

光学分割法によるethyl (R)-(+)および(S)-(-)-2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy] propanoateの調製
とその除草活性

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Original Article

Preparation of Optically Pure Ethyl (*R*)-(+)- and (*S*)-(-)-2-[4-(6-Chloro-2-quinoxalinyloxy)phenoxy]propanoate by Resolution Method and Their Herbicidal ActivitiesGozyo SAKATA, Kenzi MAKINO, Kazuya KUSANO, Jun SATOW,
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Optically pure ethyl (*R*)-(+)- and (*S*)-(-)-2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoate ((*R*)-(+)-**1** and (*S*)-(-)-**1**) were synthesized from the corresponding propanoic acids ((*R*)-(+)-**1**-acid and (*S*)-(-)-**1**-acid), which were prepared from the racemic compound by optical resolution with cinchonidine and cinchonine. Both (*R*)-(+)- and (*S*)-(-)-**1**-acid were converted into the corresponding acyl chlorides followed by the reaction with ethanol in the presence of pyridine to afford optically pure (*R*)-(+)- and (*S*)-(-)-**1**, respectively. Optical purity was determined by the measurement of 200 MHz NMR spectra using Eu(HFC)₃ shift reagent and by the preferential crystallization. It became clear that optically pure (*R*)-(+)-**1** had $[\alpha]_D^{20} + 39.9^\circ$ (CHCl₃, *c*=1.20%). The growth inhibiting activity against rice plants in petridish and the post-emergence herbicidal activity against *Echinochloa crus-galli* and *Digitaria adscendens* were examined. The herbicidal activity was influenced mainly by chiral center at the propanoic acid moiety and the (*R*)-(+)-isomer was the most active.

INTRODUCTION

Ethyl 2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoate (**1**) (code No. NCI-96683)^{1,2} is a new compound with a potent, selective herbicidal activity against annual and perennial grass weeds. This compound possesses one asymmetric center on the propanoic acid moiety as shown in Fig. 1. There is great interest in the comparison of their biological activities among two enantiomers ((*R*)-(+)-**1** and (*S*)-(-)-**1**) and the racemate. In our preceding paper, the syntheses of the optical active (*R*)-(+)-**1** and (*S*)-(-)-**1** by using of ethyl (*S*)-(-)-lactate were reported.³ In this paper, we wish to report the preparation of optically pure (*R*)-(+)-**1** and (*S*)-(-)-**1** by resolution method and further to present their comparative biological activities.

MATERIALS AND METHODS

1. Apparatus

Chemical structures, chemical purities and optical rotations were determined by the same method reported in the preceding paper.^{2,3} Optical purities were confirmed by the measurement of 200 MHz NMR spectra using Eu(HFC)₃ shift reagent in carbon tetrachloride and deuteriobenzene (4:1) solution. All melting points are uncorrected.

2. Syntheses of Compounds

2.1 Optical resolution of racemic 2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoic acid

Optically pure *R*-(+)-2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoic acid ((*R*)-(+)-**1**-acid) was prepared from racemic-**1**-acid by fractional crystallization of its cinchonidine salts. The fractional crystallization of dia-

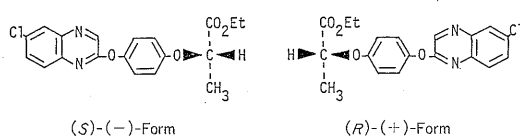


Fig. 1 Stereoisomers of ethyl 2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoate.

stereoisomer from aqueous acetonitrile was repeated six times to obtain optically pure (R)-(+)-**1**-acid, mp 156.0–157.0°C; $[\alpha]_D^{20} +29.5^\circ$ (MeOH, $c=1.00\%$); $^1\text{H NMR } \delta_{\text{DMSO}-d_6}^{\text{CDCl}_3}$ ppm: 1.55 (3 H, d, $J=6.6$ Hz), 4.76 (1 H, q, $J=6.6$ Hz), 6.89 (2 H, d, $J=8.8$ Hz), 7.19 (2 H, d, $J=8.8$ Hz), 7.55 (1 H, d d, $J=8.0, 1.8$ Hz), 7.71 (1 H, d, $J=8.0$ Hz), 7.99 (1 H, d, $J=1.8$ Hz), 8.71 (1 H, s); IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3420, 2950, 1736, 1605, 1570, 1492, 1438, 1395, 1304, 1183, 1132, 822; MS m/z : 344 (M^+ , base peak), 299 ($\text{M}^+-\text{CO}_2\text{H}$), 272, 243, 163.

