Insecticidal Activity of the Pyrethrins
and Related Compounds

VII. a Insecticidal dihalovinyl analogues of cis and trans chrysanthemates

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Eighteen esters of resolved cis- and trans-3-(2,2-difluoro, -dichloro or -dibromo-vinyl)-2,2-dimethylcyclopropanecarboxylic acids with 5-benzyl-3-furylmethyl, 3-phenoxybenzyl and α-cyano-3-phenoxybenzyl alcohols were prepared and evaluated for insecticidal activity against Musca domestica L. and Phaedon cochlareae Fab. Chlorine and bromine substituted esters are more active, in general, than those with fluorine, and in the most active esters, the cis isomer is more effective than the trans.

1. Introduction

5-Benzyl-3-furylmethyl (1R,trans)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (NRDC 134; 4A), the dichloro analogue of bioresmethrin (1A),\(^1\) has outstanding insecticidal activity. Related dihaloesters also have valuable properties. 3-Phenoxybenzyl esters, for example the (±)-cis, trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (NRDC 143, permethrin\(^3,4\)), have enhanced stability in air and light, as well as low mammalian toxicity, and thus have much greater potential as agricultural insecticides than traditional pyrethroids. Recently, [1S]-α-cyano-3-phenoxybenzyl cis-[1R,3R]-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate\(^5,6\) (one isomer of 7C) was found to be more active than any previous insecticide. The insecticidal activities of racemic dibromo\(^7\) and difluoro\(^8\) vinyl 5-benzyl-3-furylmethyl esters have also been reported.

The variation of insecticidal potency with changes in both halogen and esterifying alcohol in this series of esters was therefore examined by bioassays under directly comparable conditions. Esters with 1S,cis and 1S,trans cyclopropane acids are much less active,\(^8-11\) so the pure 1R,cis and 1R,trans isomers were used to simplify interpretation of results.

\(^b\) For system of nomenclature adopted, see footnote in reference 12.
2. Experimental

2.1. Preparation of materials

Six of the esters examined were described earlier.\(^5^{,11,12}\) N.m.r. spectra were recorded on a Perkin–Elmer R10 spectrometer (60 MHz) using dilute solutions in carbon tetrachloride with tetramethylsilane (for \(^1\text{H}\)) or fluorotrichloromethane (for \(^19\text{F}\)) as internal references at 60 MHz or 56.45 MHz respectively. Chemical shifts are on the \(\tau\) scale (for \(^1\text{H}\)) or in parts/10\(^6\) upfield of the reference (for \(^19\text{F}\)). Mass spectra were recorded on a Perkin–Elmer–Hitachi RMU 6E double-focusing spectrometer (70 eV; direct insertion).

\(1\text{R,Trans}\)- and \(1\text{R,cis}\)-3-(2,2-difluorovinyl)-2,2-dimethylcyclopropanecarboxylic acids (cf\(^8,13\)). Methyl \(1\text{R,trans}\) caronaldehyde (3.0 g, 0.021 mol), sodium chlorodifluoroacetate (3.6 g, 0.023 mol), triphenylphosphine (7.9 g, 0.030 mol) and dimethylformamide (20 ml) were stirred for 20 h at 90°, then the reaction mixture was cooled and shaken with water and ether. The ether layer was separated, washed (saturated Na\(_2\text{CO}_3\), NaCl), dried (Na\(_2\)SO\(_4\)), and distilled, finally at 63°/20 mm, to give methyl \(1\text{R,trans}\)-3-(2,2-difluorovinyl)-2,2-dimethylcyclopropanecarboxylate (2.07 g, 57%) \(n_D^{20}\) 1.4209, n.m.r. peaks at \(\tau\) 5.95 (ddd, 2, 8, 25 Hz, \(=\text{CH}\)), 6.38 (s, OMe), 8.09 (dd, 2, 5, 8 Hz, 3-H), 8.58 (d, 5 Hz, 1-H), 8.76 and 8.87 (2 \(\times\) s, CMe\(_2\)) and at 88.3 (ddd, 2, 25, 43 Hz, \(F\) trans to \(=\text{CH}\)) and 85.8 parts/10\(^6\) (dd, 2, 43 Hz, \(F\) cis to \(=\text{CH}\)).

Similarly, methyl \(1\text{R,cis}\)-caronaldehyde gave methyl \(1\text{R,cis}\)-3-(2,2-difluorovinyl)-2,2-dimethylcyclopropanecarboxylate (2.07 g, 57%) \(n_D^{20}\) 1.4288, n.m.r. peaks at \(\tau\) 5.37 (ddm, 8, 25 Hz, \(=\text{CH}\)), 6.40 (s, OMe), 8.3 (m, 1-H+3-H) and 8.8 (s, CMe\(_2\)) and at 92.0 (ddd, 2, 25, 46 Hz, \(F\) trans to \(=\text{CH}\)) and 86.3 parts/10\(^6\) (dd, 2, 46 Hz, \(F\) cis to \(=\text{CH}\)).

