New Trihaloimidazole Derivatives Possessing a High Insecticidal Activity against the Pyrethroid-Resistant Colony of the German Cockroach, *Blattella germanica* (Dictyoptera: Blattellidae)

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Many kinds of 1-substituted-2,4,5-trihaloimidazole derivatives were synthesized and their insecticidal action against the pyrethroid-resistant colony (O-colony) of the German cockroach, *Blattella germanica*, which showed cross-resistance to various pyrethroid insecticides, was investigated by means of topical application and by a heating fumigant method. Also studied was their acute oral toxicity to mice. A strong correlation was observed between the insecticidal activity to cockroaches and the toxicity to mice in most of these derivatives, however, between the two species, 1-(4-halobutyloxymethyl)-2,4,5-trichloroimidazoles showed a superior selective toxicity. Among these compounds, 1-(4-chlorobutyloxymethyl)-2,4,5-trichloroimidazole (S-377) was finally selected as the candidate compound for controlling the pyrethroid-resistant colony of German cockroaches, especially as a heating fumigant agent. The insecticidal activity of S-377 against the O-colony was higher than that against susceptible strains by both the topical application and the heating fumigant method. Therefore, the S-377 is expected to be applicable in the practical field of controlling German cockroaches as a new active ingredient of insecticides.

**Key words:** trihaloimidazole, German cockroach, pyrethroid resistance, fumigant, selective toxicity

**INTRODUCTION**

The development of pyrethroid resistance in German cockroaches, *Blattella germanica*, was first reported by Keller et al. (1956) on natural pyrethrins. Today as synthetic pyrethroids are being employed ever more widely in controlling cockroaches, the low susceptibility of German cockroaches to various pyrethroid compounds has been reported.

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SCOTT and MATSUMURA (1981, 1983) reported that a DDT-resistant strain of German cockroaches selected by DDT showed cross resistance to permethrin, allethrin and fenvalerate to which they had never been exposed. As regards the field colony of German cockroaches, resistance to tetramethrin was reported in Czechoslovakia (LEDVINKA et al., 1984), and cross resistance to allethrin, permethrin, cypermethrin, ethofenprox and the like was reported in Japan (UMEDA et al., 1988). Such reports highlighted the need for insecticides which could supplement pyrethroids in controlling the resistant colonies of German cockroaches.

To attain this goal, a study was started to find an alternative cockroach insecticide having a different mode of action from that of pyrethroids. In the screening process, special consideration was given not only to the superior insecticidal activity against a pyrethroid-resistant colony of German cockroaches but also to good compatibility as an active ingredient for heating fumigant. In addition, the reduced toxicity against mice was also considered.

It is known that 2,4,5-trihaloimidazole compounds have an insecticidal activity (WASCO, 1969; MARTIN and PISSIOTAS, 1974). It is also known that the 2,4,5-trihaloimidazole derivatives, specifically 1-n-pentyloxyxymethyl-2,4,5-trichloroimidazole, have a superior insecticidal activity against cockroaches (RUTZ and GUBLER, 1972, 1973). Since all such compounds, however, do not have sufficient insecticidal activity against cockroaches or have a high toxicity to mammals, they have not been practically used.

In such circumstances, we found a new compound S-377 out of trihaloimidazole derivatives, which showed a superior insecticidal activity against the pyrethroid-resistant colony of German cockroaches, while exhibiting fewer of the disadvantages described above. In this article, the processes of screening of the trihaloimidazole derivatives and selecting the S-377 are described.

MATERIALS AND METHODS

Syntheses of chemicals. Trihaloimidazole derivatives, except for 1-acyloxyxymethyl-2,4,5-trihaloimidazoles, were prepared by the reaction of 2,4,5-trihaloimidazoles with appropriate halides in the presence of a base. 1-Acloyxymethyl compounds were prepared by heating a mixture of 2,4,5-trihaloimidazoles, paraformaldehyde, acid anhydrides and catalytic amount of p-toluenesulfonic acid. The structure of all compounds was confirmed by IR and 1-H-NMR spectroscopy including the elemental analyses. Typical procedures were as follows:

1-(4-Chlorobutyloxyxymethyl)-2,4,5-trichloroimidazole (S-377): To a stirred solution of 2,4,5-trichloroimidazole (0.69 g, 4 mmol) in N,N-dimethylformamide (5 ml) sodium hydride (0.16 g, 4 mmol, 60% dispersion in mineral oil) was added at room temperature and, after stirring for 15 min, 4-chlorobutyloxymethyl chloride (0.63 g, 4 mmol) was added by drops. After the resulting mixture was stirred for 8 hr at room temperature, it was poured into water (50 ml). The mixture was extracted twice with diethyl ether (30 ml × 3). The ether layers were combined, washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to obtain an oily residue. This was purified by column chromatography to give a colorless oil (0.88 g), nD25.8 = 1.5140. Found: C, 32.95; H, 3.54; N, 9.85. Calcd. for C₈H₁₀Cl₄N₂O: C, 32.91; H, 3.45; N, 9.59%.

