H, br s), 7.19 (2H, d, J_{HF}=10.2 Hz), 7.22 (2H, d, J_{HF}=8.3 Hz). Thus obtained bis[2-chloro-4-fluoro-5-(methoxycarbonylamino)phenyl] carbonate (270 g, 0.60 mol), potassium carbonate (83 g, 0.6 mol) and methanol (1.5 *l*) were put in a three-necked flask equipped with a reflux condenser, and the mixture was heated at 50°C for 2 hr with stirring. Then, methanol was removed off by distillation and the solid obtained was dissolved in acetic acid (100 ml) and poured into ice-cold water. The white solid deposited was filtrated, washed with water and fully dried to give a white solid of methyl *N*-(4-chloro-2-fluoro-5-hydroxyphenyl)carbamate (263 g, 1.20 mol) quantitatively. Mp: 140.0–141.0°C; ^{1}H-NMR ($CDCl_3$, TMS, ppm): δ 3.79 (3H, s), 5.53 (1H, s), 6.75 (1H, br s), 7.05 (1H, d, J_{HF}=10.5 Hz), 7.82 (1H, d, J_{HF}=7.5 Hz).

1.2.2 Synthesis of substituted phenyl isocyanates

(1) Synthesis of 4-chloro-5-cyclopentyloxy-2-fluorophenyl isocyanate

a) Synthesis of methyl N-(4-chloro-2-fluoro-5-cyclopentyloxyphenyl)carbamate

An acetone (7.5 *l*) solution of methyl *N*-(4-chloro-2-fluoro-5-hydroxyphenyl)carbamate (1.64 kg, 7.47 mol), cyclopentyl *p*-toluenesulfonate (1.80 kg, 7.48 mol), potassium carbonate (1.03 kg, 7.46 mol) and potassium iodide (12.3 g, 1.0 mol%) in a three-necked flask (10 *l*) equipped with a mechanical stirrer and a reflux condenser was heated under reflux for 4 hr. The mixture was acidified with 0.5 N hydrochloric acid (20 *l*) with vigorous stirring. The white solid deposited was isolated by filtration, washed well with water, and then dried to give methyl *N*-(4-chloro-2-fluoro-5-cyclopentyloxyphenyl) carbamate (2.0 kg, 6.95 mol) in 93% yield. Mp: 120.0–123.0°C (recrystallized from toluene); ^{1}H-NMR ($CDCl_3$, ppm, TMS): δ 1.62 (2H, m), 1.86 (2H, m), 1.90 (4H, m), 3.80 (3H, s), 4.79 (1H, m), 6.82 (1H, br s), 7.09 (1H, d, J_{HF}=10.4 Hz), 7.86 (1H, br d, J_{HF}=5.8 Hz).

b) Synthesis of 4-chloro-5-cyclopentyloxy-2-fluoroaniline

To an ethanol (3.0 *l*) solution of methyl *N*-(4-chloro-2-fluoro-5-cyclopentyloxyphenyl)carbamate (2.25 kg, 7.85 mol) was added 4 N sodium hydroxide solution (4.75 *l*), and the mixture was heated under reflux for 5 hr. The resulting mixture was cooled to room temperature, diluted with water (5.0 *l*), and extracted with toluene (5.0 *l*×2). The organic layers combined were washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 4-chloro-5-cyclopentyloxy-2-fluoroaniline (1.75 kg, 7.62 mol) in 98% yield as pale orange liquid. Bp: 143–145°C/1.5 mmHg; ^{1}H-NMR ($CDCl_3$/DMSO-d_6, ppm, TMS): δ 1.61 (2H, m), 1.86 (6H, m), 3.68 (2H, br s), 4.67 (1H, m), 6.37 (1H, d, J_{HF}=8.3 Hz), 6.99 (1H, d, J_{HF}=10.4 Hz).

c) Synthesis of 4-chloro-5-cyclopentyloxy-2-fluorophenyl isocyanate

To a toluene solution (50 ml) of trichloromethyl chloroformate (15 ml, 123 mmol) was added dropwise a toluene (50 ml) solution of 4-chloro-5-cyclopentyloxy-2-fluoroaniline (23.0 g, 100 mmol) and triethylamine (0.5 ml) with sufficient stirring under cooling in an ice-cold water bath. The reaction mixture was stirred for 1 hr at ambient temperature and then heated at 100–110°C to evaluate excess phosgene gas and hydrogen chloride gas formed. After the completion of the reaction, toluene was distilled off under reduced pressure to give a reddish brown liquid of 4-chloro-5-cyclopentyloxy-2-fluorophenyl isocyanate almost quantitatively. ^{1}H-NMR ($CDCl_3$, TMS, ppm): δ 1.50–2.10 (8H, m), 4.67 (1H, m), 6.60 (1H, d, J_{HF}=7.5 Hz), 7.12 (1H, d, J_{HF}=10.5 Hz).

(2) Synthesis of 5-(1-butyn-3-yl)oxy-4-chloro-2-fluorophenyl isocyanate

a) Synthesis of methyl N-[5-(1-butyn-3-yl)oxy-4-chloro-2-fluorophenyl]carbamate

An acetonitrile (0.6 *l*) solution of methyl *N*-(4-chloro-2-fluoro-5-hydroxyphenyl)carbamate (146 g, 0.66 mol), 1-butyn-3-yl *p*-toluenesulfonate (149 g, 0.66 mol), potassium carbonate (91.7 g, 0.66 mol) and potassium iodide (12.3 g, 1.0 mol%) in a three-necked flask (3.0 *l*) equipped with a mechanical stirrer and a reflux condenser was heated under reflux for 3 hr. The mixture was poured into 1 N hydrochloric acid (1.5 *l*) with stirring. The pale brown solid deposited was isolated by filtration, washed well with water, and then dried to give methyl *N*-[5-(1-butyn-3-yl)oxy-4-chloro-2-fluorophenyl] carbamate (136 g, 0.50 mol) in 86% yield. Mp: 78.0–80.0°C; ^{1}H-NMR ($CDCl_3$, TMS, ppm): δ 1.71 (3H, d, J=6.3 Hz), 2.55 (1H, d, J=1.5 Hz), 3.82 (3H, s), 4.92 (1H, dq, J=6.3 and 1.5 Hz), 7.15 (1H, d, J_{HF}=10.0 Hz), 8.09 (1H, d, J_{HF}=7.5 Hz).