Saponification of the \(cis\) and \(trans\) methyl esters (0.5 g) by refluxing with sodium hydroxide (0.2 g) in water (1 ml) and ethanol (10 ml) for 1 h gave the \(1\text{R,trans}\) acid (0.41 g, 87%), \(n_D^{20}\) 1.4400, and the \(1\text{R,cis}\) acid (0.44 g, 93%), \(n_D^{20}\) 1.4456.

\(1\text{R,Cis}\)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylic acid. Methyl\((1\text{R},\text{cis})\) caronaldehyde (2.0 g, 0.014 mol), triphenylphosphine (7.1 g, 0.027 mol), carbon tetrabromide (4.5 g, 0.014 mol) and dichloromethane (80 ml) were stirred for 20 h at 20°, then the product was concentrated \textit{in vacuo} and extracted with petroleum ether. The extracted material was refluxed with acetic acid (12 ml), 48% hydrobromic acid (8 ml) and water (4 ml) for 3 h, then water was added, and the product was extracted with ether. The ether layer was extracted with 5% NaOH, which was acidified to precipitate the acid (2.48 g, 57%), m.p. 122–124°, n.m.r. peaks at \(\tau\) –0.6 (s, CO\(_2\)H), 3.25 (d, 8 Hz, \(=\text{CH}\)), 8.1 (m, 1-H+3-H) and 8.7 (s, CMe\(_2\)).

Esters. The remaining 12 esters were prepared by the method previously described,\(^13\) from the acid (synthesis described above or elsewhere\(^11,12\)) and 5-benzyl-3-furylmethyl alcohol,\(^2\) 3-phenoxybenzyl alcohol\(^14\) or (\(\pm\))-a-cyano-3-phenoxybenzyl alcohol.\(^15\) The purity of each ester was confirmed by mass spectrometry (the molecular ion, based on Cl=35 or Br=79, was as shown in each case) and by n.m.r., the spectra...
showing the expected peaks from a combination of alcohol and acid, and no significant signals from impurities.

5-Benzyl-3-furylmethyl (1R,trans)-3-(2,2-difluorovinyl)-2,2-dimethylcyclopropanecarboxylate (2A), \( \eta_{D}^{20} \) 1.5142, M, 346 (NRDC 173). 5-Benzyl-3-furylmethyl (1R, cis)-3-(2,2-difluorovinyl)-2,2-dimethylcyclopropanecarboxylate (3A), \( \eta_{D}^{20} \) 1.5136, M, 346 (NRDC 174). 5-Benzyl-3-furylmethyl (1R,cis)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate (7A), \( \eta_{D}^{20} \) 1.5624, M, 466 (NRDC 165). 3-Phenoxybenzyl (1R,trans)-3-(2,2-difluorovinyl)-2,2-dimethylcyclopropanecarboxylate (2B), \( \eta_{D}^{20} \) 1.5293, M, 358 (NRDC 171). 3-Phenoxybenzyl (1R,cis)-3-(2,2-difluorovinyl)-2,2-dimethylcyclopropanecarboxylate (3B), \( \eta_{D}^{20} \) 1.5349, M, 358 (NRDC 172). 3-Phenoxybenzyl (1R,trans)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate (6B), \( \eta_{D}^{20} \) 1.5828, M, 478 (NRDC 163). 3-Phenoxybenzyl (1R,cis)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate (7B), \( \eta_{D}^{20} \) 1.5848, m.p. 93 °C, M, 478 (NRDC 157). (\( \pm \))-\( \alpha \)-Cyano-3-phenoxybenzyl (1R,trans)-3-(2,2-difluorovinyl)-2,2-dimethylcyclopropanecarboxylate (2C), \( \eta_{D}^{20} \) 1.5330, M, 383 (NRDC 169). (\( \pm \))-\( \alpha \)-Cyano-3-phenoxybenzyl (1R,cis)-3-(2,2-difluorovinyl)-2,2-dimethylcyclopropanecarboxylate (3C), \( \eta_{D}^{20} \) 1.5355, M, 383 (NRDC 170). (\( \pm \))-\( \alpha \)-Cyano-3-phenoxybenzyl (1R,trans)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (4C), \( \eta_{D}^{20} \) 1.5498, M, 415 (NRDC 166). (\( \pm \))-\( \alpha \)-Cyano-3-phenoxybenzyl (1R,cis)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (5C), \( \eta_{D}^{20} \) 1.5622, M, 415 (NRDC 168). (\( \pm \))-\( \alpha \)-Cyano-3-phenoxybenzyl (1R,trans)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate (6C), \( \eta_{D}^{20} \) 1.5664, M, 503 (NRDC 158).

2.2. Biological testing

Activity against houseflies, Musca domestica L., and mustard beetles, Phaedon cochleariae, Fab., was assessed by methods described previously.