1-(Butanoyloxyxymethyl)-2-bromo-4,5-dichloroimidazole: A mixture of 2-bromo-4,5-di-
chloroimidazole (1.08 g, 5 mmol), paraformaldehyde (0.15 g, 5 mmol), butanoic anhydride (5 ml) and p-toluenesulfonic acid (0.10 g, 0.58 mmol) was heated at 140–150°C for 5 hr. After cooling to room temperature, excess butanoic anhydride was removed under reduced pressure. The obtained oily residue was purified by column chromatography to give a colorless oil (0.76 g), $n_D^{28} = 1.5231$. Found: C, 30.36; H, 2.93; N, 8.66. Calcd. for $C_8H_6BrCl_2N_2O_2$: C, 30.41; H, 2.87; N, 8.87%.

The insecticides used as standards and their purities are as follows: permethrin, 91.8% and methoxadiazione [5-methy-3-(2-methoxyphenyl)-1,3,4-oxadiazol-2(3H)-one], 99.0%. Both chemicals were synthesized at Sumitomo Chemical Co., Ltd.

Insects. The following two strains of the German cockroach, Blattella germanica, were the same as those used in the previous report (Umeda et al., 1988):

1. A susceptible strain introduced from Nagoya University in 1961 and reared in our laboratory without exposure to insecticides.

2. The O-colony which was collected in Osaka Prefecture in 1980. Although it was considered that the cockroaches had been selected by permethrin in the field, they were not selected by any insecticide after collection.

Both strains were reared in our laboratory at 28 ± 1°C, 50 to 60% RH and 16L:8D, and fed with dry rat food and water. Adults, seven to 14 days after emergence, were used.

The sensitivity of the O-colony to organophosphorous compounds such as fenitrothion and carbamate compounds such as propoxur was at the same level as that of the susceptible strain. Most of pyrethroid compounds, however, showed the cross resistance in the O-colony, and the resistance ratio, reached values of twenty or more (Umeda et al., 1988).

Lethal activity to German cockroaches. The lethal activity of insecticides was determined by a topical application method. The procedure was shown in the previous report (Umeda et al., 1988).

Heating fumigant activity against German cockroaches. The electrically heating fumigant tests was conducted as follows:

Four polyethylene cups (10 cm in diameter, 8 cm in height) coated with butter on the inside were placed at the four corners on the bottom of a glass chamber [size (70 cm)$^3$; volume 0.34 m$^3$]. Ten male adults of the German cockroach were released into each of two cups on diagonally opposite corners, and ten female adults were released into each of the remaining two. An electric fumigating heater (manufactured by Matsushita Electric Works, Japan) was placed at the center of the bottom of the glass chamber, and a porous ceramic plate (size 4.0 cm × 4.0 cm, 1.2 cm in thickness; weight 18.5 g) (prepared by Kyocera, Japan) impregnated with acetone-solved chemicals (13.7 mgAI/plate; corresponding to 40 mgAI/m$^3$), was placed onto the heater. The plate was heated to about 200°C by applying current for 20 min. As time elapsed, the number of knocked-down insects was tallied to calculate the $KT_{50}$ (50% knock-down time) value. At 80 min after the current was first applied, the cups containing the test insects were taken out of the chamber, and the insects were bred on diet and water. After 48 hr, the number of dead and alive insects was examined to obtain a mortality.

Acute oral toxicity to mice. Each of the test chemicals was diluted with corn oil, and the dilute solution was forced into the stomachs of six-week-old male mice of ICR strain weighing 24 to 31 g (5 mice per group), to which no food had been given for
about 20 hr, at a rate of 0.1 ml/10 g of body weight. The mice were observed for 4 hr after the administration of the chemical and were then bred on diet and water in a cage. The number of dead and alive animals was observed over a seven day period to calculate the \( \text{LD}_{50} \) value.

