

Henrick C A, Staal G B & Siddall J B. Alkyl 3,7,11-trimethyl-2,4-dodecadienoates, a new class of potent insect growth regulators with juvenile hormone activity. *J. Agr. Food Chem.* 21:354-9, 1973.  
[Research Laboratory, Zoecon Corporation, Palo Alto, CA]

This paper describes a new class of insect growth regulators with very potent juvenile hormone activity (juvenoids), including isopropyl (2E,4E)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate (methoprene) and ethyl (2E,4E)-3,7,11-trimethyl-2,4-dodecadienoate (hydroprene). This was the first practically useful class of juvenoids, and three commercial products for insect control (methoprene, hydroprene, and kinoprene) were developed from this series. [The *SCI*® indicates that this paper has been cited in over 145 publications.]

## Methoprene and Hydroprene: Potent Juvenile Hormone Mimics

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August 11, 1989

Zoecon Corporation was incorporated in the state of Delaware on August 30, 1968, at 10:00 a.m. They were exciting times. Zoecon was set up by Syntex Corporation to develop the novel concept that insect pests could be selectively controlled, without environmental problems, by using analogs of their natural juvenile hormone. Carroll M. Williams at Harvard University had postulated<sup>1</sup> as early as 1956 that analogs of the then-unknown insect juvenile hormone (JH) had potential as "third generation insecticides." When Herbert Rölller and his coworkers at the University of Wisconsin successfully carried out the structural elucidation of the first natural JH (JH I) in 1967,<sup>2</sup> the way seemed open to exploit these discoveries for insect control.

When we moved into our new laboratory in Palo Alto on April 1, 1969, there were only 12 of us in the building, although our staff reached 39 by the end of that year. Our staff included John B. Siddall, a brilliant and gentle Englishman who was sadly to die in 1981 of acute leukemia at an early age; Gerardus B. Staal, an experienced Dutch entomologist; and me, an Australian organic chemist. Our staff had little or no business training and negligible knowledge of the agrochemical industry. Our confidence

and naivety were both extraordinary. In retrospect these qualities were important for success since at that time few of the conventional agrochemical companies were willing to invest the level of effort that we applied to such a chancy undertaking.

Hydroprene,<sup>3</sup> the first of this class of compounds, was prepared (as ZR-394; ZR-512 was a re-preparation) in October 1970 and showed high activity against many insect species. However, our excitement really began with the synthesis of methoprene.<sup>4</sup> I prepared the first sample of racemic methoprene (as ZR-484; ZR-515 was a re-preparation) in March 1971 and left on a short vacation. On my return we already had preliminary bioassay results and knew immediately that we had discovered something significant. The  $LC_{50}$  against the yellow-fever mosquito was a phenomenal 0.00017 ppm. Methoprene became our first commercial product, and it has been used worldwide as the standard juvenoid since its discovery. The first registered use pattern<sup>5</sup> was for the control of floodwater mosquitoes under the trademark Altosid Insect Growth Regulator. Methoprene was the first "biorational" insecticide, a term coined by Zoecon scientists in 1974 to describe our approach to developing new environmentally safe pesticides.<sup>6</sup> Methoprene is remarkably nontoxic to mammals with acute oral toxicity to rats of  $LD_{50} > 34,500$  mg/kg. It is in a sense also nontoxic to young insects in that it has no effect on early larval instars and only affects the last larval stages by interfering with metamorphosis.

Siddall and I subsequently shared the 1979 Inventor of the Year award for the invention of methoprene from our then-parent corporation, Occidental Petroleum.

Since the appearance of our initial paper, a great deal of research has been carried out in this field.<sup>7,8</sup> Methoprene has been used for many different applications, highlighted by its application (Precor) for indoor flea control due to its incredibly high activity against fleas.

Zoecon Corporation has changed considerably over the past decade. My friend and colleague Staal and I are still located at the same address, but we are now part of the Research Division of Sandoz Crop Protection Corporation. The commercial success of methoprene and subsequently hydroprene (for cockroach control)<sup>9</sup> has fully justified the initial enthusiasm and marked the beginning of the use of biorational insecticides for the selective control of insect pests in an environmentally safe manner.

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