b) Synthesis of 5-(1-butyn-3-yl)oxy-4-chloro-2-fluoroaniline

To an ethanol (1.0 *l*) solution of methyl *N*-[5-(1-butyn-3-yl)oxy-4-chloro-2-fluorophenyl]carbamate (326 g, 1.20 mol) was added 2 N sodium hydroxide solution (0.66 *l*), and the mixture was heated under reflux for 4 hr. The resulting mixture was cooled to room temperature and poured into ice-cold water (2.0 *l*) with stirring. The pale brown solid deposited was isolated by filtration, washed well with water, and then dried to give 5-(1-butyn-3-yl)oxy-4-chloro-2-fluoroaniline (236 g, 1.10 mol) in 92% yield. Mp: 74.5–75.5°C; ^{1}H-NMR ($CDCl_3$, TMS, ppm): δ 1.63 (3H, d, J=6.3 Hz), 2.48 (1H, d, J=1.5 Hz), 3.46 (2H, br s), 4.72 (1H, dq, J=6.3 and 1.5 Hz), 6.62 (1H, d, J_{HF}=7.5 Hz), 7.01 (1H, d, J_{HF}=10.0 Hz).

c) Synthesis of 5-(1-butyn-3-yl)oxy-4-chloro-2-fluorophenyl isocyanate

To an ethyl acetate (1.5 *l*) solution of 5-(1-butyn-3-yl) oxy-4-chloro-2-fluoroaniline (300 g, 1.40 mol) in a three-necked flask equipped with a dropping funnel and a distillation apparatus was added dropwise trichloromethyl chloroformate (284 g, 1.44 mol) at room temperature, and the reaction mixture was heated at about 80–100°C with stirring to remove ethyl acetate, excess of phosgene and hydrogen chloride gas by distillation. To the residue was added carbon tetrachloride (300 ml) at room temperature and the mixture was allowed to stand for 1 hr. After the insoluble urea derivative was filtered out, the carbon tetrachloride was evaporated under reduced pressure to give a reddish brown liquid of 5-(1-butyn-3-yl)oxy-4-chloro-2-fluorophenyl isocyanate (316 g, 1.32 mol) in 94% yield. ^{1}H-NMR ($CDCl_3$, TMS, ppm): δ 1.70 (3H, d, J=7.0 Hz), 2.51 (1H, d, J=2.0 Hz), 4.78 (1H, dq, J=7.0 and 2.0 Hz), 6.90 (1H, d, J_{HF}=8.0 Hz), 7.19 (1H, d, J_{HF}=10.0 Hz).

(3) Synthesis of 4-chloro-2-fluoro-5-(methoxycarbonyloxy)phenyl isocyanate

An ethyl acetate (150 ml) solution of trichloromethyl chloroformate (19 ml, 158 mmol) was placed in a three-necked flask (500 ml) equipped with a dropping funnel and a distillation apparatus. An ethyl acetate (50 ml) solution of 4-chloro-2-fluoro-5-(methoxycarbonyloxy) aniline (21.9 g, 100 mmol) was added dropwise into the solution in 20 min at room temperature. Then, the reaction mixture was heated at about 80°C with stirring to remove ethyl acetate, excess of phosgene and hydrogen chloride gas by distillation. To the residue was added carbon tetrachloride (150 ml) at room temperature and the mixture was allowed to stand for 1 hr. After the insoluble urea derivative was filtered out, the carbon tetrachloride was evaporated under reduced pressure to give a dark brown liquid of 4-chloro-2-fluoro-5-(methoxycarbonyloxy)phenyl isocyanate (20.6 g, 84 mmol) in 84% yield. ^{1}H-NMR ($CDCl_3$, TMS, ppm): δ 3.87 (3H, s), 6.89 (1H, d, J_{HF}=6.8 Hz), 7.31 (1H, d, J_{HF}=8.6 Hz).

1.2.3 Synthesis of 1,3-oxazolidine-2,4-dione derivatives [Route-A, B]

*(1) Synthesis of 3-(4-chloro-5-cyclopentyloxy-2-fluorophenyl)-5-isopropylidene-1,3-oxazolidine-2,4-dione (**25**)*

To a toluene (40 ml) suspension of potassium carbonate (1.05 g, 7.5 mmol) and ethyl 2-hydroxy-3-methyl-3-butenoate (13.1 g, 88.2 mmol) in a flask (100 ml) was added 4-chloro-5-cyclopentyloxy-2-fluorophenyl isocyanate (19.2 g, 71.3 mmol) with stirring while maintaining the reaction temperature at room temperature. After 1 hr, the reaction mixture was heated up to 80°C and stirred for 2 hr. The resulting mixture was washed with 1 N sodium hydroxide solution (10 ml) and 1 N hydrochloric acid (10 ml), and the organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was distilled off under reduced pressure, and the residual pale brown liquid was dissolved in an approximately equal volume of hexane and allowed to stand at room temperature. White crystals deposited were isolated by filtration, washed with hexane and well dried to give 3-(4-chloro-5-cyclopentyloxy-2-fluorophenyl)-5-isopropylidene-1,3-oxazolidine-2,4-dione (21.1 g, 59.3 mmol) in 82% yield. Mp: 98–99.5°C (104.5–105°C; recrystallized from toluene/hexane); ^{1}H-NMR ($CDCl_3$, TMS, ppm): δ 1.64 (2H, m), 1.85 (2H, m), 1.90 (4H, m), 2.06 (3H, s), 2.30 (3H, s), 4.74 (1H, m), 6.84 (1H, d, J_{HF}=6.4 Hz), 7.30 (1H, d, J_{HF}=9.1 Hz).

*(2) Synthesis of 3-[5-(1-butyn-3-yl)oxy-4-chloro-2-fluorophenyl)-5-isopropylidene-1,3-oxazolidine-2,4-dione (**31**)*

To an ethyl acetate (100 ml) solution of 5-(1-butyn-3-yl)oxy-4-chloro-2-fluorophenyl isocyanate (24.0 g, 100 mmol), methyl 2-hydroxy-3-methyl-3-butenoate (14.3 g, 110 mmol) and propylene oxide (1.0 ml) in a flask (300 ml) was added dropwise an ethyl acetate (10 ml) solution of triethylamine (1.02 g, 10.0 mmol) with stirring while maintaining the reaction temperature below 50°C. Then, the mixture was heated under reflux for 2 hr. After cooling, to the resulting mixture was added 1 N hydrochloric acid and extracted with ethyl acetate (100 ml×2). The organic layers combined were washed with 1 N sodium hydroxide solution (10 ml) and 1 N hydrochloric acid (10 ml), and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and a mixture of toluene and hexane was added to the residual pale brown liquid to crystallize the desired product. Yellowish white crystals deposited were isolated by filtration, washed with hexane and well dried to give 3-[5-(1-butyn-3-yl)oxy-4-chloro-2-fluorophenyl]-5-isopropylidene-1,3-oxazolidine-2,4-dione (28.7 g, 85 mmol) in 85% yield. Mp: 102–103°C; ^{1}H-NMR ($CDCl_3$, TMS, ppm): δ 1.70 (3H, d, J=6.0 Hz), 2.03 (3H, s), 2.28 (3H, s), 2.52 (1H, d, J=1.5 Hz), 4.80 (1H, dq, J=6.0 and 1.5 Hz), 7.12 (1H, d, J_{HF}=6.0 Hz), 7.32 (1H, d, J_{HF}=9.0 Hz).

