Active Insight: The Pyrethroids

In this series, the chemistry of major insecticide groups will be examined

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The development of the currently used residual pyrethroids is a classical study in insecticide development chemistry.
Pyrethroids are synthetic (man-made) compounds, though the design of the molecules was derived from the chemistry of natural pyrethrins.
Pyrethrins are natural insecticides, extracted from certain species of *Chrysanthemum* daisies, most usually *Chrysanthemum cinerariaefolium*. The insecticidal components are contained within the seed cases of the plant and are extracted shortly after flower bloom. Pyrethrins consist of six insecticidally active components. Named after their structural and isomeric layout, these are pyrethrin-I (Figure 1) and pyrethrin-II; cinerin I (Figure 2) and cinerin II; and jasmolin I and jasmolin II.

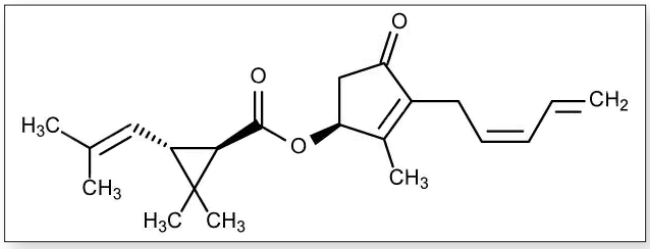

Figure 1. Pyrethrin I

LaForge and Haller in 1936 were the first to determine the structure of these pyrethrins, which they showed were esters of chrysanthemic acid. It was this knowledge of the structural chemistry of pyrethrins which lead to the development of synthetic equivalents, the pyrethroids.

Pyrethrins are contact poisons which penetrate the insect nervous system. There they bind to sodium channels that are found along the length of the nerve cells. These sodium channels are responsible for nerve signal transmission. When the pyrethrins bind to sodium channels the normal action of the channels is blocked which leads to hyperexcitation, loss of function, and eventually causes the shutdown of the nervous system leading to death.

A concern with the pyrethrins was that often

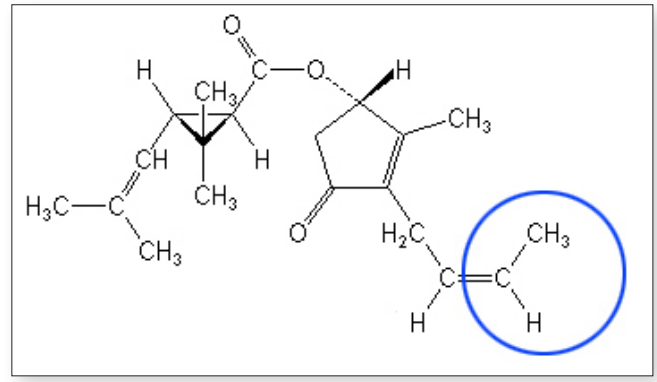

Figure 2. Cinerin I

the insect was 'knocked down', but it would later recover. This was because the pyrethrins are quickly detoxified by enzymes in the insect. It is for this reason that synergists such as piperonyl butoxide are usually added, to delay the enzyme action. The other issue is that they rapidly breakdown on exposure to sunlight, so pyrethrins provide no residual activity.

The drive to create synthetic variations was driven by the desire to improve upon this natural chemistry. The pyrethrins consist of an alcohol moiety (part) and a carboxylic acid moiety, joined together by an 'ester bond'. The pyrethroids were derived following this same structural route, making changes to the alcohol or acid moieties, and later the ester linkages, in order to improve the efficacy and residual performance of the molecules.

The first pyrethroid developed was allethrin (Figure 3), in 1949, by three scientists working for the United States Department of Agriculture (USDA). At the time, this was hailed as a major milestone in the field of chemical research, comparable to the development of synthetic rubber. The stability of allethrin made it superior to the natural pyrethrins in both kill and knock-down effects against mosquitoes.