Optically pure (S)-(-)-2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoic acid ((S)-(-)-**1**-acid) was prepared using (S)-(-)-**1**-acid recovered from the filtrate, which had been used to obtain the diastereoisomer of (R)-(+)-**1**-acid and cinchonidine. Cinchonine was used as the resolution reagent and fractional crystallization from aqueous ethanol was repeated five times to obtain optically pure (S)-(-)-**1**-acid, mp 156.0–157.0°C; $[\alpha]_D^{20} -29.4^\circ$ (MeOH, $c=1.00\%$).

2.2 Synthesis of optically pure ethyl (R)-(+)- and (S)-(-)-2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoate ((R)-(+)-**1** and (S)-(-)-**1**)

The optically pure (R)-(+) and (S)-(-)-**1**-acid were converted into the corresponding acyl chlorides with thionyl chloride at 60°C. Optically pure (R)-(+)-**1** and (S)-(-)-**1** were synthesized by the reaction of the acyl chlorides with ethanol in the presence of pyridine in chloroform at 10°C (R)-(+)-**1** had; mp 76.0–77.0°C; $[\alpha]_D^{20} +35.9^\circ$ (CHCl_3 , $c=1.20\%$). (S)-(-)-**1** had; mp 76.0–77.0°C; $[\alpha]_D^{20} -35.8^\circ$ (CHCl_3 , $c=1.20\%$).

3. Biological Test

The growth inhibiting activities of the racemic, optically pure (R)-(+) and (S)-(-)-**1** were examined with seeds of rice plants

(*Oryza sativa*) in petridish. Ten ml solutions of each compound containing 0.1% ethanol were poured into each petridish. Then ten rice seeds were planted in each and incubated at 25°C under fluorescent lamps. One week after treatment, the length of shoot and root was measured. The herbicidal activities against *Echinochloa crus-galli* (ECHCG*) and *Digitaria adscendens* (DIGSA*) were determined in plastic boxes (15×22 cm and 6 cm in depth) under greenhouse conditions. Each plastic box was filled with a sterilized clay loam soil and *E. crus-galli* and *D. adscendens* were seeded 1.5 cm in depth. At the 2–3 leaf stage, plants were sprayed with a solution of each compound formulated as a emulsifiable concentrate. After three weeks, the herbicidal activity was evaluated and rated by a standard.

The percent range for the growth inhibiting activity and the post-emergence herbicidal activity is set at 100 for no inhibition (untreatment) and at zero for complete inhibition. The activity expressed as I_{50} indicates the concentration level (ppm and g/a) required for 50% inhibition of the shoot and root growth to the control.

RESULTS AND DISCUSSION

1. Synthesis

Optically active (R)-(+) and (S)-(-)-2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoic acid ((R)-(+)-**1**-acid and (S)-(-)-**1**-acid) were prepared from the racemic acid by optical resolution. The combination of several natural alkaloids such as quinine, quinidine, cinchonine, cinchonidine, brucine and strychnine as the resolution reagent, and the solvent, aqueous acetonitrile and aqueous ethanol were examined. As the result, cinchonidine/aqueous acetonitrile and cinchonine/aqueous ethanol were preferable to obtain (R)-(+)-**1**-acid and (S)-(-)-**1**-acid, respectively. Fractional crystallization was repeated six times for the determination of specific rotation of optically pure (R)-(+)-**1**-acid as shown in Fig. 2. The specific rotation of (R)-(+)-**1**-acid obtained from the last filtrate agreed very well with that of (R)-(+)-**1**-acid obtained from the last

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

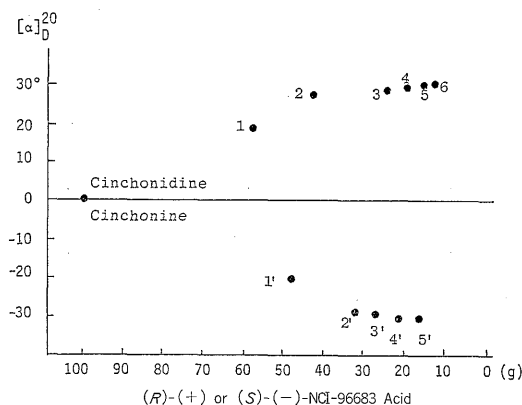


Fig. 2 Optical resolution of (\pm)-2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoic acid and its optical rotations.^{a)}

^{a)} 1 and 2': Diastereoisomer formation, 1': (S)-(-)-**1** acid from filtrate, 2-6 and 3'-5': Fractional crystallization.

crystal. Then we determined that the specific rotation of optically pure (*R*)-(+)-**1**-acid was +29.5° (MeOH, *c*=1.00%). In the same procedure, optically pure (*S*)-(-)-**1**-acid was obtained and its specific rotation was -29.4°

(MeOH, *c*=1.00%).