1.2.4 Synthesis of 1,3-oxazolidine-2,4-dione derivatives [Route-C]

*(1) Synthesis of 3-(4-chloro-2-fluoro-5-hydroxyphenyl)-5-isopropylidene-1,3-oxazolidine-2,4-dione (**18**)*

To a benzene (50 ml) solution of 4-chloro-2-fluoro-5-(methoxycarbonyloxy)phenyl isocyanate (2.45 g, 10.0 mmol) and ethyl 2-hydroxy-3-methyl-3-butenoate (1.44 g, 10.0 mmol) was added a catalytic amount of triethylamine (0.5 ml) and the mixture was stirred for 0.5 hr at room temperature. The resulting mixture was washed with 1 N hydrochloric acid and the organic layer was dried and concentrated under reduced pressure. The

slightly yellow oil obtained was purified using a silica gel column (ethyl acetate/hexane) to give ethyl 2-[*N*-{4-chloro-2-fluoro-5-(methoxycarbonyloxy)phenyl} carbamoyloxy]-3-methyl-3-butenoate in 85% yield. Then, a benzene (20 ml) solution of ethyl 2-[*N*-{4-chloro-2-fluoro-5-(methoxycarbonyloxy)phenyl} carbamoyloxy]-3-methyl-3-butenoate (1.95 g, 5.0 mmol) and sodium acetate (20.5 mg, 0.25 mmol) was refluxed for 12 hr. The resulting mixture was washed with 1 N hydrochloric acid and the organic layer was dried and concentrated under reduced pressure. The oily product obtained was purified using a silica gel column (ethyl acetate/hexane) to give 3-[4-chloro-2-fluoro-5-(methoxycarbonyloxy)phenyl]-5-isopropylidene-1,3-oxazolidine-2,4-dione (1.27 g, 4.69 mmol) in 74% yield. ^{1}H-NMR ($CDCl_3$, TMS, ppm): δ 2.05 (3H, s), 2.28 (3H, s), 3.95 (3H, s), 7.32 (1H, d, J_{HF}=6.0 Hz), 7.42 (1H, d, J_{HF}=8.5 Hz). A methanol (100 ml) solution of 3-[4-chloro-2-fluoro-5-(methoxycarbonyloxy)phenyl]-5-isopropylidene-1,3-oxazolidine-2,4-dione (3.44 g, 10.0 mmol) and potassium carbonate (1.38 g, 10.0 mmol) was heated with stirring under reflux for 2 hr. The resulting mixture was quenched with saturated ammonium chloride solution (100 ml) and extracted with ether (100 ml×3). The organic layers combined were dried over anhydrous magnesium sulfate and condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 3-(4-chloro-2-fluoro-5-hydroxyphenyl)-5-isopropylidene-1,3-oxazolidine-2,4-dione (1.60 g, 5.60 mmol) as a pale yellow solid in 56% yield. Mp: 133–135°C (141–142.5°C; recrystallized from toluene); ^{1}H-NMR ($CDCl_3$, TMS, ppm): δ 2.06 (3H, s), 2.30 (3H, s), 5.68 (1H, s), 7.00 (1H, d, J_{HF}=6.5 Hz), 7.28 (1H, d, J_{HF}=8.7 Hz).

*(2) Synthesis of 3-(4-chloro-2-fluoro-5-propargyloxyphenyl)-5-isopropylidene-1,3-oxazolidine-2,4-dione (**29**) by alkylation of 3-(4-chloro-2-fluoro-5-hydroxyphenyl)-5-isopropylidene-1,3-oxazolidine-2,4-dione*

An acetonitrile (30 ml) solution of 3-(4-chloro-2-fluoro-5-hydroxyphenyl)-5-isopropylidene-1,3-oxazolidine-2,4-dione (0.72 g, 2.52 mmol) and sodium carbonate (0.16 g, 1.51 mmol) was heated under reflux for 1 hr. After addition of propargyl bromide (0.60 g, 3.0 mmol), the mixture was further refluxed for another hour. The resulting mixture was quenched with 0.1 N hydrochloric acid (50 ml) and extracted with chloroform (25 ml×3). The organic layers combined were dried and evaporated to give a pale yellow oil, which was purified by silica gel column chromatography (ethyl acetate/hexane) to give 3-(4-chloro-2-fluoro-5-propargyloxyphenyl)-5-isopropylidene-1,3-oxazolidine-2,4-dione (0.53 g, 1.64 mmol) in 65% yield. Mp: 134–135.5°C; ^{1}H-NMR ($CDCl_3$, TMS, ppm): δ 2.06 (3H, s), 2.29 (3H, s), 2.58 (1H, t, J=1.5 Hz), 4.77 (2H, d, J=1.5 Hz), 7.07 (1H, d, J_{HF}=6.0 Hz), 7.36 (1H, d, J_{HF}=9.0 Hz).

In a similar manner, various 3-(substituted phenyl)-5-alkylidene-1,3-oxazolidine-2,4-diones were synthesized by reacting 2-hydroxy-3-butenoates with the corresponding aryl isocyanates and by alkylating 3-(2,4-dihalo-5-hydroxyphenyl)-5-alkylidene-1,3-oxazolidine-2,4-diones. Physical and spectral properties of the representative oxazolidinedione derivatives are summarized in Tables 1 and 2.

2. Evaluation of Herbicidal Activity

2.1 Evaluation with pre- and early post-emergence application under flooded conditions

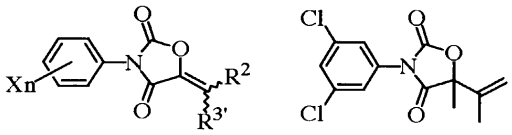
Clay loam soil (clay: 24.9%, total carbon: 1.8%, pH: 5.3) was filled in a plastic pot (30 cm^2) and puddled after addition of fertilizer. The soil containing seeds of *Cyperus difformis* (Cd), broadleaf weeds (Bl) such as *Lindernia procumbens, Rotala indica, Elatine triandra* and *Ammannia multiflora, Monochoria vaginalis* (Mv) and *Scirpus juncoides* (Sj) was spread onto the pot and then seeds of *Echinochloa oryzicola* (Eo) or *Echinochloa crus-galli* (Ec) were sown. After rice seedlings at 2-leaf stage (*Oryza sativa* (Os), cv. Koshihikari) were transplanted, the pot was maintained under flooded conditions at a 2 cm depth of water.

