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Original Article

Syntheses and Selective Herbicidal Activities of Ethyl 2-[4-(6-Chloro-2-quinoxalinyloxy)phenoxy]propanoate and Its Related Compounds

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Several derivatives of heterocyclicoxy phenoxy propanoic acid derivatives have been known as selective herbicide. During extensive investigations on the series with various condensed heterocyclic moieties, the quinoxalinyloxy phenoxy propanoic acid derivatives were found to show an excellent herbicidal activity against grass weeds. Data of herbicidal activities of 22 derivatives of 2-[4-(2-quinoxalinyloxy)phenoxy]propanoic acid against annual and perennial weeds were described. Among them, the title compound, (code No. NCI-96683), especially showed potent herbicidal activity against both annual and perennial grasses, *i.e., Echinochloa crus-galli, Digitaria sanguinalis, Eleusine indica, Setaria viridis, Panicum dichotomiflorum, Avena fatua* and *Sorghum halepence* with no significant phytotoxicity to broadleaf crops such as *Glysine max* (soybean), *Gossypium* spp. (cotton), *Beta vulgaris* (sugarbeet) and *Brassica napus* L. (rapeseed). In the field trials, this herbicide effectively controlled annual grasses at the rate of 0.05–0.15 kg a.i./ha and perennial grasses at the rate of 0.11–0.22 kg a.i./ha. It is proposed as a potent novel post emergence herbicide.

INTRODUCTION

Recently, several derivatives of heterocyclicoxy phenoxy propanoic acid having pyridine (**III**; fluazifop), benzothiazole (fenthiaprop) or benzoxazole (fenoxaprop) as the heterocyclic moiety have been developed as selective herbicide.[1–3] They are effective for controlling gramineous weeds without any phytotoxicity to broadleaf crop plants as well as broadleaf weeds especially in a post emergence treatment. On the other hand, a phenoxy phenoxy propanoic acid derivative (**II**; diclofop) was also known as a selective herbicide.[4] We were interested in these structures and their mode of action and studied further to find new compounds having similar herbicidal activities.

When the *para* position of 2-phenoxypropanoic acid derivatives (**I**) was substituted with halogen or trifluoromethyl group, auxin activity was generally observed. However, if the same position of **I** was replaced with substituted phenoxy or pyridinyloxy group, strong grass killer property appeared and anti-auxin activity against gramineous weeds was observed in spite of the presence of its 2-phenoxypropanoic acid structure.[5–7] Therefore, these substituted phenoxy and pyridinyloxy group moiety seemed to be an important factor for the appearance of their anti-auxin property, whereas these groups are apparently a structural requirement for the high auxin activity of auxin-type herbicides such as 2,4-D, mecroprop and triclopyr.

Under the above assumptions, we paid attention to 2-(2-naphthoxy)propanoic acid derivatives which also had strong auxin type herbicidal activity. Further, it was found in

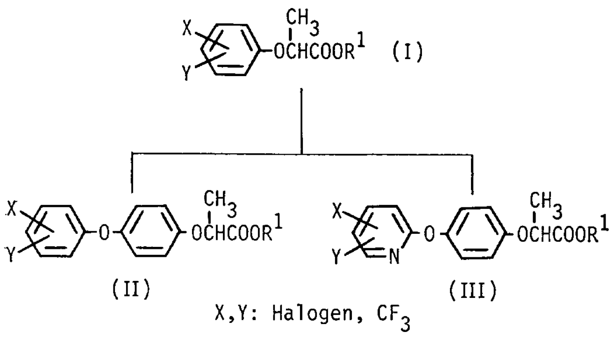


Fig. 1 The structure of grass killer herbicides.

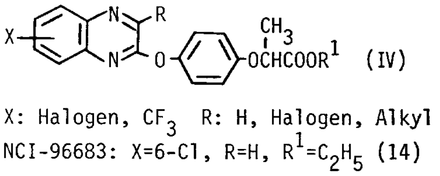


Fig. 2 2-[4-(2-Quinoxalinyloxy)phenoxy]propanoic acid derivatives.

our study that 2-(2-quinolyloxy)propanoic acid derivatives also showed similar properties.[8]

Thus, we synthesized first two series of new compounds, 2-[4-(2-quinolyloxy)phenoxy]-propanoic acid derivatives and 2-[4-(2-naphthoxy)phenoxy]propanoic acid derivatives, and found that several of their compounds showed strong grass killer activities.[9] Next, we extended this idea to other condensed heterocycles such as isoquinoline, quinazoline, phthalazine, quinoxaline and benzotriazine as the heterocyclic moiety. As a result, we found that 2-[4-(2-quinoxalinyloxy)phenoxy]propanoic acid derivatives (**IV**), especially NCI-96683 (**14**), showed excellent grass killer activities.

