Gas-liquid Chromatographic Determination of a New Pyrethroid, Permethrin (S-3151) and Its Optical Isomers

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Gas-liquid chromatographic (GLC) methods were developed for the determination of 3-phenoxybenzyl dl-cis,trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylate (S-3151, permethrin or Exmin ®), its geometrical and optical isomers and its impurities. dl-Trans and dl-cis isomers were separated from each other on a 2% LAC-2R-446 column and determined by using dioctyl phthalate as an internal standard, and the overall content of S-3151 was obtained by the sum of them. Optical isomers, namely, d-cis, l-cis, d-trans and l-trans forms were hydrolysed to the corresponding acids, which were derivatized to the diastereoisomer esters with d- or l-2-octanol and separated from one another on a 10% silicone DC QF-1 column. The optical isomer ratios were determined by the peak area ratios. The impurities of S-3151 were identified by mass spectrometer combined with GLC on a 2% PEG-20 M column and they were determined by programmed temperature GLC.

3-Phenoxybenzyl dl-cis,trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylate (S-3151, permethrin or Exmin ®) is a new synthetic pyrethroid which has been known to possess high activity not only against household insects¹⁻⁴ but also against agricultural and woody insects.⁵⁻⁷ S-3151 is an ester formed between 3-phenoxybenzyl alcohol and dl-cis, trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (DCPI). DCPI has the same structure as chrysanthemumic acid except for having a 2,2-dichlorovinyl group in the molecule instead of a 2-methyl-1-propenyl group. Therefore, S-3151 has four optical isomers, that is, d-trans, l-trans, d-cis and l-cis forms like the esters of chrysanthemumic acid. These isomers of S-3151 have very different degrees of toxicity to insects,⁹ depending upon the configurations of the acid moiety. The esters of d-configuration are much more toxic to insects than those of l-configuration and cis-isomer is about 2 times more effective than trans isomer against housefly and cockroach.⁴ Therefore, it is both necessary and important to determine the compositions of the geometrical and optical isomers of technical preparations of S-3151 as well as its overall chemical content.

In the present investigation, analytical methods were studied for the determination of S-3151 isomers by gas-liquid chromatography (GLC). dl-Trans and dl-cis isomers of S-3151 were separated from each other on the column of LAC-2R-446. The overall chemical content of technical S-3151 preparations was determined by the sum of the two geometrical isomers using dioctyl phthalate as an internal standard, and the composition of dl-trans and dl-cis isomers was determined by the two peak ratio. On the other hand, to separate the optical isomers, S-3151 preparations were hydrolysed to the corresponding DCPI, which was derivatized to the diastereoisomer esters with d- or l-2-octanol, and separated from one another on the column of QF-1 as in the case of chrysanthemumic acid esters already reported.¹⁰ Hence, the optical isomer compositions of S-3151 could be determined by peak area ratios of the chromatogram.

In addition, most of the impurities in the technical preparations of S-3151 were identified by mass spectrometry combined with GLC and their contents were determined using programmed temperature GLC.

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REAGENTS AND APPARATUS

**S-3151 analytical standard.** Recrystallize twice a technical preparations of S-3151 from hexane. Use this purified *dl-cis* isomers as the analytical standard, mp 52–56°C.

**Internal standard solution.** Weigh about 600 mg of dioctyl phthalate (Tokyo Kasei Co., Ltd.) accurately into a 100 ml volumetric flask, and dilute to the volume with chloroform and mix well.

**Calibration standard solution.** Weigh accurately about 20, 40 and 60 mg of S-3151 analytical standard, and add 5 ml aliquot of internal standard solution to each of them and mix well.

**Potassium hydroxide solution.** Weigh 66.5 g of JIS guaranteed potassium hydroxide, dissolve with 500 ml of deionized water and dilute to 1000 ml with methanol.