Each test compound was dissolved in a mixture of dimethyl sulfoxide (1.0 ml) and 1,3-dimethyl-2-imidazolidinone (0.1 ml), and the solution was diluted with water containing an emulsifier (Sorpol 2564) to give an aq. emulsion. The final concentration of Sorpol was 0.02%. Such an emulsion was gently added to the water surface at the predetermined rate just after transplanting of the rice seedlings (pre-emergence application; +0) or 7 days after the transplanting at about 1-leaf stage of Eo (early post-emergence application; +7). Fourteen days after the treatment, the weed control and rice safety were evaluated by a visual rating scale of 0 (no weed control or crop injury) to 10 (complete kill of weed and crop), and the results obtained by two replications were shown in Tables 3 to 6.

2.2 Evaluation with pre-emergence application under upland soil conditions

Gardening soil (Kureha Chemical Co.) was filled in a rectangle plastic pot (60 cm^2), and seeds of *Echinochloa crus-galli* (Ec), *Digitaria ciliaris* (Dc), *Amaranthus viridis* (Av), *Chenopodium album* (Ca), and *Zea mays* (Zm) were sown on the surface and covered with spreading a small amount of the same soil. The emulsion of each test compound prepared as described above was diluted and uniformly sprayed over the soil surface at the rate of 500 g a.i./ha. Fourteen days after the treatment, the weed control and crop safety were visually evaluated by the same rating scale described above. The results obtained by two replications were shown in Table 6.

Table 1 Physical and spectral properties of 3-(halogenated phenyl)-5-alkylidene-1,3-oxazolidine-2,4-diones.



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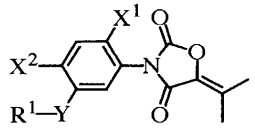
No.	Xn	R^2	$R^{3'}$	Mp (°C)	^{1}H NMR spectrum ($CDCl_3$, TMS, ppm, δ)	IR (KBr, cm^{-1})
1	2-Cl	CH_3	CH_3	103–105	2.07 (3H, s), 2.30 (3H, s), 7.32–7.50 (3H, m), 7.54–7.59 (1H, m)	1820, 1740, 1690
2	3-Cl	CH_3	CH_3	118–119	2.06 (3H, s), 2.31 (3H, s), 7.39–7.43 (3H, m), 7.51–7.53 (1H, m)	1820, 1750, 1690
3	4-Cl	CH_3	CH_3	135–135.5	2.05 (3H, s), 2.30 (3H, s), 7.43 (4H, s)	1813, 1730, 1685
4	2,4-Cl_2	CH_3	CH_3	108–108.5	2.07 (3H, s), 2.29 (3H, s), 7.28 (1H, dd), 7.41 (1H, dd), 7.58 (1H, d)	1824, 1746, 1695
5	3,4-Cl_2	CH_3	CH_3	146–149	2.05 (3H, s), 2.30 (3H, s), 7.33–7.66 (3H, m)	1814, 1735, 1688
6	3,5-Cl_2	CH_3	CH_3	112–114	2.05 (3H, s), 2.28 (3H, s), 7.37 (1H, dd), 7.50 (2H, d)	1812, 1743, 1683
7	2,4,6-Cl_3	CH_3	CH_3	177–182 (subl.)	2.08 (3H, s), 2.30 (3H, s), 7.48 (2H, s)	1810, 1753, 1685
8	4-F	CH_3	CH_3	117–119	2.03 (3H, s), 2.28 (3H, s), 7.30 (4H, m)	1819, 1722, 1683
9*)	4-Cl	CH_3	C_2H_5	79–111	1.12 and 1.15 (total 3H, each t), 2.00 and 2.23 (total 3H, each s), 2.37 and 2.70 (total 2H, each q), 7.39 (4H, s)	1820, 1740
10*)	4-F	CH_3	C_2H_5	66.5–70	1.17 (3H, t), 2.03 and 2.28 (total 3H, each s), 2.42 and 2.75 (total 2H, each q), 7. 14 (2H, dd), 7.43 (2H, m)	1818, 1728, 1690
11*)	4-Cl	CH_3	C_4H_9	57.8–67.0	0.95 (3H, m), 1.2–1.37 (4H, m), 1.83 & 2.23 (total 3H, each s), 2.13–2.60 (2H, m), 7.38 (4H, s)	1820, 1730, 1685
12*)	4-Cl	CH_3	C_6H_{13}	54.5–56.5	0.92 (3H, t), 1.35 (8H, m), 1.68 and 2.23 (total 3H, each s), 2.0–2.4 (2H, m), 7.43 (4H, s)	1817, 1730, 1690
13	4-Cl	C_2H_5	C_2H_5	100–102	1.13 and 1.15 (total 6H, each t), 2.40 (2H, q), 2.72 (2H, q), 7.43 (4H, s)	1805, 1730, 1680
14	4-Cl	$-(CH_2)_5-$		95–98	1.67 (6H, m), 2.45 (2H, t), 2.84 (2H, t), 7.39 (4H, s)	1818, 1730, 1680
15	3,5-Cl_2	—	—	94.5–96.5	1.80 (3H, s), 1.93 (3H, d), 5.17(1H, q), 533 (1H, s), 743 (3H, m)	1820, 1750

*) Mixture of *E*- and *Z*-isomers with respect to the stereochemistry of the double bonds at the 5-position of the oxazolidine ring.

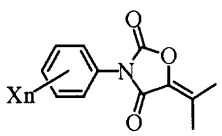
Table 2 Physical and spectral properties of 3-(2,4-dihalo-5-alkoxyphenyl)-5-alkylidene-1,3-oxazolidine-2,4-diones.



