The Importance of Synthetic Pyrethroids*

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The intensive research which finally elucidated the structure of the pyrethrins and cinerins in natural pyrethrum made possible the synthesis of a number of analogous compounds. This permitted investigation of the effect of variations of molecular form on toxicity, and led to production of some synthetic pyrethroid insecticides.

The relations between structure and toxicity have been well reviewed by Elliott. In general, comparatively small changes in the main structure of the molecule lead to more or less complete loss of toxicity, suggesting that steric relations are important in the toxic action. Changes are possible in the unsaturated side-chain (R) of the keto-alcohol; and these have been exploited to produce the new synthetic insecticides allethrin, furethrin and cyclethrin. Recently, some experimental variations of the acid part of the molecule have revealed a promising compound, in which a phenyl group is substituted (at R) for the isobutylene group on the cyclopropane ring (Weiser). (See accompanying figure.)

The complexity of the subject is increased by the fact that both the acid and keto-alcohol components of pyrethroids can exist as cis- or trans-forms and as dextro- or laevo-rotatory forms, so that there are eight possible isomers. The relative toxicity of these to insects has been investigated, directly and indirectly, by Elliott et al. and by Gersdorff & Mitlin.

* Revised version of note submitted to WHO Expert Committee on Insecticides, September 1959


These workers found that the (+) forms of the acid component conferred very much more activity than the (−) forms. It seems that the (+) forms of the keto-alcohol are also more insecticidal than the (−)
forms, though the difference is not so great. Finally, the trans-isomers are generally about twice as active as the cis-isomers. These differences are cumulative, so that (+) (+) trans-forms may be 150 or more times as insecticidal as the (−) (−) cis-isomers.

Natural pyrethrum contains (+) trans acids and (+) cis keto-alcohols, whereas the synthetic products are cis-trans racemic mixtures. From what has been said above, it will be evident that the double dextroform in the natural product tends to make it more lethal to most insects than the synthetic materials.

Insecticidal value of synthetic pyrethroids

The published evidence of the relative insecticidal powers of natural and synthetic pyrethroids is very largely based on houseflies. Only allethrin has been more widely tested on other insects. This is a pity, because there is evidence that the relative values may change greatly with different insects (Elliott et al. c).

There is a further complication in the different results obtained by different authors. Thus, the potency of allethrin compared to natural pyrethrins has been reported as × 6 (Gersdorff), × 1.2 (Stoddard & Dove), × 1 (Moore) and × 0.5 (Nash). Some of these discrepancies may be due to the methods of measurement; others may be due to different proportions of isomers in the samples used.

Houseflies, however, are one of the few species for which approximate parity of allethrin has been claimed. For most other insects pyrethrins are more potent, as can be seen from the tabulation below:

<table>
<thead>
<tr>
<th>Insect</th>
<th>Potency of Allethrin (pyrethrins −1)</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimex lectularius</td>
<td>0.56</td>
<td>Busvine &amp; Nash</td>
</tr>
<tr>
<td>Rhodnius prolixus</td>
<td>0.12</td>
<td>&quot;</td>
</tr>
<tr>
<td>Pediculus humanus</td>
<td>0.24</td>
<td>&quot;</td>
</tr>
<tr>
<td>Xenopsylla cheopis</td>
<td>0.17</td>
<td>&quot;</td>
</tr>
<tr>
<td>Aedes aegypti</td>
<td>0.38</td>
<td>&quot;</td>
</tr>
<tr>
<td>Ornithodoros moubata</td>
<td>0.13</td>
<td>&quot;</td>
</tr>
<tr>
<td>Aedes aegypti (larvae)</td>
<td>0.4</td>
<td>Ginsburg</td>
</tr>
<tr>
<td>Periplaneta americana</td>
<td>0.4</td>
<td>Bishopp</td>
</tr>
<tr>
<td>Plutella maculipennis</td>
<td>1.8</td>
<td>Elliott et al.</td>
</tr>
<tr>
<td>Macrosiphon solani folu</td>
<td>0.06</td>
<td>&quot;</td>
</tr>
<tr>
<td>Phaedon cochleariae</td>
<td>0.2</td>
<td>&quot;</td>
</tr>
<tr>
<td>Oryzaephis surinamensis</td>
<td>0.4</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

So far as the other synthetic compounds are concerned, there appear to be data only for houseflies. Furethrin was found to be about one-third as potent as allethrin by Gersdorff & Mitlin but only 0.13 times as potent by Weiser. Cyclethrin was found 0.6 times as potent as allethrin by Granett & Haynes and 0.25 times by Weiser. The only information about the new compound with the altered acid component was given by Weiser, who found it to be 3.7 times as potent as allethrin, though less active for knock-down.