In this paper, we wish to report syntheses and structure activity relationship of **IV** and further to present the herbicidal activities of the most promising compound **14**.

MATERIALS AND METHODS

1. *Apparatus*

NMR spectra were obtained on a JEOL FX-90 spectrometer locked on the tetramethylsilane as an internal reference. IR spectra were measured on a JASCO A-3 Infrared Spectrometer. Mass spectra were measured on a JEOL D-300, JMA-3500 and DX-300, JMA-3100. All melting points are uncorrected.

2. *Syntheses of Compounds*

2.1 *Preparation of 2-[4-(2-quinoxalinyloxy)phenoxy]propanoic acid derivatives (**IV**) (General procedure)*[10]

Method A)

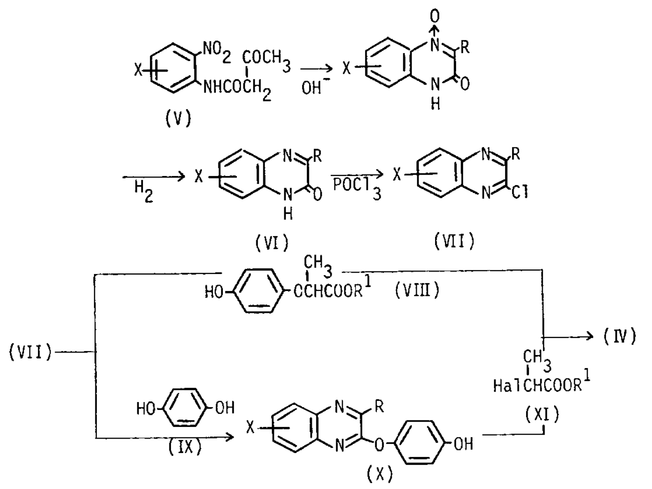
Substituted 2-chloroquinoxalines (**VII**) were condensed with 2-(4-hydroxyphenoxy)propanoic acid derivatives (**VIII**) in the presence of inorganic base such as sodium hydroxide, potassium hydroxide or anhydrous potassium carbonate in an inert solvent such as dimethylformamide, dimethyl sulfoxide or acetonitrile to afford compounds **IV**.

Method B)

4-(2-Quinoxalinyloxy)phenol derivatives (**X**) were synthesized from **VII** and hydroquinone (**IX**) in the presence of inorganic base such as sodium hydroxide, potassium hydroxide or anhydrous potassium carbonate in dimethylformamide.[11] Compounds **X** were condensed with 2-halopropanoic acid derivatives (**XI**) in a similar manner to afford compounds **IV**. Their structure was confirmed by IR, NMR and Mass spectra.

2.2 *Preparation of substituted 2-chloroquinoxaline (**VII**)*

2-Chloro-, 2,3-dichloro-, 2,6,7-trichloro- and 2-chloro-3-methylquinoxaline were purchased (Aldrich reagent). Other compounds of **VII** were prepared from substituted 2(1H)-quinoxalinones (**VI**) using Vilsmeier reagent or phosphoryl chloride. Compounds **VI** (R=H) were mainly prepared from intramolecular cyclization reaction of substituted 2′-nitroacetoacetanilides (**V**) in aqueous basic medium followed by the reduction of resulting 2(1H)-quinoxalinone 4-oxide derivatives with sodium borohydride.[12] Compounds **VI** (X=H, R=Et, *n*-Pr) were prepared by the condensation reaction of *o*-phenylenediamine with 2-ketobutylic acid or 2-oxopentanoic acid, respectively.[13] Compounds **VI** (X=6-F, 6-Cl, 6-CF_3, R=CH_3) were prepared by the intramolecular cyclization reaction of **V** in basic condition followed by the reaction of ethyl acetoacetate *in situ*.[14] These reactions are shown in Scheme 1 and a typical example of preparation of compounds **IV** is mentioned *2.3*.



Scheme 1 Synthetic routes of 2-[4-(2-quinoxalinyloxy)phenoxy]propanoic acid derivatives.