No.	X^1	X^2	Y	R^1	Mp (°C)	^{1}H NMR spectrum ($CDCl_3$, TMS, ppm, δ)	IR (KBr, cm^{-1})
16	Cl	Cl	O	$(CH_3)_2CH$	136–138	1.38 (6H, d), 2.07 (3H, s), 2.28 (3H, s), 4.53 (1H, sep), 6.96 (1H, s), 7.62 (1H, s)	1820, 1745, 1695
17	Cl	Cl	O	$HC\equiv CCH_2$	143.5–145.5	2.06 (3H, s), 2.30 (3H, s), 2.57 (1H, t), 4.77 (2H, d), 7.03 (1H, s), 7.59 (1H, s)	2140, 1804, 1740, 1685
18	F	Cl	O	H	141–142.5	2.06 (3H, s), 2.30 (3H, s). 5.68 (1H, s), 7.00 (1H, d), 7.28 (1H, d)	1820, 1735
19	F	Cl	O	CH_3	107–109	2.07 (3H, s), 2.30 (3H, s), 3.89 (3H, s), 6.86 (1H, d), 7.33 (1H, d)	1820, 1740, 1690
20	F	Cl	O	C_2H_5	80.7–81.6	1.47 (3H, t), 2.06 (3H, s), 2.30 (3H, s), 4.08 (2H, q), 6.84 (1H, d), 7.32 (1H, d)	1817, 1742, 1690
21	F	Cl	O	C_6H_{13}	49–51	0.91 (3H, t), 1.34–1.55 (6H, m), 1.83 (2H, tt), 2.06 (3H, s), 2.30 (3H, s), 3.98 (2H, t), 6.83 (1H, d), 7.32 (1H, d)	1820, 1750, 1690
22	F	Cl	O	$(CH_3)_2CH$	88–90.5	1.38 (6H, d), 2.06 (3H, s), 2.28 (3H, s), 4.44 (1H, sep), 6.85 (1H, s), 7.28 (1H, s)	1813, 1746, 1695
23	F	Cl	O	$CH_3CH_2C(CH_3)H$	oil	1.00 (3H, t), 1.32 (3H, d), 1.63–1.72 (1H, m), 1.74–1.84(1H, m), 2.06 (3H, s), 2.30 (3H, s), 4.25 (1H, tq), 6.85 (1H, d), 7.32 (1H, d)	1817, 1746, 1686
24	F	Cl	O	$CH_3CH_2C(C_2H_5)H$	40.5–40.7	0.97 (6H, t), 1.68–1.76 (4H, m), 4.09 (1H, tt), 2.06 (3H, s), 2.30 (3H, s), 6.83 (1H, d), 7.30 (1H, d)	1821, 1747, 1690
25	F	Cl	O	cyclo-C_5H_9	104.5–105	1.64 (2H, m), 1.85 (2H, m), 1.90 (4H, m), 2.06 (3H, s), 2.30 (3H, s), 4.74 (1H, m), 6.84 (1H, d), 7.30 (1H, d)	1820, 1743, 1693
26	F	Cl	S*	cyclo-C_5H_9	129–130	1.40–2.47 (8H, m), 2.04 (3H, s), 2.27 (3H, s), 3.40–3.77 (1H, m), 7.30 (1H, d), 7.32 (1H, d)	1820, 1740, 1690
27	F	Cl	O	cyclo-C_6H_{11}	73–75	1.17–1.96 (10H, m), 2.04 (3H, s), 2.28 (3H, s), 4.20 (1H, m), 6.82 (1H, d), 7.26 (1H, d)	1820, 1750, 1695
28	F	Cl	O	$H_2C=CHCH_2$	68.5–69.4	2.04 (3H, s), 2.29 (3H, s), 4.56 (2H, m), 5.27 (1H, m), 5.43 (1H, m), 5.99 (1H, m), 6.83 (1H, d), 7.28 (1H, d)	1820, 1750, 1695
29	F	Cl	O	$HC\equiv CCH_2$	134–135.5	2.06 (3H, s), 2.29 (3H, s), 2.58 (1H, t), 4.77 (2H, d,), 7.07 (1H, d), 7.36 (1H, d)	2180, 1815, 1742, 1692
30	F	Cl	S*	$HC\equiv CCH_2$	139–140	2.06 (3H, s), 2.26 (1H, t), 2.29 (3H, s), 3.62 (2H, d), 7.37 (1H, d), 7.50 (1H, d)	1807, 1740, 1680
31	F	Cl	O	$HC\equiv CC(CH_3)H$	102–103	1.70 (3H, d), 2.03 (3H, s), 2.28 (3H, s), 2.52 (1H, d), 4.80 (1H, dq), 7.12 (1H, d), 7.32 (1H, d)	2120, 1820, 1736, 1680
32	F	Br	O	$HC\equiv CCH_2$	140–142.5	2.03 (3H, s), 2.27 (3H, s), 2.57 (1H, t), 4.73 (2H, d), 7.00 (1H, d), 7.47 (1H, d)	2140, 1815, 1741, 1690

*) Sulfur-modified compounds (**26**, **30**) were synthesized from the corresponding 5-alkylthiophenyl isocyanates prepared according to the reported method. [14]

Table 3 Herbicidal activity of 3-(halogenated phenyl)-5-isopropylidene-1,3-oxazolidine-2,4-diones and other compounds with pre-emergence application under flooded conditions.



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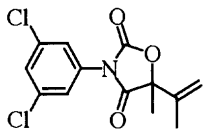

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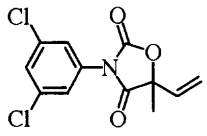
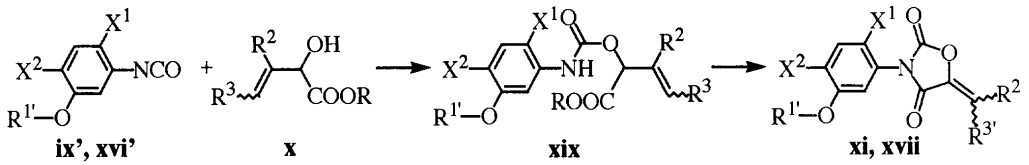


vinclozolin

Compd. No.	Xn	Herbicidal activity[a]					Injury
		Eo[b]	Cd[c]	Bl[d]	Mv[e]	Sj[f]	Os[g]
1	2-Cl	0	0	0	0	0	0
2	3-Cl	0	3	3	3	1	0
3	4-Cl	10	10	10	10	10	3[h]
4	2,4-Cl_2	10	10	10	10	10	2[h]
5	3,4-Cl_2	1	10	10	8	8	1[h]
6	3,5-Cl_2	0	3	5	5	3	0
7	2,4,6-Cl_3	3	10	10	10	2	0
15	3,5-Cl_2	8	3	6	3	2	0
vinclozolin	—	9	5	5	5	3	0

[a] Dosage: 2.5 kg a.i./ha; DAT: 14 days; Rating scale: 0 (no weed control or crop injury) -10 (complete kill of weed and crop). [b] Eo: *Echinochloa oryzicola*. [c] Cd: *Cyperus difformi*. [d] Bl: Broadleaf weeds. [e] Mv: *Monochoria vaginalis*. [f] Sj: *Scirpus juncoides*. [g] Os: *Oryza sativa*. [h] Leaf sheath browning was observed as a rice injury.



ix', xvi' **x** **xix** **xi, xvii**

X^1, X^2=halogen; R=alkyl; $R^{1'}$=alkoxycarbonyl, alkyl, cycloalkyl, alkenyl, alkynyl, benzyl, etc; R^2, R^3=H, alkyl, aryl; $R^{3'}$=CH_2R^3

Fig. 3 Reaction of substituted phenyl isocyanates with 2-hydroxy-3-alkenoates.

