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Deltamethrin: The Cream of the Crop†

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ABSTRACT: Replacement of the pyrethronyl alcohol portion of the natural pyrethrins with the 5-benzyl-3-furylmethyl moiety gave bioresmethrin, a synthetic pyrethroid of high potency and safety but with limited photostability. Introduction of novel substituents at the 3-position of the cyclopropane ring then led to the discovery of insecticidally active compounds with greatly improved potency. Systematic changes of both the alcohol and acid components gave second-generation pyrethroids (permethrin, cypermethrin, and deltamethrin) with improved potency and photostability suitable for agricultural use. Metabolic studies showed that the photostabilized compounds remained biodegradable. Deltamethrin, discovered in 1974, was the cream of the crop and remains 36 years later as one of the most important synthetic pyrethroid insecticides.

KEYWORDS: deltamethrin, pyrethrins, pyrethroids, photostability

INTRODUCTION

I was a research chemist at Rothamsted from 1971 to 1985 and personally carried out many of the syntheses described here. My colleagues and collaborators were Michael Elliott and Norman Janes with an outstanding group of biologists. This review gives my personal observations of the exciting developments during that period that favorably changed insecticide chemistry and pest management science.

RETHRONYL TO BENZYLFURYLMETHYL PYRETHROIDS

The pyrethrins were the prototypes for the synthetic pyrethroids, which are flexible molecules having insecticidal action associated with their ability to adopt a conformation in which all of the structural features essential for potency are appropriately oriented with respect to one another and to a complementary receptor.[1] The chrysanthemic acid portion of pyrethrin I (**1**) and *S*-bioallethrin (**2**) has the 1*R*,*trans* configuration, and the ester function is at C-1 of the cyclopropane ring[2] (Figure 1). In 1967, Elliott et al.[3] announced the discovery of a number of novel pyrethroid insecticides derived from esters of 5-benzyl-3-furylmethylalcohol (5B3FA) with 1*R*,*trans*-chrysanthemic acid. Bioresmethrin (**3**) was more effective against several insect species than the natural pyrethrin I (**1**). It was also less toxic to mammals and maintained the nonresidual properties of the natural compounds.

The insecticidal properties of 5B3FA esters were further explored by variation of the acid portion, in particular, by examining the nature of the substituent at C-3 of the cyclopropane ring in more detail (Figure 1; Table 1). The introduction of various functional groups at this position was of interest. Methyl caronaldehyde (**15**) represented a convenient starting point for such a synthetic program (Figure 2) and was readily available by ozonolysis of methyl chrysanthemate. Treatment with a Wittig reagent or undergoing such condensation reactions would yield the desired products (Figure 2). The 5B3F esters were prepared from these intermediates using appropriate chemistry.[3] Simple changes at C-3 in the cyclopropane ring of bioresmethrin were found to give compounds with similar or improved insecticidal activity (**4**−**7**) while still maintaining low mammalian toxicity.[4] In particular, the methyl groups of the isobutenyl function at C-3 could be replaced with halogen atoms to give potent compounds with novel acid moieties (**5**). However, the inherent properties of these early pyrethroids would restrict their use. They were unstable in air and light, and although active against agricultural pests, they were not adequately effective in the field. Chemical considerations and spectroscopic evidence indicated that the furan ring of these esters was a probable site for photosensitized attack by oxygen.

PHENOXYBENZYL AND α-CYANOPHENOXYBENZYL PYRETHROIDS

In the early 1970s Sumitomo reported insecticidal activity in chrysanthemate esters containing 3-phenoxybenzyl (**8**) and α-cyano-3-phenoxybenzyl alcohols (Figure 3). Esters of the novel acid components were prepared using these potentially photostabilized alcohols. The insecticidal activity of some of these compounds relative to bioresmethrin is shown in Table 1. For simplicity, the stereochemistry about the cyclopropane ring had the 1*R*,*trans* assignment so that the natural compound could be compared to that of the synthetic analogues. The insecticidal activity of these novel benzyl alcohols was encouraging, and there were indications that they were active against several other insect species. Initial stability studies of the new esters to light were promising and indicated that the novel chlorinated compounds biopermethrin (**9**) and permethrin (**10**) were more photostable than bioresmethrin (**3**). This property alone would extend the scope for pest control. In addition, the oral toxicity to rats of permethrin (**10**) (1500 mg kg^{-1}), a mixture of four isomers, was