2.3 *Preparation of ethyl 2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoate (**14**) (NCI-96683)*

In 150 ml of acetonitrile, 2,6-dichloroquinoxaline (2.0 g, 10 mmol), ethyl 2-(4-hydroxyphenoxy)propanoate (2.1 g, 10 mmol) and anhydrous potassium carbonate (2.1 g, 15 mmol) were added and the mixture was refluxed for 8 hr. After cooling, the precipitate was filtered off and the filtrate was evaporated. The residue was dissolved in chloroform and washed with 5% aqueous sodium hydroxide, next with water and dried over anhydrous sodium sulfate. Removal of the solvent gave a solid, which was purified with column chromatography (silica gel, $CHCl_3$) to afford 3.2 g (yield 86%) of white crystal of **14**, mp 92–93°C. ^{1}H NMR $\delta_{TMS}^{CDCl_3}$ ppm: 1.27 (3 H, t, J=6.9 Hz), 1.63 (3 H, d, J=6.9 Hz), 4.24 (2 H, q, J=6.9 Hz), 4.74 (1 H, q, J=6.9 Hz), 6.91 (2 H, d, J=9.4 Hz), 7.18 (2 H, d, J=9.4 Hz), 7.51 (1 H, d d, J=9.2, 2.0 Hz), 7.67 (1 H, d, J=9.2 Hz), 8.01 (1 H, d, J=2.0 Hz), 8.62 (1 H, s). IR ν_{max}^{KBr} cm^{-1}: 3400, 2940, 1735, 1597, 1570, 1560, 1490, 1429, 1388, 1292, 1232, 1201, 1182, 1125, 920, 815. MS *m/z*: 372 (M^+), 299 (M^+-CO_2Et), 271 ($M^+-CH(CH_3)CO_2Et$), 244 ($M^+-CH(CH_3)-CO_2Et-CH=N$), 163.

3. *Biological Test*

3.1 Pre and post emergence herbicidal activities of compounds **1–12** were observed using gramineous plants, *Oryza sativa* (ORYSA*), *Echinochloa crus-galli* (ECHCG*), *Digitaria sanguinalis* (DIGSA*), *Eleusine indica* (ELEIN*), *Setaria viridis* (SETVI*), *Panicum dichotomiflorum* (PANDI*), *Avena fatua* (AVEFA*) and *Sorghum halepence* (SORHA*).

In soil treatment, plastic boxes having a length of 15 cm, a width of 22 cm and a depth of 6 cm were filled with a sterilized diluvium soil and seeds of above gramineous plants were sown to a depth of about 1.5 cm. Each solution of compounds **1–12** was uniformly sprayed on the surface of the soil at each dose of the active ingredient as shown in Table 1. The solution of each compound was uniformly mixed by diluting with water of wettable powder or emulsifiable concentrate. After three weeks, the herbicidal effects were observed and rated by the following standards.

Standard rating; 5: Growth inhibition of more than 90% (substantial suppression), 4: Growth inhibition of 70 to 90%, 3: Growth inhibition of 40 to 70%, 2: Growth inhibition 20 to 40%, 1: Growth inhibition of 5 to 20%, zero: Growth inhibition of less than 5% (non herbicidal effect).

In foliage treatment, when the weeds were grown to 3–4 leaf stage in same plastic boxes, each solution of the herbicidal compounds was uniformly sprayed on the foliage at a given dose rate. Two weeks after treatment, the herbicidal effects were evaluated and rated by the same manner.

3.2 The post emergence herbicidal activities and crop selectivities of compounds **1**, **6**, **8**, **10** and **12–22** were examined in greenhouse using ECHCG, DIGSA, AVEFA, SORHA, soybean, cotton, sugarbeet and rapeseed. The dose of each compound was 1.0 kg/ha and the treatment methods and rating were the same as mentioned in *3.1*.

RESULTS AND DISCUSSION

1. *Syntheses*

In the first place, facile syntheses of substituted 2-chloroquinoxalines (**VII**) were studied in detail. Although several methods have been reported to prepare 2(1 H)-quinoxalinone derivatives (**VI**) (R=H), the facile and efficient

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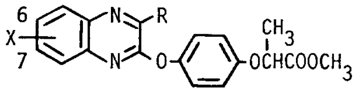
* WSSA-approved computer code from "Important Weeds of the World" 3rd ed., 1983.

one was the intramolecular cyclization of 2′-nitroacetoacetanilides (**V**) in aqueous basic medium followed by the reduction of resulting 2(1 H)-quinoxalinone 4-oxide derivatives. In this method, the selection of suitable reducing reagents were necessary to prevent the formation of 3,4-dihydro-2(1 H)-quinoxalinones. It was found that sodium borohydride and sodium hydrogensulfite were most suitable for the reduction of 2(1 H)-quinoxalinone 4-oxide derivatives. Compounds **VI** ($R=CH_3$) except for **VI** ($X=H, R=CH_3$) were newly synthesized by the method described above *2.2*.