RESULTS AND DISCUSSION

1. Synthesis

Although 3-aryl-1,3-oxazolidine-2,4-dione derivatives could be prepared by the reaction of aryl isocyanates with 2-hydroxyalkanoates or cyanohydrins under basic conditions,[15-19] no effective method has been reported for the introduction of an alkylidene moiety at the 5-position of the oxazolidine ring. In the course of the studies on the synthesis of new oxazolidine heterocycles, we found that 2-hydroxy-3-*alkenoates* (**x**) could be used with an advantage for the introduction of the alkylidene moiety at the 5-position of the oxazolidine ring by the cyclic condensation with substituted phenyl isocyanates (**ix'** and **xvi'**) as depicted in Fig. 3. This cyclic condensation is consisted of the three successive reactions; reaction of the 2-hydroxy-3-alkenoate with the isocyanate affording carbamate derivatives (**xix**), intramolecular cycloamidation, and olefin isomerization. The carbamate derivatives (**xix**) were isolated only when the addition reaction was carried out at a low temperature. Since the olefin isomerization proceeded too fast to monitor by an usual NMR measurement, the cycloamidation and isomerization seemed to take place simultaneously. In this step, when the R^2 and $R^{3'}$ groups were different, the product obtained was a mixture of the *E*- and *Z*-isomers. When the R^2 group was a bulky group such as a substituted phenyl group, the *Z*-isomer formed predominantly due to the steric hindrance between the R^2 group and the 4-carbonyl group of the oxazolidine ring. 2-Hydroxy-3-alkenoates (**x**), the starting materials, were produced by the acid-catalyzed ring-opening isomerization of 3,3-disubstituted glycidates[20] which were prepared by the conventional Darzens condensation of carbonyl compounds with α-haloacetate in the presence of base such as sodium methoxide.

With regard to modification of the phenyl group at the 3-position of the oxazolidine ring, we employed two routes (Route-A and B) for regio-selective nitration. In the case of Route-B, it should be noted that industrially inexpensive phosgene can be used for carbonation and each intermediate (**xii**-**xv**) was easily obtained as a pure

solid by simple filtration whereas in the case of Route-A in which alkyl chloroformates had to be used for the preparation of alkyl carbonates (**ii**). Additionally, although the diphenyl carbonate bond was quite stable under acidic conditions, it was easily cleaved to give phenols (**vi**) in basic medium. Therefore, the key carbamates (**vii**) could also be synthesized in good yields by the alkylation of the phenol derivatives (**vi**) prepared *in situ* under mild basic conditions.

We have developed another synthetic route for the alkylation of the oxygen atom at the 5-position of the phenyl group. It was expected that the Route-C was synthetically much more advantageous because, by alkylating the phenol precursors (**xviii**) at the final stage, various alkyl groups could be introduced at the 5-position. However, from the viewpoint of total yield, the Route-A gave a better result than the Route-C because the yield of alkylation of the *N*-protected phenols (**vi**) was generally much higher than that of **xviii**.

2. *Herbicidal Activity and Selectivity*

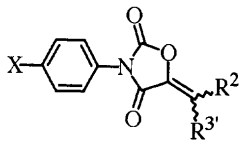
2.1 *Effects of chlorinated phenyl moiety on herbicidal activity*

The herbicidal activities of 3-(chlorinated phenyl)-1,3-oxazolidine-2,4-diones (**1**–**7** and **15**) and vinclozolin with pre-emergence application at a high rate of 2.5 kg a.i./ha are summarized in Table 3. While vinclozolin and its derivative (**15**), which are substituted with a methyl and vinyl groups at the 5-position of the oxazolidine ring, showed a strong growth inhibition against Eo and low to moderate activity against other weeds, the corresponding 5-isopropylidene derivative (**6**) bearing the same 3,5-dichlorophenyl group exhibited no growth inhibitory activity against Eo. Interestingly the 3-(4-chlorophenyl)- and 3-(2,4-dichlorophenyl)-5-isopropylidene-1,3-oxazolidine-2,4-diones (**3** and **4**), however, showed potent herbicidal activity against all the paddy weeds together with a weak rice injury owing to leaf sheath browning. On the other hand, the compounds (**1** and **2**) having a chlorine atom at the 2- or 3-position of the phenyl group were almost inactive or less active, and the compounds (**5** and **7**) having another chlorine atom at the 3- or 6-position showed also a weak activity against Eo. Consequently, in the case of 3-(chlorinated phenyl)-5-isopropylidene-1,3-oxazolidine-2,4-diones, the chlorine atom at the 4-position of the phenyl group is of importance to elicit higher herbicidal activities and further substitution with chlorine atom(s) except at the 2-position of the phenyl group is undesirable.

2.2 *Effects of 5-alkylidene moiety on herbicidal activity*

In order to elucidate the effects of the 5-alkylidene moiety on the herbicidal activity, the series of 3-(4-halogenated phenyl)-5-alkylidene-1,3-oxazolidine-2,4-diones were evaluated. Table 4 summarizes the herbicidal activities of representative 5-alkylidene oxazolidinedione derivatives (**3** and **8**–**14**) with pre-emergence application at 1.25 kg a.i./ha under flooded conditions. Among these compounds, the isopropylidene and 2-butylidene derivatives (**3** and **9**) exhibited the highest activity against Eo as well as other lowland weeds. The 2-hexylidene, 3-pentylidene, and cyclopentylidene derivatives (**11**, **13** and **14**) showed a strong activity against Cd, Bl and Mv, while their activities to Eo were poor. Above all, the herbicidal activity of 2-octylidene derivative (**12**) bearing the longest carbon chain was the lowest. A change of 4-chlorine atom to a fluorine atom (**8** and **10**) decreased the activity to Eo. In

Table 4 Herbicidal activity of 3-(4-halogenated phenyl)-5-alkylidene-1,3-oxazolidine-2,4-diones with pre-emergence application under flooded conditions.



Compd. No.	X	R^2	$R^{3'}$	Herbicidal activity[a]					Injury
				Eo[b]	Cd[c]	Bl[d]	Mv[e]	Sj[f]	Os[g]
3	Cl	CH_3	CH_3	9	10	10	10	10	1
8	F	CH_3	CH_3	1	10	4	4	0	0
9	Cl	CH_3	C_2H_5	10	10	10	10	10	2
10	F	CH_3	C_2H_5	1	10	10	10	6	0
11	Cl	CH_3	C_4H_9	4	10	10	10	10	1
12	Cl	CH_3	C_6H_{13}	1	8	4	5	1	0
13	Cl	C_2H_5	C_2H_5	1	10	10	9	3	0
14	Cl	-$(CH_2)_5$-		1	10	10	10	8	0

[a] Dosage: 1.25 kg a.i./ha; DAT: 14 days; Rating scale: 0 (no weed control or crop injury)–10 (complete kill of weed and crop). [b] Eo: *Echinochloa oryzicola*. [c] Cd: *Cyperus difformis*. [d] Bl: Broadleaf weeds. [e] Mv: *Monochoria vaginalis*. [f] Sj: *Scirpus juncoides*. [g] Os: *Oryza sativa*.