RESULTS

Screening of 2,4,5-trihaloimidazole derivatives

As regards the three types of trihaloimidazole rings, the effect of substituent \( R \) at 1-position on the lethal activity against the O-colony was examined by the topical application method (Table 1). Regardless of the substituent \( R \), the order of the lethal activity was 2,4,5-trichloro type \( \geq \) 2-bromo-4,5-dichloro type \( \geq \) 2,4,5-tribromo type. In addition, compounds whose substituent \( R \) was an alkyl group with three or more carbon atoms, and an alkoxyethyl group with five or more carbon atoms, exhibited inferior insecticidal activity in all types of trihaloimidazole rings.

From the above results, 2,4,5-trichloroimidazole was selected as a basic structure in proceeding with further study. The effect of the type and the length of the substituent \( R \) at 1-position on the insecticidal activity against the O-colony and the acute oral toxicity to mice were examined successively for selected 2,4,5-trichloroimidazole derivatives (Table 2).

Generally, when the substituent \( R \) was an alkyl group (including the case of un-substitution) or an alkoxyethyl group, the smaller the number of carbon atoms in the

<table>
<thead>
<tr>
<th>( R )</th>
<th>( (X^1, X^2) ) and ( \text{LD}_{50} ) ( \mu \text{g/male} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>(Br, Br) 0.27, 0.19 (Br, Cl) 0.19, 0.12 (Cl, Cl) 0.12</td>
</tr>
<tr>
<td>-CH₃CH₂</td>
<td>(Br, Br) 0.35, 0.32 (Br, Cl) 0.25, 0.18 (Cl, Cl) 0.15</td>
</tr>
<tr>
<td>-CH₃CH₂CH₂</td>
<td>(Br, Br) 1.0, 1.0 (Br, Cl) 1.0, 1.0 (Cl, Cl) 1.0</td>
</tr>
<tr>
<td>-CH₃CN</td>
<td>(Br, Br) 0.35, 0.25 (Br, Cl) 0.12, 0.12 (Cl, Cl) 0.15</td>
</tr>
<tr>
<td>-CH₂OC(CH₃)₂CH₃</td>
<td>(Br, Br) 0.32, 0.25 (Br, Cl) 0.15, 0.15 (Cl, Cl) 0.15</td>
</tr>
<tr>
<td>-CH₂OCCH₂CH₂(CH₃)₂</td>
<td>(Br, Br) 1.0, 0.50 (Br, Cl) 1.0, 0.50 (Cl, Cl) 1.0</td>
</tr>
<tr>
<td>-CH₂OCCH(CH₃)</td>
<td>(Br, Br) 0.41, 0.20 (Br, Cl) 0.19, 0.19 (Cl, Cl) 0.19</td>
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<tr>
<td>-CH₂OCH₂CH₃</td>
<td>(Br, Br) 0.25, 0.25 (Br, Cl) 0.15, 0.15 (Cl, Cl) 0.15</td>
</tr>
<tr>
<td>-CH₂O(CH₃)₂CH₃</td>
<td>(Br, Br) ( \approx ) 1.0, 0.33 (Br, Cl) 0.44, 0.44 (Cl, Cl) 0.44</td>
</tr>
<tr>
<td>-CH₂O(CH₃)₂CH₂</td>
<td>(Br, Br) 1.0, 1.0 (Br, Cl) 1.0, 1.0 (Cl, Cl) 1.0</td>
</tr>
</tbody>
</table>
side chain, the higher was the insecticidal activity against the cockroaches (in both the topical application test and the heating fumigant test). The oral toxicity to mice showed a similar tendency, i.e. a strong correlation was observed between the insecticidal activity and the toxicity to mice in these compounds. In the case when the substituent R was an acyloxyethyl group, the insecticidal activity tended to exhibit a similar pattern, however, the toxicity to mice was almost unchanged. The toxicity value was relatively high (LD$_{50}$ = 30 to 100 mg/kg) in all cases.

On the other hand, when the substituent R was a haloalkoxyethyl group, the relationship was different from that observed in other substituents. When the number of carbon atoms in the haloalkoxy chain was four, the insecticidal activity was relatively high, specifically in the fumigant test. The toxicity of the haloalkoxyethyl type to mice, however, showed a tendency similar to that of alkyl and alkoxyethyl types. That is, as the number of carbon atoms was increased, the toxicity to mice decreased.

From the above results, the halobutylalkoxyethyl group was selected for the substituent for R as the most suitable group in selective toxicity. The 1-(4-halobutylalkoxy-methyl)-2,4,5-trichloroimidazoles selected were examined successively with respect to the difference in terminal halogen atom Y in the butyl chain (Table 3).

As regards the insecticidal activity against the O-colony of German cockroaches, the compounds in which Y is a fluorine, chlorine or bromine atom were found to be superior, in both the lethal and fumigant activity, to the compounds in which Y is an iodine atom. Of the three superior types, two, the chloro and the bromo compounds, were selected from the aspect of their lower oral toxicity to mice (LD$_{50}$ > 300 mg/kg).