**Toluene.** Dry JIS guaranteed reagent on sodium metal.

**Pyridine.** Dry JIS guaranteed reagent on potassium hydroxide.

**Pyridine solution.** Weigh about 200 mg of dried pyridine, add 10 ml of dried toluene and mix well.

**Thionyl chloride solution.** Weigh about 840 mg of thionyl chloride (Wako Pure Chemical Industries Ltd.), add 10 ml of dried toluene and mix well.

**d- or l-2-Octanol solution.** Weigh about 2.3 g of *d*- or *l*-2-octanol (Aldrich Chemical Co., Inc.), add 10 ml of dried toluene and mix well.

**Diluted hydrochloric acid.** 10% aqueous solution.

**Other reagents.** JIS guaranteed reagents.

**Gas chromatograph.** Yanagimoto model G–80 gas chromatograph for the determination of the content of S–3151 and Shimadzu model GC–5A gas chromatograph for the determination of the optical isomers and impurities. Each of them is equipped with a flame ionization detector (FID).

**Integrator.** Shimadzu model ITG–4A digital integrator.

**Gas chromatograph-mass spectrometer.** Shimadzu model LKB 9000 gas chromatograph-mass spectrometer equipped with GC–MS PAC–300 data processing system.

ANALYTICAL METHODS

**Determination of S–3151**

**Preparation of calibration curve.** Chromatograph each 1.0 μl of calibration standard solutions under the following GLC operating conditions. Calculate the peak areas of S–3151 and the internal standard by the digital integrator. Plot the peak area ratios of S–3151 to the internal standard against the weight ratios.

**GLC operating conditions**

Column: A glass column 3 mm in internal diameter (i.d.) and 0.75 m in length, packed with 2% LAC–2R–446 on 60–80 mesh Chromosorb W (AW, DMCS); column temperature, 200°C; injection port temperature, 250°C; detector temperature, 250°C; carrier gas, nitrogen, 40 ml/min; air, 1.2 liter/min; hydrogen, 40 ml/min; sensitivity x attenuation, 10−4 x 1/8.

**Determination of content**

Weigh accurately a sample containing about 80 mg of S–3151, add 5 ml aliquot of the internal standard solution and mix well to make a sample solution. Chromatograph 1.0 μl of this sample solution under the same conditions as described in the section of preparation of calibration curve and determine peak area ratios of *dl-cis* S–3151 and *dl-trans* S–3151, respectively, to internal standard. Calculate percentage of S–3151 as follows;

\[
\text{Content} (\%) = \frac{(R_c + R_t)(W_i/W_s)5}{100} \times 100
\]

where, \(R_c\) and \(R_t\) are weight ratios of *dl-cis* S–3151 and *dl-trans* S–3151, respectively, to internal standard obtained by the calculation curve, and \(W_i\) and \(W_s\) are weights (mg) of dioctyl phthalate and the sample, respectively.

**Determination of geometric isomers**

Using the peak areas of *dl-cis* and *dl-trans* S–3151, which were obtained in the determination of S–3151, calculate the isomer compositions of the sample as follows;

\[
\text{*dl-cis* isomer} (\%) = \frac{A_c}{A_c + A_t} \times 100
\]

\[
\text{*dl-trans* isomer} (\%) = \frac{A_t}{A_c + A_t} \times 100
\]

where, \(A_c\) and \(A_t\) are the peak areas of *dl-cis* and *dl-trans* isomers, respectively.

**Determination of optical isomers**

Weigh about 20 mg of sample, add 5 ml of methanol and dissolve. Add 20 ml of potassium hydroxide solution to this solution and reflux the mixture for 30 min. After cooling, dilute the solution with 20 ml of water and wash with three portions of 10 ml of chloroform. Acidify the aqueous layer with about 8 ml of diluted hydrochloric acid and then extract with three portions of 10 ml of chloroform. Combine the chloroform layers, dry the chloroform solution over anhydrous sodium sulfate and remove the solvent in vacuo. To the residue, add 0.25 ml aliquots of pyridine solution, thionyl chloride solution and *l*– or *d*-2-
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Octanol solution, successively, and heat the mixture on a boiling water bath for 20 min. Chromatograph 0.5 µl of this mixture under the following GLC operating conditions and calculate the peak areas of the isomer peaks by the digital integrator. Determine the isomer composition of the sample according to the following equations:

\[
d\text{-trans} (%) = a + \frac{p}{100-2p} \times (a-b)
\]
\[
l\text{-trans} (%) = b - \frac{p}{100-2p} \times (a-b)
\]
\[
d\text{-cis} (%) = c + \frac{p}{100-2p} \times (c-d)
\]
\[
l\text{-cis} (%) = d - \frac{p}{100-2p} \times (c-d)
\]

where, \(a, b, c\) and \(d\) are the peak area ratios of \(d\)-trans, \(l\)-trans, \(d\)-cis and \(l\)-cis forms, respectively, and \(p\) is the enantiomer ratio (%) contained in the \(d\)- or \(l\)-2-octanol reagent, which was determined by the previously reported method.\(^{10}\)

GLC operating conditions

Column: A glass column 3 mm in i.d. and 5.0 m in length, packed with 10% silicone DC QF-1 on 60-80 mesh Chromosorb W (AW, DMCS); column temperature, 175°C; injection port temperature, 200°C; detector temperature, 200°C; carrier gas, nitrogen, 40 ml/min; air, 1.2 liter/min; hydrogen, 40 ml/min; sensitivity x attenuation, 10 x 4.

Determination of impurities

Weigh about 200 mg of a sample and add 3 ml of chloroform and dissolve. Chromatograph 1.0 µl of this solution under the following programmed temperature GLC conditions and calculate the areas of the peaks by the triangulation method. Determine each component of the impurities as follows:

\[
\text{Component } i \text{ (%) } = \frac{A_i}{A_0} \times P
\]

where, \(A_i\) and \(A_0\) are the peak areas of \(i\) component and S-3151, respectively, and \(P\) is the content (%) of S-3151. GLC operating conditions

Column: A glass column 3 mm in i.d. and 1.0 m in length, packed with 2% PEG-20 M on 60-80 mesh Chromosorb W (AW, DMCS); programmed column temperature range, 50 to 230°C at 5°C/min; injection port temperature, 250°C; detector temperature, 250°C; carrier gas, nitrogen, 40 ml/min; air, 1.2 liter/min; hydrogen, 40 ml/min; sensitivity x attenuation, 10 x 1 and 10 x 4.

RESULTS AND DISCUSSION

To find appropriate GLC conditions for the separation and determination of S-3151 isomers, Chromosorb W (AW, DMCS, 60-80 mesh) was coated with silicone XE-60, SE-30, OV-1, OV-17, QF-1, free fatty acid phase (FFAP), diethylene glycol succinate polyester (DEGS) and LAC-2R-446. The \(d\)-cis and \(d\)-trans isomers of S-3151 were partially separated from each other on a number of the columns tested. The \(d\)-cis isomer was eluted before the \(d\)-trans isomer. However, it was difficult to resolve S-3151 isomers as distinct symmetric peaks on a chromatogram. The GLC separation of the geometrical isomers of S-3151 was better on the column of LAC-2R-446 than on the other columns and that was good enough to calculate the peak areas of the two isomers. Moreover, they were separated from the impurities, and therefore this column was chosen as the column for the determination of geometrical isomers of S-3151. Since an FID detector exhibited essentially the same molar sensitivity to both isomers as shown in Table I, each of the isomers of S-3151 could be accurately determined using purified \(d\)-cis S-3151 as an analytical standard of S-3151 and diocetyl phthalate as an internal standard, and the overall content of S-3151 was determined by the sum of the two geometrical isomers. The geometrical isomers were determined on the same chromatogram. Figures 1 and 2 give a chromatogram and a calibration curve, respectively.