The allethrin molecule is closely similar to that of cinerin I. Apart from stereochemical considerations, which will be discussed later, the only difference is that in allethrin, the 2-butenyl group, in the alcohol moiety, was replaced by an allyl carbon side chain. This is seen clearly in the diagrams below.

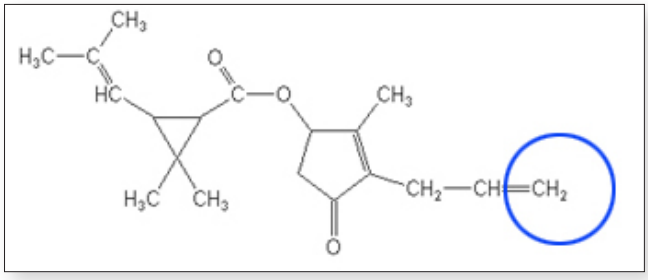

Figure 3. Allethrin

Allethrin's successful discovery was followed by the development of further pyrethroids through the 1960's; e.g. tetramethrin, resmethrin, and phenothrin. Known as Type I pyrethroids, these were more insecticidally active than pyrethrins, whilst retaining their low toxicity to mammals. They were also unstable in sunlight, so they still provided no residual protection. They remain to this day commonly used in flying insect killer aerosols and mosquito coils.

Whilst the low mammalian toxicity of pyrethrins and Type I pyrethroids is good for the environment, they provide poor efficacy when applied in situations where residual performance is important. This changed in 1974, when a team of scientists at Rothamsted Experimental Station in the UK, (now Rothamsted Research), developed the first Type II residual pyrethroids. Located at Harpenden in England, Rothamsted is one of the oldest agricultural research institutions in the world, having been founded in 1843 by John Bennet Lawes, on his inherited sixteenth century estate, Rothamsted Manor.

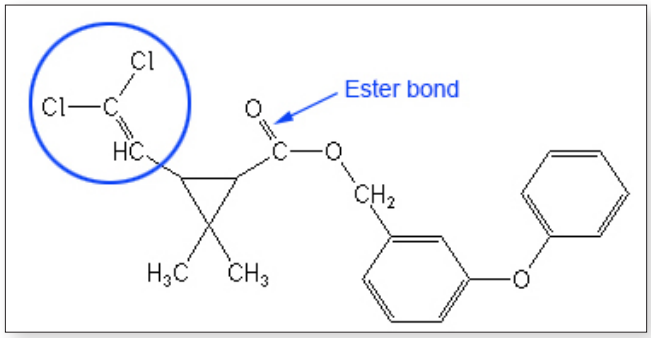

Figure 4. Permethrin

The first of these Type II residual pyrethroids was permethrin, which still possessed the basic cyclopropane carboxylic ester structure of the earlier Type I pyrethroids. The important point to note with the permethrin molecule though is the presence of the chlorine atoms at the end of the acid moiety, as highlighted in Figure 4. A Co-efficient of Insecticidal Activity (CoIA) Chart used to compare the potency of different pyrethroids rates permethrin as 10.

Cypermethrin was developed rapidly after permethrin. Cypermethrin, as the name suggests, is closely similar to permethrin, except it introduces a cyano-group on the alcohol moiety (Figure 5). This provided improved residual performance and insecticidal activity, with cypermethrin rated to have a CoIA of 25; 2.5 times greater than permethrin.

Within two weeks of developing the very first light stable pyrethroid, permethrin, the Rothamsted team developed the most potent pyrethroid, deltamethrin. This development 'simply' involved a substitution of the chlorine atoms at the end of the acid moiety in cypermethrin, with bromine atoms (Figure 6).