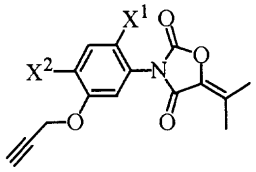
conclusion, the herbicidal activity was remarkably lowered with lengthening the carbon chain in the R^2 or $R^{3'}$ group. Similar tendency was also observed in the other 3-(2,4-dihalo-5-alkoxyphenyl)-5-alkylidene-1,3-oxazolidine-2,4-dione derivatives.

2.3 Effects of substituents at 2, 4 and 5-positions of the phenyl group

The substituent effect of 2,4-dihalogen atoms on the phenyl group was investigated by fixing the symmetrical isopropylidene group as the most effective alkylidene moiety and also fixing the substituent at the 5-position of phenyl group as a propargyloxy group which was one of the most effective group on enhancing the herbicidal activity of the oxazolidinedione derivatives. Table 5 shows herbicidal activity of 3-(2,4-dihalo-5-propargyloxyphenyl)-5-isopropylidene-1,3-oxazolidine-2,4-dione derivatives (**17**, **29** and **32**) by early post-emergence treatment at 50 g a.i./ha under flooded conditions. The herbicidal activities of all these compounds were much higher than those of the 4-halophenyl derivatives (**3** and **8**). In particular, the 2-fluoro-4-chloro derivative (**29**) exhibited the highest activity against Eo among the compounds tested.

Furthermore, it has been demonstrated that the introduction of a suitable substituent such as an alkoxy, alkylthio or alkoxycarbonyl group at the 5-position of the phenyl group is remarkably effective on enhancing both the herbicidal activity and the crop safety in the potential cyclic imide-type herbicides such as flumiclorac-pentyl,[21] fluthiacet-methyl[22] or isopropazol.[23] In fact with the present oxazolidinediones, the herbicidal activities of 4-chloro-2-fluoro-5-alkoxyphenyl derivatives were far higher than that of 2,4-

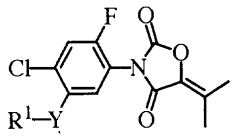
Table 5 Herbicidal activity of 3-(2,4-dihalo-5-propargyloxyphenyl)-5-isopropylidene-1,3-oxazolidine-2,4-diones with early post-emergence.



Compd. No.	X^1	X^2	Dosage (g a.i./ha)	Herbicidal activity[a] Ec[b]	Mv[c]	Am[d]
17	Cl	Cl	50	9	10	9
29	F	Cl	50	10	10	10
32	F	Br	50	8	10	10

[a] DAT: 14 days; Rating scale: 0 (no weed control or crop injury)-10 (complete kill of weed and crop). [b] Ec: *Echinochloa crus-galli* (1L). [c] Mv: *Monochoria vaginalis*. [d] Am: *Ammannia multiflora*.

Table 6 Herbicidal activity of 3-(5-alkoxy-4-chloro-2-fluorophenyl)-5-isopropylidene-1,3-oxazolidine-2,4-diones with pre-emergence application under flooded and field conditions.



Compd. No.	R^1	Y	Herbicidal activity[a] Paddy field[b] Ed[d]	Cd[e]	Bl[f]	Mv[g]	Sg[h]	Os[i]	Upland field[c] Ec[j]	Dc[k]	Av[l]	Ca[m]	Zm[n]
18	H	O	0	3	1	1	0	0	0	0	0	1	0
19	CH_3	O	3	10	10	8	1	0	6	9	8	9	3
20	C_2H_5	O	3	10	10	10	6	1	5	9	10	9	1
21	C_6H_{13}	O	1	8	7	9	6	0	1	1	10	5	0
22	$(CH_3)_2CH$	O	10	10	10	10	9	0	9	10	10	10	1
23	$CH_3CH_2C(CH_3)H$	O	8	10	10	10	10	1	2	8	9	1	0
24	$CH_3CH_2C(C_2H_5)H$	O	6	10	10	10	9	0	3	6	9	9	0
25	cyclo-C_5H_9	O	10	10	10	10	10	0	6	9	10	5	1
26	cyclo-C_5H_9	S	10	10	10	10	9	0	1	1	6	3	0
27	cyclo-C_6H_{11}	O	10	10	10	10	8	0	1	3	3	2	1
28	$H_2C=CHCH_2$	O	8	10	10	10	9	0	3	9	8	7	1
29	$HC\equiv CCH_2$	O	10	10	10	10	10	3	8	10	10	10	1
30	$HC\equiv CCH_2$	S	10	10	10	10	10	0	5	3	10	10	0
31	$HC\equiv CC(CH_3)H$	O	10	10	10	10	10	2	10	10	10	10	1
oxadiazon	—	—	9	10	10	10	10	0	10	10	10	10	4

[a] DAT: 14 days; Rating scale: 0 (no weed control or crop injury)-10 (complete kill of weed and crop), [b] Dosage: 25 g a.i./ha. [c] Dosage: 500 g a.i./ha. [d] Eo: *Echinochloa oryzicola*. [e] Cd: *Cyperus difformis*. [f] Bl: Broadleaf weeds. [g] Mv: *Monochoria vaginalis*. [h] Sj: *Scirpus juncoides*. [i] Os: *Oryza sativa*. [j] Ec: *Echinochloa crus-galli*. [k] Dc: *Digitaria ciliaris*. [l] Av: *Amaranthus viridis*. [m] Ca: *Chenopodium album*. [n] Zm: *Zea mays*.

dichloro compound (**4**) as well. Table 6 summarizes the pre-emergence herbicidal activities and crop injuries of the representative 3-(4-chloro-2-fluoro-5-alkoxyphenyl)-5-isopropylidene-1,3-oxazolidine-2,4-dione derivatives under paddy and upland soil conditions in the greenhouse.

In the case of upland soil application, the compounds with a secondary alkoxy group such as an isopropyloxy (**22**), *sec*-butyloxy (**23**), 3-pentyloxy (**24**) or cyclopentyloxy group (**25**) at the 5-position of the phenyl group showed a highly herbicidal activity among the alkyloxy- and cycloalkoxy-substituted derivatives (**19**–**27**). The activity is obviously depended on the carbon chain length of alkyl groups, and the isopropyloxy derivative (**22**) exhibited the highest activity. Introduction of an alkenyloxy or alkynyloxy group (**28**–**31**) increased the activity, and particularly, the compound **31** (KPP-300) which had the 1-butyn-3-yloxy group at the 5-position showed the highest herbicidal activity among all the compounds tested. Substitution of the oxygen atom with sulfur one at the 5-position of the phenyl group resulted in a significant loss of the activity.

