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Nicotinoid Insecticides and the Nicotinic Acetylcholine Receptor

With 114 Figures, Including 9 in Color

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Preface

Insect pest control has continuously evolved from inorganics to botanicals, to chlorinated hydrocarbons, to organophosphorus compounds and methylcarbamates, then synthetic pyrethroids and most recently synthetic nicotinoids as the major classes. These insecticides allowed high standards of crop protection at minimal cost. A limitation in each new class of compounds is the selection of resistant strains and ultimate control failures and this serves as a driving force to discover and develop replacement compounds to circumvent resistance and overcome problem areas. The nicotinoids now play a critical role in meeting this need.

Three generations of chemicals are involved in the history of nicotinoid insecticides. The first generation was the botanical nicotine used for at least three centuries to control sucking insect pests but largely replaced in the 1940s and 1950s by the more effective organophosphorus compounds and methylcarbamates, some with systemic properties. Synthesis programs based on nicotine as a prototype did not yield compounds that could compete with other synthetic insecticides. The second generation was the nitromethylene type such as nithiazine, discovered by Shell scientists in a screening/optimization program. The nitromethylenes had the potency, selectivity, and systemic properties but lacked the field effectiveness largely because of photolability (so close yet so far from a major commercial product). The third generation required a series of advances made by Bayer researchers starting from nithiazine as the model and enhancing its photostability and potency with a nitroimine and chloropyridyl moiety, respectively, to give imidacloprid, the subject of much of this monograph.

Synthetic nicotinoids are the only major new class of insecticides introduced in the past 40 years. Imidacloprid is currently the top-selling insecticide. Acetamiprid, nitenpyram, and thiamethoxam (CGA 293-343) are increasingly important compounds. The next decade will set the pattern and establish most of the nicotinoids for future use. They will move from controlling only sucking insects to broader scope for chewing insects as well and will undoubtedly grow in number and importance in pest management. This has become the nicotinoid era.

"Nicotinoid insecticides" is the terminology used in the monograph title to include nicotine and the synthetic analogs of discernable structural and conformational similarities and the same mode of action in insects. Nicotinoids are related to nicotine as pyrethroids are to the pyrethrins. Definitions of this type become more diffuse as the knowledge base and diversity of compounds are increased, especially (as with the pyrethroids) if subsequent chemical structures become increasingly dissimilar from the nicotine and imidacloprid prototypes. "Neonicotinoids" as a term emphasized the relationship to nicotine and implied their improved properties; interestingly, neonicotine was the name used in 1931 for the botanical insecticide anabasine. Other names are based on substituents: chloronicotinyls, chloropyridyls, thianicotinyls, nitromethylenes, nitroguanidines, cyanoguanidines, etc.

Nicotinoid insecticide toxicology includes mode of action, metabolism, safety, and resistance. Insecticide safety is a primary consideration and the studies with imidacloprid and others are reassuring for the future. Biodegradability is an intrinsic feature of the effective structural types for now. The safety of the newer synthetic nicotinoid insecticides appears to reside in fundamental differences in the insect nicotinic acetylcholine receptor and that of mammalian nerve and muscle, an intrinsic target-site specificity. There are many closely related natural toxicants and candidate or commercial neuroactive pharmaceuticals, indicating the care necessary to maintain the required safety margin and unique selectivity for insects versus mammals. Insect toxicology and insecticide use are dominated by the specter of resistance, which has already appeared with the nicotinoids. The integration of nicotinoids into diverse pest management programs will help slow this development and prolong the benefits to be gained from this group of highly effective insecticides.

This monograph is based in part on a symposium by the same title held in September 1997 in Las Vegas, Nevada, as a part of the American Chemical Society National Meeting. This symposium was in honor of Professor Izuru Yamamoto on the occasion of his receiving the International Award for Research in Agrochemicals from the Division of Agrochemicals of the American Chemical Society. Each contribution has been revised, expanded, and brought up-to-date. Each author is thanked for a thorough and critical analysis of the relevant topic. The research at Berkeley was supported by Grant R01 ES08424 from the National Institute of Environmental Health Sciences of the National Institutes of Health. We dedicate this book to our students and colleagues who share with us a fascination for the chemistry and action of bioactive compounds and the goal of applying this knowledge for the benefit of all (except the insect pests).

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