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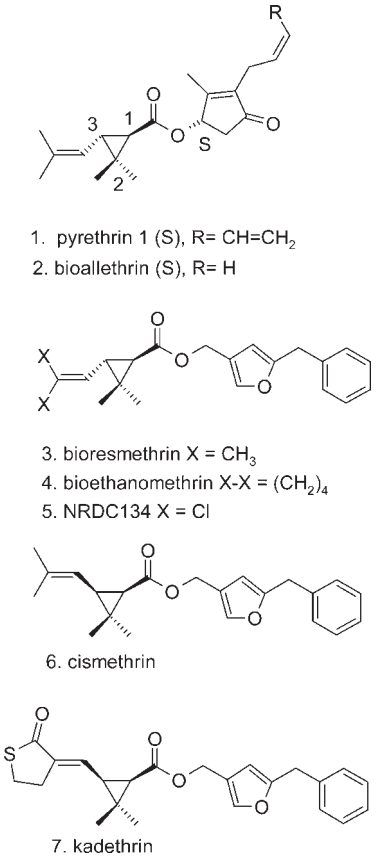

Figure 1. Rethronyl and benzylfurylmethyl pyrethroids.

Table 1. Toxicity of Pyrethroids to Houseflies (*Musca domestica* L.) and Mustard Beetles (*Phaedon cochleariae* Fab.) with Topical Application Compared with Bioresmethrin as the Standard

		relative toxicity	
	pyrethroid	housefly	mustard beetle
rethronyl and benzylfurylmethyl			
1	pyrethrin I (*S*)	2	150
2	bioallethrin (*S*)	9	4
3	bioresmethrin	100	100
4	bioethanomethrin	150	180
5	NRDC 134	240	280
6	cismethrin	42	52
7	kadethrin	39	52
phenoxylbenzyl and α-cyanophenoxybenzyl			
8	biophenothrin	31	72
9	biopermethrin	86	240
10	permethrin	69	140
11	cypermethrin	260	430
12	NRDC 156	~1000	~1000
13	deltamethrin	2800	5500
14	fenvalerate	47	100

lower than that of pyrethrin I (**1**) (260−420 mg kg^{-1}).[5,6] Esterification of the *cis*−*trans*-(±)-dichlorovinyl acid with

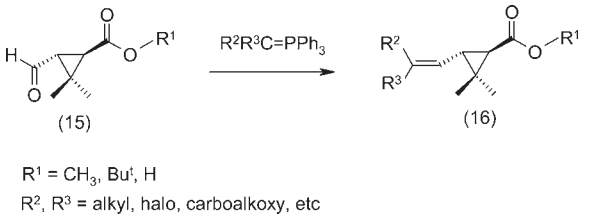

Figure 2. Modifications of the acid moiety.

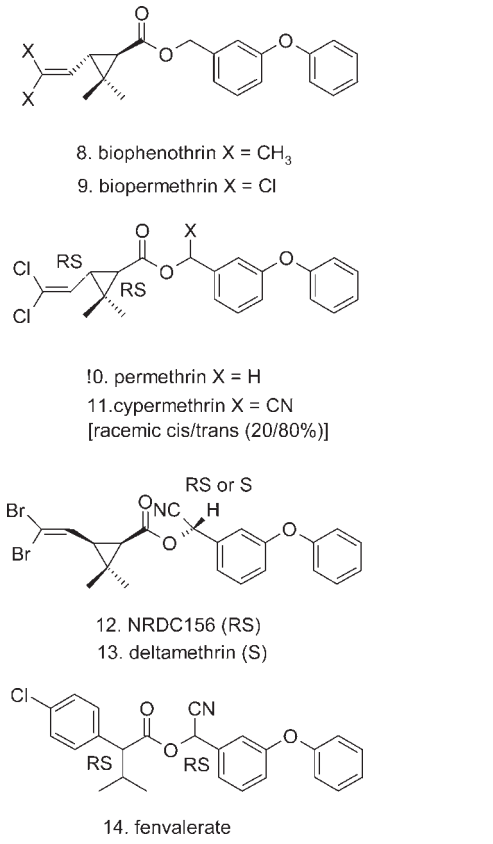

Figure 3. Phenoxybenzyl and α-cyanophenoxybenzyl pyrethroids.

α-cyano-3-phenoxybenzyl alcohol yielded cypermethrin (**11**), a mixture of eight isomers, the increased insecticidal activity of which was several-fold higher than that of permethrin. In the chrysanthemate series preferred compounds have the 1*R*,*trans* or 1*R*,*cis* stereochemistry relative to the carboxylic function about the cyclopropane ring.