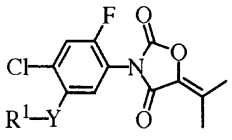
On the other hand, in the pre-emergence application under paddy soil conditions, almost all the compounds exhibited an excellent herbicidal activity against Cd, Bl, Mv and Sj even at a low dosage of 25 g a.i./ha. Regarding the herbicidal activity against Eo, the compounds (**22**, **25**, **26**, **29**, **30** and **31**) carrying a secondly alkyloxy, alkenyloxy or alkynyloxy group at the 5-position of the phenyl group, had an better efficacy than the others.

2.4 Selectivity between rice and early watergrass

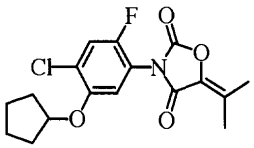
In order to investigate the influence of substituents at the 5-position of the phenyl group on the selectivity between rice and early watergrass, the phytotoxicities of typical 1,3-oxazolidine-2,4-diones (**22** and **25**–**31**) against Os and Eo were examined with pre- and early post-emergence application under flooded conditions. Results are summarized in Table 7. The value of ED_{10} means the dosage giving 10% injury to Os and ED_{90} means the effective dosage giving 90% damage to Eo, and thus, the ratio of ED_{10}/ED_{90} represents the selectivity between Os and Eo precisely.

As shown in Table 7, although the 5-alkynyloxy derivatives (**29** and **31**) exhibited a higher herbicidal activity (ED_{90}: 1.6–12.5 g a.i./ha) against Eo than the other compounds, and especially, KPP-300 (**31**) having the 1-butyn-3-yloxy group at the 5-position exhibited the highest activity, the selectivities were very low (ED_{10}/ED_{90}: 2–4) and they caused severe leaf sheath browning in rice plants even at a low dosage (ED_{10}: 6.3–25 g a.i./ha). By contrast, the herbicidal activities of the 5-cycloalkyloxy derivatives (**25** and **27**) were slightly lower (ED_{90}: 12.5–25 g a.i./ha) than those of the 5-alkynyloxy derivatives (**29** and **31**), and no injury was observed even at a high dosage of 200–800 g a.i./ha with pre- and post-emergence applications. In particular, the compound (**25**) having the cyclopentyloxy group, namely KPP-314 was confirmed to show a good efficacy for controlling Eo (ED_{90}: 200 g a.i./ha), being comparable to those of the compounds **29** and **31**, indicating that KPP-314 had the widest safety margin (ED_{10}/ED_{90}: 1.6) among the com-

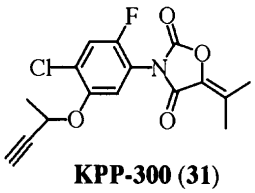
Table 7 Selectivity of 3-(5-alkoxy-4-chloro-2-fluorophenyl)-5-isopropylidene-1,3-oxazolidine-2,4-diones between rice and early watergrass.



22, 25~31



KPP-314 (25)



KPP-300 (31)

Compd. No.	R^1	Y	Phytotoxicity[a] ED_{10} (Os[d])		Activity[b] ED_{90} (Eo[e])		Select. index[c] ED_{10}/ED_{90}	
			pre[f]	post[f]	pre	post	pre	post
22	$(CH_3)_2CH$	O	100	150	25	25	4	6
25	cyclo-C_5H_9	O	200	400	12.5	25	16	16
26	cyclo-C_5H_9	S	200	800	25	100	8	8
27	cyclo-C_6H_{11}	O	200	200	25	25	8	8
28	$H_2C=CHCH_2$	O	50	100	50	100	1	1
29	$HC\equiv CCH_2$	O	6.25	25	3.13	12.5	2	2
30	$HC\equiv CCH_2$	S	50	200	12.5	100	4	2
31	$HC\equiv CC(CH_3)H$	O	6.25	12.5	1.56	6.25	4	2
oxadiazon	—	—	200	400	25	50	8	8

[a] Phytotoxicity (ED_{10}): Dosage (g a.i./ha) giving 10% injury to Os. [b] Activity (ED_{90}): Dosage (g a.i./ha) giving 90% damage to Eo. [c] Select. index (ED_{10}/ED_{90}): Ratio representing the selectivity between Os and Eo. [d] Os: *Oryza sativa*. [e] Eo: *Echinochloa oryzicola*. [f] DAT: 14 days.

pounds tested. When the 5-alkylthio derivatives **26** and **30** were compared with the corresponding 5-alkoxy derivatives **25** and **29**, respectively, replacement of the oxygen atom with sulfur was found to result in a poor herbicidal activity with early post-emergence treatment.

In conclusion, these results indicate that the substituent at the 5-position of the phenyl group primarily affects both the herbicidal activity and the crop safety of the oxazolidinedione derivatives synthesized in this study. Although the compound (**31**, KPP-300) having the 1-butyn-3-yloxy group showed the most potent herbicidal activity, the cyclopentyloxy group is the best substituent when the purpose is to screen a candidate for the selective herbicide. Further detailed characterization of KPP-314 will be described in another paper.

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要　　約

新規オキサゾリジンジオン誘導体の合成と除草活性

平井憲次，矢野智行，松川智子
鵜飼貞行，長戸松陰，堀　正大

置換フェニルイソシアネートと2-ヒドロキシ-3-アルケン酸エステルとの反応により，3位に種々の置換フェニル基を有する5-アルキリデン-1,3-オキサゾリジン-2,4-ジオン誘導体を合成し，それらの除草活性を調べた．その結果，これらオキサゾリジンジオン誘導体の除草活性は，主に3位フェニル環上の置換基と5位アルキリデン基の影響を受けることが判った．特にフェニル環2位と4位にハロゲン原子を有し，5位にアルコキシ基を有する化合物が高い活性を示し，オキサゾリジン環5位のアルキリデン基上に炭素鎖の長い置換基を導入すると活性は低下した．また，作物に対する安全性はフェニル環5位の置換基によって大きく影響を受け，特にシクロペンチルオキシ基の導入はイネに対する薬害を大幅に軽減させた．評価試験の結果に基づき，合成した一連の化合物群の中から，3-(4-クロロ-5-シクロペンチルオキシ-2-フルオロフェニル)-5-イソプロピリデン-1,3-オキサゾリジン-2,4-ジオン（KPP-314）を新しい除草剤開発候補化合物として選抜した．このKPP-314は，プレ及びポスト土壌処理により，150～450 g a.i./haの低い薬量で，ヒエや多くの1年生水田雑草に対して優れた除草活性を示し，かつイネ/ヒエ間の幅広い属間選択性を有するものであり，KPP-314を有効成分とする新しい水田用除草剤の開発に至った．