Compounds **VI** (R=H) were chlorinated with thionyl chloride in the presence of dimethylformamide (Vilsmeier reagent) affording **VII** (R=H) in good yield. However, in the case of **VI** ($R=CH_3$), Vilsmeier reagent could not be used because it gave only polymerized materials. Compounds **VI** ($R=CH_3$) were chlorinated with phosphoryl chloride in 60–70% yield. The melting points of **VII** ($X=6$-F, $R=CH_3$), **VII** ($X=6$-Cl, $R=CH_3$) and **VII** ($X=6$-CF_3, $R=CH_3$) are 142–144°C, 128–129°C and 113–114°C, respectively.

To synthesize 2-[4-(2-quinoxalinyloxy)phenoxy]propanoic acid derivatives (**IV**), method A and B were investigated as mentioned in *2.1*. In method B, 4-(2-quinoxalinyloxy)phenol derivatives (**X**) were synthesized by the condensation of compounds **VII** and hydroquinone (**IX**) in the presence of inorganic

Table 1 2-[4-(2-Quinoxalinyloxy)phenoxy]propanoic acid derivatives and their herbicidal activities.



Compound			Rate (kg/ha)	Activity (Pre/Post)[a]							
No.	X (mp °C)	R		a	b	c	d	e	f	g	h[b]
1	H (130–132)	H	1.25	5/5	5/5	4/4	5/5	5/5	5/4	5/4	5/4
2	H (103–105)	Cl	10.0	0/1	0/1	0/2	0/0	0/0	0/0	0/0	0/0
3	H (98– 99)	Me	10.0	1/0	2/1	2/0	2/1	1/0	2/1	0/0	1/0
4	H (103–104)	Et	10.0	1/0	1/0	2/0	1/0	1/0	1/0	0/0	0/0
5	H (90– 91)	*n*-Pr	10.0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
6	6-F (124–125)	H	0.08	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5
7	6-F (107–110)	Me	10.0	2/1	3/1	3/1	2/2	2/1	2/1	2/1	1/1
8	6-Cl (124–125)	H	0.08	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5
9	6-Cl (124–126)	Me	10.0	1/1	2/1	2/1	1/1	1/1	2/1	1/1	0/0
10	6-CF_3 (93– 95)	H	0.08	3/4	5/5	5/5	5/5	5/5	5/5	5/4	5/4
11	6-CF_3 (84– 85)	Me	10.0	0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/0
12	7-Cl (103–105)	H	2.0	5/4	4/4	5/3	4/5	4/4	5/3	4/4	4/4

[a] Growth inhibition: 5, 100% kill; zero, no effect.

[b] a: *Oryza sativa*, b: *Echinochloa crus-galli*, c: *Digitaria sanguinalis*, d: *Eleusine indica*, e: *Setaria viridis*, f: *Panicum dichotomiflorum*, g: *Avena fatua*, h: *Sorghum halepence*.

base such as sodium hydroxide, potassium hydroxide or anhydrous potassium carbonate in dimethylformamide. It was found in our study that the condensation of compounds **VII** with one molar equivalent of compound **IX** in basic medium gave 1,4-bis(2-quinoxalinyloxy)benzenes first and then cleavaged to compounds **X** nucleophilically. Compounds **X** were condensed with 2-halopropanoic acid derivatives (**XI**) to afford the desired compounds **IV**. We synthesized 22 compounds of **IV** in this study by the method A and B.

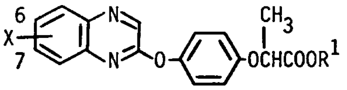
2. *Biological Activity*

In the structure and herbicidal activity relationships of compounds **IV**, the most remarkable feature for compounds **IV** was the influence of the substituent groups on 3-position of the quinoxaline ring. If 3-position of the quinoxaline ring was substituted with halogen or alkyl group, the herbicidal activity was very low even at 10 kg a.i./ha treatment. On the other hand, the same position was unsubstituted, the compounds **IV** (R=H) showed strong herbicidal activity against gramineous weeds even at 0.08–1.25 kg a.i./ha treatment.