Next, the esterification of optically active acids so as to give (*R*)-(+)-**1** and (*S*)-(-)-**1** was investigated. (*R*)-(+)-**1** acid was esterified with ethyl alcohol in the presence of acid catalyzer, BF₃ or CCBT (6-chloro-1-*p*-chlorobenzenesulfonyloxy-benzotriazole). However, the yields were low and chemical and optical purities were not satisfactory. On the other hand, the acylation of (*R*)-(+)-**1**-acid with thionyl chloride followed by the reaction of the resulting acyl chloride with ethanol in the presence of pyridine was the most suitable for both the optical and chemical purity of the product. Racemization did not occur at all. In this procedure, the yield and optical purity of (*R*)-(+)-**1** was influenced by the kind of base. When triethylamine was used, racemization of (*R*)-(+)-**1** was observed. The synthetic routes and the results are shown in Fig. 3 and Table 1.

Further purification by the preferential crystallization was investigated. When optically active (*R*)-(+)-**1** (*R/S*=92.5/7.5) was recrystallized from EtOH/*m*-hexane, (*S*)-(-)-**1** contained in the starting (*R*)-(+)-**1** was not de-

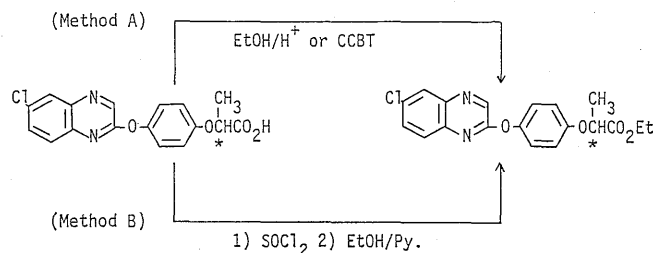


Fig. 3 Esterification routes of optically active 2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoic acid.

Table 1 Esterification of optically active 2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoic acid.

Reagent	Method	Yield (%)	[α] _D ²⁰ (°)	Chemical purity (%)
EtOH/H ⁺	A	76	+32.5	99.0
EtOH/BF ₃ -Et ₂ O	A	93	+27.4	70.6
EtOH/CCBT-Et ₃ N	A	90	+33.9	95.0
EtOH/CCBT-Py.	A	89	+32.1	90.0
1. SOCl ₂ 2. EtOH/Et ₃ N	B	76	+33.2	99.0
1. SOCl ₂ 2. EtOH/Py.	B	99	+35.9	99.0

Table 2 Growth inhibiting activity of ethyl (\pm), (*R*)-(+)- and (*S*)-(-)-2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoate.

	Rice plants ^{a)}		<i>Echinochloa crus-galli</i> ^{b)} (g/a)	<i>Digitaria adscendens</i> ^{b)} (g/a)
	Shoot (ppm)	Root (ppm)		
<i>I</i> ₅₀ : (<i>R</i>)-(+)- 1	1.2×10^{-2}	6.8×10^{-3}	5.4×10^{-2}	8.0×10^{-2}
(<i>S</i>)-(-)- 1	5.2	2.3	3.5	3.5
(\pm)- 1	2.0×10^{-2}	1.4×10^{-2}	8.0×10^{-2}	4.0×10^{-1}
(<i>S</i>)-(-)- 1 / <i>(R)</i> -(+)- 1	433	338	65	44
(\pm)- 1 / <i>(R)</i> -(+)- 1	1.6	2.0	1.5	1.8

^{a)} Inhibition of elongation.

^{b)} Inhibition of growth control.