3. Discussion

The relative molar potencies, summarised in Table 1 and Figure 1, show that esters with dichloro- and dibromovinyl side chains, cis or trans to the ester group, are more active than compounds with difluorovinyl substituents in almost all cases. The difference in potency is greatest with esters of 3-phenoxybenzaldehyde cyanohydrin. In cis esters, there is a trend for activity to increase in the order F < Cl < Br, but in the trans series, bromo compounds are generally less effective than chloro. Comparisons with the reference compound, bioresmethrin, which has a trans dimethylvinyl side chain shows that in the 5-benzyl-3-furylmethyl series, all three halogens are some two or three times more effective than methyl. The most active of the 18 esters examined, the 1R,cis-dibromovinyl acid with the racemic cyanohydrin of 3-phenoxybenzaldehyde, is an outstandingly potent compound, and the two isomeric forms have been prepared separately, as described elsewhere.

In this series of compounds, there appears to be no clear correlation of insecticidal potency with physical properties, such as atomic dimensions or the electronic effects of halogen substituents on olefinic bonds. In pyrethroids, substituents on the 3-position with a wide range of sizes are effective in both cis and trans configurations, so
Table 1. Relative toxicities (molar basis) of insecticidal esters of 2,2-dimethyl-3-(2,2-dihalovinyl)cyclopropanecarboxylic acids

<table>
<thead>
<tr>
<th>Halogen in 2,2-dihalovinyl group</th>
<th>Isomer</th>
<th>5-Benzyl-3 furlymethylen esters; (-A)</th>
<th>3-Phenoxybenzyl esters; (-B)</th>
<th>(±)-α-Cyano-3-phenoxybenzyl esters; (-C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>1R, trans; (2-)</td>
<td>390&lt;sup&gt;c&lt;/sup&gt;</td>
<td>61</td>
<td>94</td>
</tr>
<tr>
<td>Cl</td>
<td>1R, trans; (4-)</td>
<td>350</td>
<td>90</td>
<td>570</td>
</tr>
<tr>
<td>Br</td>
<td>1R, trans; (6-)</td>
<td>210</td>
<td>110</td>
<td>550</td>
</tr>
<tr>
<td>F</td>
<td>1R, cis; (3-)</td>
<td>260</td>
<td>170</td>
<td>150</td>
</tr>
<tr>
<td>Cl</td>
<td>1R, cis; (5-)</td>
<td>280</td>
<td>200</td>
<td>1300</td>
</tr>
<tr>
<td>Br</td>
<td>1R, cis; (7-)</td>
<td>360</td>
<td>260</td>
<td>1200</td>
</tr>
</tbody>
</table>

<sup>a</sup> HF = houseflies; *Musca domestica*, L. LD<sub>50</sub> for bioresmethrin: 0.005 µg/insect.

<sup>b</sup> MB = mustard beetles; *Phaedon cochleariae*, Fab. LD<sub>50</sub> for bioresmethrin: 0.007 µg/insect.

<sup>c</sup> All relative toxicities are based on bioresmethrin = 100 as standard, and are calculated on a molar basis. Each compound was tested at least twice against each species, and results are means of these individual tests.

Table 2. Chemical shifts of the $-\text{CH} = \text{CX}_2$ group in the n.m.r. spectra of dihalovinyl esters

<table>
<thead>
<tr>
<th>X</th>
<th>1R, cis esters</th>
<th>1R, trans esters</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>5.37</td>
<td>6.00</td>
</tr>
<tr>
<td>Cl</td>
<td>3.77</td>
<td>4.40</td>
</tr>
<tr>
<td>Br</td>
<td>3.26</td>
<td>3.93</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>4.69</td>
<td>5.17</td>
</tr>
</tbody>
</table>
the size of the substituents cannot be a dominating factor. The electronic inductive effects of halogens are in the order \( F > Cl > Br \), and are in the opposite direction to their mesomeric effects;\(^{17}\) their influences on the chemical shifts of the vinylic proton in the esters are listed (Table 2). An unsaturated 3-substituent is present in all the most potent pyrethroids,\(^ {3,5} \) but the relative activities of the compounds described here and elsewhere,\(^ {12} \) in which the level of potency also depends on the nature of the esterifying alcohol, do not yet give a sufficiently clear pattern for predicting new active compounds, and experimental investigation of appropriate combinations is necessary.

To relate structure with activity, the potencies of the esters and their isomers are most appropriately compared on a molar basis, as in Table 1 and Figure 1. However, other factors such as activity per unit weight (rather than per mole) and availability and cost of intermediates for synthesis are important when practical development is considered. The smaller molecular weights of the fluoro-analogues do not compensate sufficiently for their lower activities, but the chlorinated and brominated esters are much closer in potency and on a weight for weight basis the chloro compounds are generally the more active. Further, a convenient procedure\(^ {11} \) is available for preparing relatively large quantities (1 kg or more) of 1,1-dichloro-4-methylpent-1,3-diene from the accessible intermediate chloral even in the laboratory. The diene with ethyl diazoacetate, prepared industrially by established routes, easily gives the mixed dichlorovinylcyclopropane acids which are components of permethrin. The bromo analogues are much less accessible.\(^ {12} \) Improved routes to both bromo- and chloro-compounds could be developed if needed, but at present on the basis

![Figure 1. Mean potencies (two species) of esters of dihalovinyl acids.](image-url)
of biological activity and cost, the chloro- compounds appear more promising for commercial development. Their use in practice will finally depend on toxicological and environmental considerations, at present being investigated.

Acknowledgements

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References