Herbicidal activities were delicately changed by the kind, number and position of substituent groups on benzene nucleus of the quinoxaline ring. Optimization of general formula of **IV** was carried out and found that the most suitable substitution position for the activity was 6-position of the quinoxaline ring and the halogen (F, Cl, Br, I) and trifluoromethyl derivatives (compound **6**, **8**, **10**, **14**, **16**, **17** and **18**) exhibited high activity. Other substituents and positions on the benzene ring showed only weak or no activity. Compound **6**, **8**, **10**, **14**, **16**, **17** and **18**, which possessed strong grass killer activities, did not show any phytotoxicity against broadleaf crop plants such as soybean, cotton, sugarbeet and rapeseed even in 1.0 kg a.i./ha post emergence treatment.

The herbicidal activity of NCI-96683 (**14**)

Table 2 The herbicidal activities and crop selectivities of 2-[4-(2-quinoxalinyloxy)phenoxy]-propanoic acid derivatives.



Compound			mp (°C)	Activity (Post) a)							
No.	X	R¹		a	b	c	d	e	f	g	h b)
1	H	Me	130–132	4	3	3	4	0	0	0	0
13	5-Cl	Me	102–104	0	0	0	0	0	0	0	0
8	6-Cl	Me	124–125	5	5	5	5	0	0	0	0
14	6-Cl	Et	92– 93	5	5	5	5	0	0	0	0
12	7-Cl	Me	103–105	3	2	3	3	0	0	0	0
15	8-Cl	Me	72– 74	0	0	0	0	0	0	0	0
16	6,7-Cl_2	Me	113–115	5	5	5	5	0	0	0	0
6	6-F	Me	124–125	5	5	5	5	0	0	0	0
17	6-Br	Me	127–129	5	5	5	5	0	0	0	0
18	6-I	Me	120–122	5	4	5	4	0	0	0	0
10	6-CF_3	Me	93– 95	5	5	5	5	0	0	0	0
19	6-Me	Me	118–120	2	1	0	0	0	0	0	0
20	6-NO_2	Me	123–125	0	0	0	0	0	0	0	0
21	6-MeO	Me	90– 92	1	0	0	0	0	0	0	0
22	6-F_2CHO	Et	79– 81	0	0	0	0	0	0	0	0

a) Dose rate of each compound is 1.0 kg a.i./ha. Growth stage of all plants are at the 3–4 leaf stage.

b) a: *Echinochloa crus-galli*, b: *Digitaria sanguinalis*, c: *Avena fatua*, d: *Sorghum halepence*, e: *Glysine max*, f: *Gossypium* spp., g: *Beta vulgaris*, f: *Brassica napus* L.

Table 3 Field test of NCI-96683 in U.S.A.

(A) Annual grass control[a]

Rate (kg/ha)	Control (%): 21 DAT[c]		
	Large crabgrass (DIGSA)	Goosegrass (ELEIN)	Fall panicum (PANDI)
0.05	93	85	70
0.10	99	95	88

(B) Johnsongrass control[b]

Rate (kg/ha)	Johnsongrass (SORHA) control (%)			Soybean injury (%)		Soybean yield (bu./A)
	11 DAT	23	102	11	23	
0.112	97	99	99	0	0	49
0.224	99	99	100	0	0	50
Untreated	0	0	0	0	0	33

[a] Growth stage of all plants is at the 4–6 leaf stage.

[b] Growth stage of soybean and johnsongrass is at the 2.5 and 5–6 leaf stage, respectively.

[c] DAT: days after treatment.

was also evaluated in a large field in Stoneville, Mississippi, U.S.A. in 1981 and showed a remarkable post emergence herbicidal activity against both annual and perennial grasses. The field trials were carried out by randomized block design using 3–4 replications. Plot size varied from 4–20 m^2. NCI-96683 was formulated as a 10% emulsifiable concentrate and was applied with an air pressurized plot sprayer equipped with Teejet nozzles at a pressure 138–276 kPa. Herbicidal activities were determined after given treatment days as the percent range for growth inhibition which were set at zero for no inhibition (untreatment) and at 100 for complete growth inhibition by visual assessment. The results of the field trials are given in Table 3.