Combination with synergists

It is generally found that synergists are more effective in activating natural pyrethrins than in activating allethrin, at least with houseflies. However, the difference is not so pronounced with other synthetic pyrethroids. For example, the increase in potency of pyrethrins, allethrin and cyclethrin (synergized with sulfoxide) was 20, 3 and 8.5, respectively; and their relative potencies based on plain pyrethrins were 20, 8 and 12.5, respectively (Granett & Haynes). Furethrin, too, seems to synergize more readily than allethrin (Incho & Ault). It is also possible that this relationship may not hold with other insects. Thus, Nash found that piperonyl butoxide actually synergized allethrin more (× 3) against bed-bugs than it did pyrethrins (× 2).

Persistence

Allethrin is more stable than natural pyrethrins, judged by bio-assay tests, either as oil films (Granett et al.; Blacketh; Busvine & Nash) or as powder preparations (Goodwin-Bailey). The difference, however, is not sensational; it does not represent a residual effectiveness of another order.

Resistance

Houseflies which had developed resistance to pyrethrins in the field in Sweden were found to be also resistant to allethrin in laboratory tests (Davies et al. r).

Practical considerations

Of the synthetic pyrethroids, only allethrin is manufactured on a large scale. The only manu-

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* Blacketh; Busvine & Nash i
* Granett & Nash (1951) J. econ. Ent., 45, 849
* Granett, P. et al. (1951) J. econ. Ent., 44, 552
* Davies, M. et al. (1958) Nature (Lond.), 182, 1816
Resistance to Pyrethrins*

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Resistance developed in the field

Pyrethrum resistance, at a level which appreciably affects control measures, has very rarely developed in the field. Indeed, there seem to be only two instances of this:

1. Strains of cockroaches collected from various parts of the United States of America were mostly found to possess low levels of pyrethrum resistance; but in one case, the level of resistance reached 13 or 30 times the normal level (the two figures refer to different test methods used by Keller et al.⁵).

According to Spear (quoted by Brown⁴), this colony required substitution of sodium fluoride for field control.

2. Houseflies in Sweden, having become resistant to chlorinated-hydrocarbon insecticides and para- thion, were controlled by synergized pyrethrum for about a year; but eventually the pyrethrum spray began to fail. Laboratory tests by Davies et al.⁶ revealed a resistance of 11 to 14 times the normal to ordinary pyrethrins and 11 times to synergized pyrethrins.

It is noteworthy that both the cockroaches and the flies had developed resistance to other insecticides in the field prior to the discovery of the pyrethrin resistance. There are other records of pyrethrin resistance being discovered in the laboratory in strains taken from the field after developing

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* Revised version of note submitted to WHO Expert Committee on Insecticides, September 1959.
⁴ Keller, J. C. et al. (1956) Pest Control, 24, 14
⁶ Davies, M. et al. (1958) Nature (Lond.), 182, 1816

resistance to chlorinated compounds. Thus, DDT-resistant flies from Torre in Pietra, Italy, were found to show a 5-fold pyrethrum resistance (Busvine⁴). Again, strains of resistant bed-bugs showed pyrethrin tolerance up to 10 times the normal. The level was roughly correlated with the DDT resistance, in different strains (Busvine⁴).

Whitehead⁷ has found that a strain of the blue tick (Boophilus decdoratus) which was resistant to DDT was definitely resistant to pyrethrins (×18), whereas other strains resistant to BHC or to BHC plus arsenite had a pyrethrin tolerance only 2 or 3 times the normal.

Lowered sensitivity of human body lice to pyrethrum powder was discovered in some instances in the very large surveys conducted by Wright & Brown⁵ and Nicoli & Sautet⁶. In most cases the pyrethrin-tolerant lice showed some DDT resistance, but there was no correlation between the levels of resistance to the two types of insecticide.

Resistance developed in the laboratory

There are a few records of development of pyrethrum resistance in houseflies by selection on a normal colony. Thus, Decker & Bruce⁵ reached a 20-fold and Harrison⁷ a 5-fold increase. In both instances there was some raising of resistance to chlorinated-hydrocarbon insecticides.

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⁴ Busvine, J. R. (1951) Nature (Lond.), 168, 193