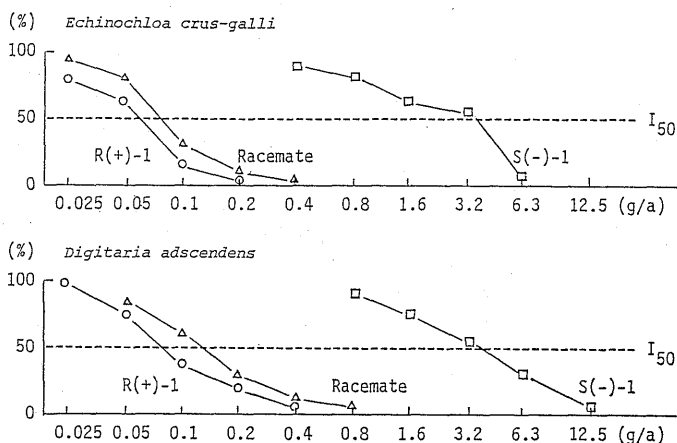


Fig. 4 Post-emergence activities of ethyl (\pm), (*R*)-(+)- and (*S*)-(-)-2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoate.

tected in the crystals and the specific rotation increased. (*R*)-(+)-**1** obtained by method B was recrystallized repeatedly but no change in the specific rotation was observed, indicating that the specific rotation of optically pure (*R*)-(+)-**1** was $+35.9^\circ$ (CHCl_3 , $c=1.20\%$). In the preceding paper,²⁾ we synthesized (*R*)-(+)-**1** from ethyl (*S*)-(-)-lactate and assumed that the specific rotation of optically pure (*R*)-(+)-**1** was $+35.2^\circ$ (CHCl_3 , $c=1.20\%$). The value of the specific rotation of optically pure (*R*)-(+)-**1** predicted by the NMR method was confirmed by the optical resolution method.

The crystal structure of (*R*)-(+)-**1** was determined by X-ray structure analysis and the (*R*)-configuration at the propanoic acid moiety was assigned.

2. Biological Activity

Comparative biological activities of racemic, optically pure (*R*)-(+)- and (*S*)-(-)-**1** are shown in Table 2 and Fig. 4. When the shoot growth inhibiting activity in the petridish against rice plants was examined, *I*₅₀ of racemic, (*R*)-(+)- and (*S*)-(-)-**1** was 0.02, 0.012 and 5.2 ppm, respectively. The activity of (*R*)-(+)-**1** was about 430 times higher than that of (*S*)-(-)-**1** and 1.6 times higher than that of the racemate.

The post-emergence herbicidal activity of (*R*)-(+)-**1** against *E. crus-galli* was about 65 times higher than that of (*S*)-(-)-**1** and 1.5 times higher than that of the racemate. On the other hand, the activity of (*R*)-(+)-**1** against *D. adscendens* was about 44 times higher than

that of (S)-(-)-**1** and 1.5 times higher than that of the racemate. When the post-emergence herbicidal activity was compared using I_{50} , the activity of (R)-(+)-**1** was about two times higher than that of the racemate and the activity of (S)-(-)-**1** was very low. It was confirmed that the herbicidal activity had a marked influence on the configuration at the propanoic acid moiety.

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要 約

光学分割法による ethyl (R)-(+ および (S)-(-)-2-[4-(6-chloro-2-quinoxalinyloxy) phenoxy]-propanoate の調製とその除草活性

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猪飼 隆, 鈴木宏一

Ethyl (R)-(+ および (S)-(-)-2-[4-(6-chloro-2-quinoxalinyloxy) phenoxy]propanoate ((R)-(+)-**1** および (S)-(-)-**1**) をそれぞれの相当する遊離酸 ((R)-(+)-**1**-acid および (S)-(-)-**1**-acid) から合成した。おのおのの酸は、そのラセミ体を cinchonidine あるいは cinchonine を用いて光学分割することにより得ることができた。つぎにそれらをアシルクロライドにした後、ピリジン存在下、エタノールでエステル化し純粋な光学活性体 (R)-(+)-**1**, (S)-(-)-**1** へ誘導した。光学純度はシフト試薬 Eu(HFC)₃ を用いた 200 MHz NMR の測定および優先晶析法を用いて決定した。その結果、光学的に純粋な (R)-(+)-**1** の旋光度は, $[\alpha]_D^{20} +35.9^\circ$ (CHCl₃, $c=1.20\%$) であることが明らかとなった。またシャーレ試験におけるイネ幼植物の生長阻害活性と、タヌビエおよびメヒシバを用いた茎葉処理除草活性を検討した結果、最も強い除草活性を示す化合物 **1** のプロピオン酸部の絶対配置は, R 配置であった。