The weeds and crop used in this evaluation and its growth stage were as follows: large crabgrass (DIGSA; 4 to 6 leaf stage), goosegrass (ELEIN; 4 to 6 leaf stage), fall panicum (PANDI; 4 to 6 leaf stage), johnsongrass (SORHA; 5 to 6 leaf stage) and soybean (GLXMA; 2.5 trifoliate), respectively.

Control of annual grasses such as large crabgrass, goosegrass and fall panicum had usually been achieved at the rate of 0.05–0.15 kg a.i./ha and johnsongrass had been controlled at the rate of 0.11–0.22 kg a.i./ha treatment in this field test. Furthermore, the phytotoxicity to soybean was not observed and its harvest was satisfactory compared with untreated block.

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REFERENCES

1) R. Nishiyama, T. Haga & N. Sakashita (Ishihara Sangyo Kaisha Ltd.): Jpn. Tokkyo Koho JP 58–40947 (1983)

2) R. Handte, H. Bieringer, G. Hörlein & F. Schwedtle: 1982 British Crop Protection Conference Weeds, Vol. 1, p. 19, 1982

3) H. Bieringer, G. Hörlein, P. Langelüddeke & R. Handte: 1982 British Crop Protection Conference Weeds, Vol. 1, p. 11, 1982

4) H. J. Nestler: 4th International Congress of Pesticide Chemistry, Zurich, Abstr., No. II-15, 1978

5) A. F. Quereshi & W. H. Vanden Born: *Weed*

Sci. **27**, 202 (1979)

6) B. G. Todd & E. H. Stobbe: *Weed Sci.* **28**, 371 (1980)
7) F. Kimura, N. Sakashita & C. Honda: *Chem. Regul. Plants* **17** (2), 170 (1982)
8) Y. Ura, G. Sakata, K. Makino, Y. Kawamura, T. Ikai, Y. Kawamura & T. Oguchi (Nissan Chem. Ind., Ltd.): Jpn. Kokai Tokkyo Koho Jp 56–7768 (1981)
9) Y. Ura, G. Sakata, K. Makino, Y. Kawamura, T. Ikai, Y. Kawamura & T. Oguchi (Nissan Chem. Ind., Ltd.): Jpn. Kokai Tokkyo Koho Jp 55–113764 (1980)
10) Y. Ura, G. Sakata, K. Makino, Y. Kawamura, T. Ikai, Y. Kawamura & T. Oguchi (Nissan Chem. Ind., Ltd.): Jpn. Kokai Tokkyo Koho Jp 56–16475 (1981)
11) G. Sakata, I. Hashiba, K. Makino, S. Fujinawa & K. Morimoto (Nissan Chem. Ind., Ltd.): Jpn. Kokai Tokkyo Koho Jp 57–163371 (1982)
12) Y. Ura, G. Sakata, K. Makino, K. Kusano & K. Morimoto (Nissan Chem. Ind., Ltd.): Jpn. Kokai Tokkyo Koho Jp 58–188575 (1982)
13) D. C. Morrison: *J. Am. Chem. Soc.* **76**, 4483 (1954)
14) G. Tennant: *J. Chem. Soc.* **1964**, 1986

要 約

Ethyl 2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoate とその関連化合物の合成ならびに選択的除草活性

坂田五常，牧野健二，河村保夫，猪飼 隆

Ethyl 2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]-propanoate (code No. NCI-96683) は，現在日産化学工業(株)によって開発中の新しい選択性除草剤である．これまで数種の heterocyclicoxy phenoxy propanoic acid 誘導体が選択性除草剤として知られていた．本研究においてヘテロ環としてさまざまなベンゼン縮合ヘテロ環を探索合成した結果，quinoxalinyloxy phenoxy propanoic acid 誘導体，とくに NCI-96683 がすぐれたイネ科雑草に対する除草活性と広葉作物選択性を示すことを見いだした．これらの誘導体は合成原料として 2-chloroquinoxaline 誘導体と hydroquinone および α-halogenopropanoic acid 誘導体を用いて合成した．NCI-96683 は，大豆，棉，甜菜，なたねなどの広葉作物に薬害を示すことなく，イヌビエ，メヒシバ，オヒシバ，エノコログサ，オオクサキビ，カラスムギおよびセイバンモロコシなどに卓効を示した．圃場試験においては，一年生イネ科雑草に対し 0.05–0.15 kg a.i./ha，多年生イネ科雑草では 0.11-0.22 kg a.i./ha で十分な除草効果が得られた．