Then, by examining the results of the thermal and storage stability (SHIRAISHI et al., unpublished), the stability in organic solvents or in fumigant carriers (SHIRAISHI et al., unpublished), the chloro compound was finally chosen from the two, being then designated as the S-377 [1-(4-chlorobutylalkoxyethyl)-2,4,5-trichloroimidazole].
Table 3. Biological activity of 1-(4-halobutoxyethyl)-2,4,5-trichlorimidazoles against O-colony of Blattella germanica and mice

\[
\begin{array}{c}
\text{Y} \\
\text{H} \\
\text{F} \\
\text{Cl (S-377)} \\
\text{Br} \\
\text{I} \\
\end{array}
\begin{array}{cccc}
\text{Topical application} & \text{LD}_{50} \mu g/\text{male} & \% \text{Mortality} & \text{Acute oral toxicity} \\
\text{(O-colony)} & & \text{(O-colony)} & \text{(Mice)} \\
\text{H} & 0.74 & 87.5 & >300 \\
\text{F} & 0.32 & 100 & <30 \\
\text{Cl (S-377)} & 0.31 & 100 & >300 \\
\text{Br} & 0.32 & 100 & >300 \\
\text{I} & >1.0 & -- & 100-300 \\
\end{array}
\]

Table 4. Insecticidal activity of S-377 against two strains of Blattella germanica by topical application and heating fumigant methods

<table>
<thead>
<tr>
<th>Insecticide</th>
<th>LD_{50} (µg/male)</th>
<th>R/S ratio</th>
<th>Heating fumigant (40 mg AI/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O-colony</td>
<td>Susceptible</td>
<td>O-colony</td>
</tr>
<tr>
<td>S-377</td>
<td>0.31</td>
<td>0.56</td>
<td>0.55</td>
</tr>
<tr>
<td>Methoxadiazone</td>
<td>0.39</td>
<td>0.26</td>
<td>1.5</td>
</tr>
<tr>
<td>Permethrin</td>
<td>5.8</td>
<td>0.13</td>
<td>46</td>
</tr>
</tbody>
</table>

**Insecticidal activity of the S-377**

Table 4 shows the insecticidal activity of the S-377 against two strains of German cockroaches compared with that of the standard chemicals (methoxadiazone and permethrin) using the topical application and the heating fumigant methods.

The insecticidal activity of the two standard chemicals, specifically of the permethrin, was lower against the O-colony than it was against the susceptible strains by either method. On the other hand, the S-377 showed a higher activity against the O-colony than against the susceptible strain by either method.

**DISCUSSION**

The 2,4,5-trihalimidazole without substitution at 1-position of imidazole ring demonstrated the highest lethal activity against the O-colony of German cockroaches among the trihalimidazole derivatives studied (Table 1). These compounds, however, showed the highest acute oral toxicity to mice as well (LD_{50}=ca. 30 mg/kg).

In consequence of many substitutions at the 1-position to reduce the toxicity to mice while maintaining the insecticidal activity, optimization was obtained in halobutoxyethyl substitution (Table 2). It is not known why such selectivity can be achieved by the haloalkoxyethyl substitution with four carbon atoms. It can be assumed that, for some reason, the compatibility in intravital target site or the mode of metabolism is different between cockroaches and mammals. It is obviously possible
that other factors are involved such as the difference in penetration of chemicals from outside of the body to the intravitral target site and in physical action when heated.

The S-377 tended to show higher insecticidal activity against the pyrethroid-resistant colony of German cockroaches than it did against the susceptible strain (Table 4). Nevertheless, it is difficult to say whether this tendency could be called negatively correlated cross resistance or not. In order to prove the hypothesis, it is necessary to investigate the mode of action of S-377 as an insecticide, as well as to examine the sensitivity of both colonies to this compound repeatedly. Judging from the fact that the S-377 exhibited a relatively rapid knockdown activity for both colonies (Table 4), it may be supposed that the target site of this compound may be located on the nervous system of the German cockroaches, and that the mode of action is different from that of pyrethroids. The mode of action of the S-377 remains to be clarified using some physiological techniques for the nervous preparation of the insect.

At any rate, the S-377 exhibited prominent insecticidal activity against German cockroaches possessing pyrethroid resistance, especially in the heating fumigant method, as well as a low toxicity to mice. Therefore, this compound is expected to be applicable in the practical field of controlling German cockroaches as a new active ingredient that could supplement conventional pyrethroid insecticides such as permethrin.

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