In 1974 Elliott spent several months at Berkeley examining the metabolism in rats of the labeled 1*R*,*trans*- and 1*R*,*cis*-esters of permethrin.[7] These insecticidal esters were orally administered to rats at about 1 mg kg^{-1} and labeled with ^{14}C in the acid and alcohol moieties. These were synthesized either from 1*R*,*trans*- or 1*R*,*cis*-acid labeled in the side chain [$Cl_2{}^{14}C{=}CH-$] or from the alcohol labeled at the benzylic-$^{14}CH_2$ or in the phenoxy substituent. The radiolabeled carbons (∗) are shown in Figure 4. They were introduced using conventional chemistry. The labeled 1*R*,*trans*- and 1*R*,*cis*-esters were readily metabolized by ester cleavage or by hydroxylation of the geminal dimethyl group in the acid, or the phenoxy group of the alcohol, and by conjugation

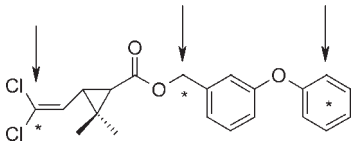

Figure 4. Radiolabeled carbons are shown by asterisks.

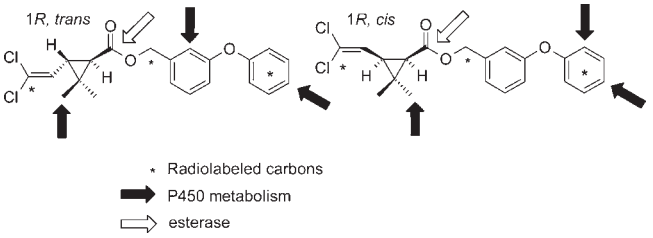

Figure 5. Metabolism in the rat.

of the resulting carboxylic acids and phenols. The metabolites were quickly excreted and did not persist significantly in tissues. This is summarized in Figure 5.

DELTAMETHRIN: THE CREAM OF THE CROP

The investigation continued by examining esters of 1*R*,*cis*-dibromovinyl acid with α-cyano-3-phenoxybenzyl alcohol. The isomer mixture (NRDC156) (**12**)[8] was isolated as a gum and was highly active as an insecticide. The molecular weight of 503 suggested that one or more of the epimers may potentially have a solid form. Consequently, the mixture was dissolved in hexane and placed in a deep freezer. Finally, after 2 months of patience, crystals separated out. Recrystallization yielded a single pure isomer, as determined by NMR spectroscopy.[8] The crystalline isomer, now known as deltamethrin (**13**), was hailed as a synthetic insecticide with a new order of activity.[8] The insecticidal potency of deltamethrin (**13**) exceeded that of all other pyrethroids reported at that time (Table 1). The activity against houseflies was further enhanced by pretreatment with the synergist sesamex, which decreased the LD_{50} from 0.00034 to 0.000018 μg per insect, a synergistic factor of 18. Combinations of novel acids and alcohols thus yielded incredibly potent insecticidal second-generation pyrethroids.[9] Much of this work could not have been predicted with respect to the level of insecticidal activity, even less so that the isomer that crystallized from the isomeric mixture (**12**) was the most potent compound deltamethrin (**13**). Even with this remarkable potency, commercialization would still require a cost-effective manufacturing route. Roussel Uclaf developed such a process based on dynamic resolution in which, after crystallization of the mixture (**12**) in a solvent, the solute was treated with a base, causing epimerization at the benzylic position and precipitating out more of the active insecticide. The absolute configuration of compound **13** has been established by X-ray analysis of crystals of deltamethrin. However, preliminary indications were obtained using in-house chemistry. α-Cyano-3-phenoxybenzyl alcohol with enhanced amounts of the (+) isomer was prepared and esterified with (1*R*,*cis*)-2,2-dimethyl-3-(2,2-dibromovinyl)cyclopropanecarboxylic acid chloride. This assignment was confirmed by NMR spectroscopy of the final esters. The absolute configuration of the α-cyano-3-phenoxybenzyl alcohol in the potent crystalline isomer was shown to be *S*.

Deltamethrin is now an established insecticide with outstanding potency, acceptable mammalian toxicity, and adequate photostability for crop protection. Relative to the Rothamsted research reviewed here, and other established insecticides, deltamethrin is the cream of the crop.

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