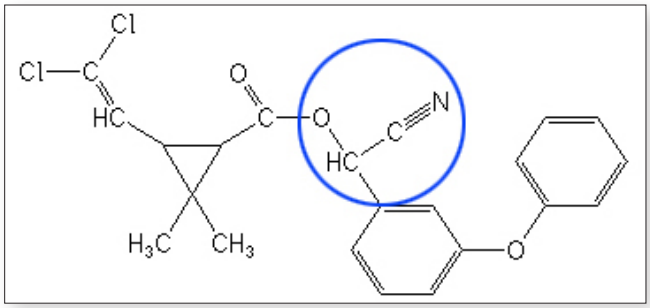

Figure 5. Cypermethrin

This substitution produced further improvements in residual performance and insecticidal activity, with deltamethrin having a CoIA of 100. The development of the Type II pyrethroids was rapid and their success in the market lead over the next decade or so to a range of further compounds, as various agri-businesses found it essential to have their own residual pyrethroids. Changes to the acid moiety lead to the development of fenvalerate, fluvalinate, tralomethrin, cyhalothrin, cyfluthrin, and bifenthrin.

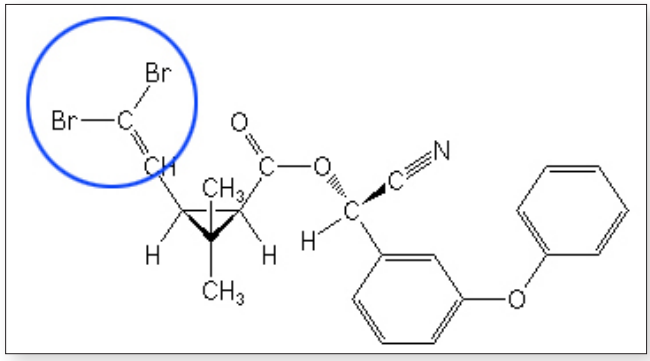

Figure 6. Deltamethrin

The presence of the cyano-group brought a degree of irritancy with it for people, and repellence for insects. In people this is generally observed as a transient parathaesia (tingling with numbness and burning). In insects this causes them to flee the area, which can lead to a spreading of the pest problem, particularly in public health situations.

Bifenthrin is an interesting pyrethroid since it uses fluorine atoms and, like permethrin, does not have a cyano-group (Figure 7). It displays high residual performance and insecticidal activity, with a CoIA of 33. Since it does not possess the cyano-group, it displays significantly lower levels of repellence, and offers interesting adaptations in the market, particularly for the residual control of mosquitoes. It also has good residual performance in the soil, making it an excellent soil termiticide.

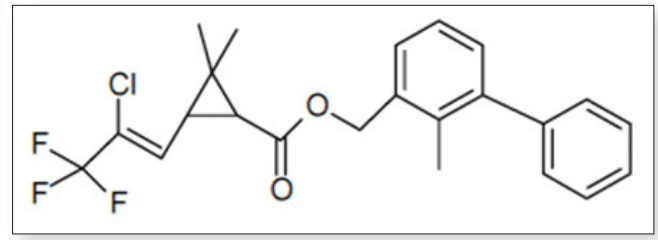

Figure 7. Bifenthrin

With the exception of deltamethrin, pyrethroids are a complex mixture of isomers. This means that they contain several molecules, all with the same chemical formula (the atoms are joined together in the same sequence), but they have a different spatial arrangement of the atoms. Technically such compounds are called stereoisomers. These stereoisomers often have different physical properties to each other, and in particular their insecticidal properties and mammalian toxicities are different. Some pyrethroids are composed of as many as eight different stereoisomers (shapes).

Permethrin was initially developed as either a 25:75 or 40:60 blend of cis:trans isomers. Originally, permethrin 25:75 was focused on public health markets, since the trans-isomer is less toxic to mammals. Thus, this was a less toxic isomer ratio. It displays slightly lower insecticidal activity, since the cis-isomer is slightly more insecticidally active.

Recent developments have seen companies exploiting the more potent stereoisomers of different pyrethroids. This produced new active constituents such as alpha-cypermethrin, followed by further purification to produce zeta-cypermethrin, with a CoIA of 40. Currently the culminant pyrethroid is the pure single isomer developed from cyhalothrin, gamma-cyhalothrin, which has a CoIA of about 140. Whilst this is a very high-performance insecticide, it is also highly irritant. ■

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