The optical isomers of S-3151 were hydrolyzed to give the corresponding isomers of DCPI, which were then derivatized to dia-
stereoisomers by esterification with d- or l-2-octanol and resolved by GLC like those of the esters of chrysathemumic acid. The diastereoisomer esters formed between DCPI and d-2-octanol were separated from one another on the column of 10% QF-1 5.0 m in length and 3 mm in inner diameter and eluted in the order as shown in Fig. 3. The composition of the four optical isomers of S-3151 was determined by their corresponding peak area ratios in the chromatogram. In the process of the esterification of DCPI with d- or l-2-octanol, di-2-octyl sulfite was produced and eluted on GLC, but its peak did not interfere with the determination of the isomers of S-3151.

The impurities of S-3151 were also separated from S-3151 and from one another on the column of PEG-20 M by programmed temperature GLC and they were identified by mass spectrometry combined with GLC and by comparing their retention times with those of authentic samples in GLC. The main impurities were found to be ethyl dl-cis,trans-3(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylate (DCPE), 3-phenoxytoluene (MTOP), 4-phenoxybenzyl dl-cis,trans-3(2,2-dichlorovinyl)-2, 2-dimethylcyclopropane-1-carboxylate (p-S-3151), 6-bromo-3-phenoxybenzyl dl-cis,trans-3(2,2-dichlorovinyl)-2, 2-dimethylcyclopropane-1-carboxylate (PHBR) and so on, which were produced in the process of the preparation of S-3151, and the geometrical isomers of DCPE and PHBR were separated from each other. Figure 4 shows a gas chro-
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FIG. 4. Programmed Temperature Gas Chromatogram of S-3151.

(1) Xylene, (2c) ethyl dl-cis 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylate (dl-cis DCPE), (2t) ethyl dl-trans 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylate (dl-trans DCPE), (3) 3-phenoxytoluene (MTOP), (4) 4-(2,2-dichlorovinyl)-5,5-dimethyloxacyclopentane-2-one (DCMO), (5) N,N-diethyl-3-phenoxycyclohexylamine (DEAM), (6) 3-phenoxycyclohexylcarboxylic acid (POAL), (7) 3-phenoxycyclohexyl alcohol (POA), (8c) 3-phenoxycyclohexyl dl-cis 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylate (dl-cis S-3151), (8t) 3-phenoxycyclohexyl dl-trans 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylate (dl-trans S-3151), (9) 4-phenoxycyclohexyl dl-cis,trans 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylate (p-S-3151), (10c) 6-bromo-3-phenoxycyclohexyl dl-cis 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylate (dl-cis PHBR), (10t) 6-bromo-3-phenoxycyclohexyl dl-trans 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylate (dl-trans PHBR).

Operational conditions: column, a glass column 3 mm in i.d. and 1.0 m in length, packed with 2% PEG-20M/Chromosorb W (AW, DMCS, 60–80 mesh); programmed column temp., 50–230°C at 5°C/min; injection port and detector temp., 250°C; carrier gas, N₂, 40 ml/min.

Table II gives the response factors of the main impurities relative to S-3151 in GLC. The response factors of the components were practically equal to that of S-3151 and each of the impurities in the S-3151 preparations could be determined by multiplying the ratio of its peak area to the combined peak area of S-3151 isomers (dl-cis

<table>
<thead>
<tr>
<th>Component(a)</th>
<th>Retention time relative to dl-trans S-3151</th>
<th>Response factor relative to S-3151</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-3151</td>
<td>1.00 (dl-trans)</td>
<td>1.00</td>
</tr>
<tr>
<td>Xylene</td>
<td>0.96 (dl-cis)</td>
<td>1.00</td>
</tr>
<tr>
<td>DCPE</td>
<td>0.29 (dl-cis)</td>
<td>1.14</td>
</tr>
<tr>
<td>MTP</td>
<td>0.42</td>
<td>1.21</td>
</tr>
<tr>
<td>POA</td>
<td>0.73</td>
<td>1.16</td>
</tr>
<tr>
<td>p-S-3151</td>
<td>1.05</td>
<td>1.00</td>
</tr>
<tr>
<td>PHBR</td>
<td>1.9 (dl-cis)</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>1.26 (dl-trans)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

(a) The same abbreviations were used for the components as in Fig. 4.

Table III. Analyses of Technical S-3151

<table>
<thead>
<tr>
<th>Components(a)</th>
<th>Percentage of components</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Content</td>
<td>91.6</td>
</tr>
<tr>
<td>dl-trans Isomer ratio</td>
<td>54.0</td>
</tr>
<tr>
<td>Xylene</td>
<td>0.1</td>
</tr>
<tr>
<td>DCPE</td>
<td>1.9</td>
</tr>
<tr>
<td>MTP</td>
<td>0.4</td>
</tr>
<tr>
<td>POA</td>
<td>0.2</td>
</tr>
<tr>
<td>p-S-3151</td>
<td>0.6</td>
</tr>
<tr>
<td>PHBR</td>
<td>1.5</td>
</tr>
<tr>
<td>DEAM</td>
<td>0.1</td>
</tr>
<tr>
<td>POAL</td>
<td>0.1</td>
</tr>
<tr>
<td>DCMO</td>
<td>0.1</td>
</tr>
</tbody>
</table>

(a) The same abbreviations were used for the components as in Fig. 4.

Table IV. Analyses of Optical Isomers in Optically Active S-3151

<table>
<thead>
<tr>
<th>Lot No.</th>
<th>Content (%)</th>
<th>Optical isomer ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>100.0</td>
<td>97.8  0.9  0.9  0.9  1.3</td>
</tr>
<tr>
<td>B</td>
<td>98.1</td>
<td>0.1  1.5  98.4 0.0 0.0</td>
</tr>
<tr>
<td>C</td>
<td>96.4</td>
<td>0.0  0.0  97.4 2.6 0.0</td>
</tr>
<tr>
<td>D</td>
<td>100.0</td>
<td>0.0  100.0 0.0 0.0 0.0</td>
</tr>
<tr>
<td>E</td>
<td>98.7</td>
<td>2.3  0.3  97.5 25.5 0.0</td>
</tr>
<tr>
<td>F</td>
<td>91.6</td>
<td>23.8 23.1 27.6 25.5 25.5</td>
</tr>
<tr>
<td>G</td>
<td>92.8</td>
<td>24.5 23.3 26.9 25.3 25.3</td>
</tr>
</tbody>
</table>

(a) Racemic sample.
plus *dl-trans* by the overall chemical content of S-3151. Table III gives the analytical results of technical preparations of S-3151. The overall content of S-3151 was in the range of 91.4 to 93.2% with the coefficient of variation being 0.60%. The *dl-trans/dl-cis* isomer ratio was in the range of 53.4/46.6 to 62.6/37.4. Table IV gives the analytical results of some samples of optically active S-3151 preparations.

Determination of S-3151 in formulations was also investigated. Table V gives the analytical results of emulsifiable concentrates of S-3151, which indicate that S-3151 in formulations could be accurately determined by the same procedure as the technical preparations of S-3151.

### Table V. Analyses of S-3151 Emulsifiable Concentrates of Known Composition

<table>
<thead>
<tr>
<th>Sample</th>
<th>S-3151 content, average (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Theoretical</td>
<td>Found</td>
</tr>
<tr>
<td>5% EC</td>
<td>5.00</td>
<td>4.95</td>
</tr>
<tr>
<td>5% EC</td>
<td>5.00</td>
<td>5.06</td>
</tr>
<tr>
<td>20% EC</td>
<td>21.0</td>
<td>20.5</td>
</tr>
<tr>
<td>20% EC</td>
<td>21.0</td>
<td>21.1</td>
</tr>
<tr>
<td>20% EC</td>
<td>20.0</td>
<td>20.0</td>
</tr>
</tbody>
</table>

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### REFERENCES

8) T. Ito, C. Hirose and Y. Funaki, submitted to *Bokyū-Kagaku*.