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AZIRIDINES AS INSECT CHEMOSTERILANTS

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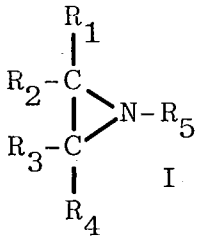
A B S T R A C T

The role of aziridinyl chemosterilants in controlling populations of harmful insects is discussed. Factors influencing sterilizing activity and applicability to practical use are reviewed.

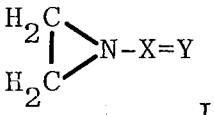
The derivatives of aziridine represent the largest and most extensively investigated category of insect chemosterilants. It was the search for cancer chemotherapeutic agents that gave the greatest impetus to the synthesis of new aziridines and well over a thousand of these compounds have been described in the literature (Bestian 1950, Dermer and Ham 1969). Several hundred aziridines were synthesized in our laboratory and tested as insect chemosterilants (Borkovec et al. 1968), however, many similar compounds were also supplied by various public and private laboratories. One of the important contributors to this program was Prof. Ernst D. Bergmann, Hebrew Uni- versity, Jerusalem (Bergmann et al. 1970, Fye et al. 1971, 1973).

The aziridine ring (Fig. 1., I) consists of one nitrogen and two



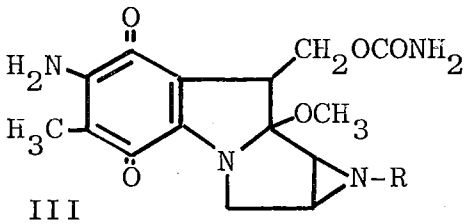
I

Ethylenimine R_{1-5} =H



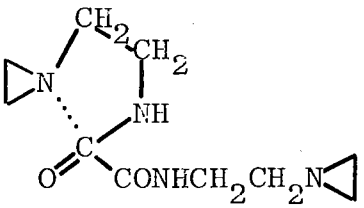
II

X= C, P, S
Y= O, S, N

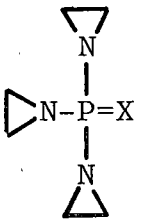


III

Mitomycin C R=H
Porfiromycin R=CH_3

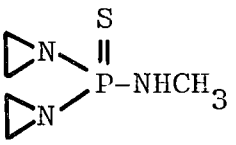


IV



V

Tepa X= O
Thiotepa X= S



VI

Fig. 1 - Structures of aziridinyl chemosterilants

carbon atoms which can be substituted by various substituents R_{1-5}. The carbon-nitrogen bond is easily broken and the resulting alkylamino group attacks nucleophilic centers in many types of molecules, including proteins, nucleic acids and other cellular constituents. Therefore, aziridines belong to a broad category of biological alkylating agents (Borkovec 1969) and most of their pharmacological properties are believed to be the result of their alkylating activity. Cytotoxicity is the most universal property of aziridines, but in insects this activity is seldom high enough to suggest possible uses as insecticides. Only the simplest aziridine, ethylenimine (Fig. 1., I), has been considered as a potential fumigant for controlling stored product pests (Harein and Soles 1964) but it was never registered for use in the United States. At lower, nontoxic doses, certain aziridines exhibit mutagenic effects in a large variety of organisms and this specific activity led to their application as chemosterilants in insects and other animals. The most important mutagenic effect that can be utilized in pest control is the induction of dominant lethal mutations in the pest's gametes, which renders the insect sexually sterile but nevertheless capable of sexual activity. Extensive studies of the relationship between structure and sterilizing activity (Borkovec 1969) led to the formulation of two simple rules concerning the effects of substituents on the aziridinyl carbon and nitrogen atoms. First, any substitution on the ring carbon (Fig. 1., I, R_{1-4}=H) leads to a decrease in sterilizing activity. Second, effective sterilants can be produced only by attaching to the ring nitrogen a polar, electron-rich system that will reduce the basicity of the aziridine.

Possible structures of such substituents are shown in Fig. 1., II. Although the two rules governing the activity of aziridines are largely empirical, very few exceptions to them have been encountered. The only C-substituted aziridines that showed high sterilizing activity (Kohls et al. 1966, Borkovec et al. 1968) belonged to a group of antibiotics related to mitomycin (Fig. 1., III). Unfortunately, the structural complexity of these compounds prevented their thorough evaluation. A possible exception to the second rule are aziridines containing an ethylamino group inserted between the aziridinyl nitrogen and the polar double bond; however, orientation and interatomic distances in the substituent indicate the formation of a pseudo 5-membered ring shown in Fig. 1., IV. Such a structure would be similar to other active 1-aziridinylcarbonyl chemosterilants and would account for their sterilizing properties. Unfortunately, only few aziridines of this type were described (Vashkov et al. 1970) and difficulties in synthesis obstruct further investigation.

Although most effective aziridinyl chemosterilants are not persistent and their acute oral toxicity in mammals is not excessive (Borkovec 1972), they are invariably mutagenic and therefore cannot be broadcast in nature in a manner similar to common insecticides. However their specific effects on the reproductive organs and gametes make possible their use as sterilants of captive insects that are to be released into natural populations. This unusual technique for controlling harmful insects and other organisms was first suggested by Knipling (1955) and its development was repeatedly reviewed by numerous authors (for references see Borkovec 1975). It is worth repeating, however, that the sterile insect release method (SIRM) is not universally applicable, that its most effective utilization requires the use of other pest control procedures, and that only a very small segment of the pest problem can be solved by its application. Furthermore, there are two competing procedures for inducing sterility in captive insects: chemicals and radiation. Certain generalizations of the advantages and disadvantages of either procedure can be made (Borkovec 1975) but it has not been possible to predict whether one or the other will produce more vigorous and competitive insects. Since only experimental evidence can answer this crucial question, research should be conducted on both alternatives.

One of the most promising areas of utilizing the SIRM is the control of insects that are vectors of human diseases. Successful field trials with ***Anopheles albimanus*** Wiedemann, a vector of malaria, were conducted in Central America (Lofgren et al. 1974) and additional studies are now in progress. An aziridinyl chemosterilant ***P,P***-bis (1-aziridinyl)–***N***–methylphosphinothioic amide (Fig. 1., VI) prepared in our laboratory was the sterilizing agent, but because the mosquitoes were treated as pupae and released as adults, the residues in the insects were low or not detectable (Seawright et al. 1973), and the environmental hazards of the procedure were negligible. Similar experiments with ***Culex pipiens fatigans*** Wiedemann, a vector of filariasis, were carried out in India (Rao 1974) with thiotepa (Fig. 1., V) as the sterilizing agent.

Application of the SIRM to insects of agricultural importance is most successful when their infestation is limited by geographical factors or by availability of host organisms. Imported and as yet unestablished pests may be suitable targets but generalizations are of little help in deciding pest control strategies. The first practical use of chemosterilants against the Mexican fruit fly, ***Anastrepha ludens*** (Loew), was not a population suppression program but a preventive measure designed to

avoid the possibility of infestation and subsequent migration of the pest (LaBrecque and Keller 1965). The aziridine tepa (Fig. 1., V) was used for sterilizing the flies as pupae, and the released adults contained no detectable residues of the sterilant (Chang and Borkovec 1966). The most ambitious application of the SIRM is the projected control and elimination of the boll weevil in the United States (Chiang et al. 1973). Although the chemosterilant used in the pilot experiment was not an aziridine, research on improved sterilization techniques employing aziridinyl compounds as well as radiation is still continuing. Undoubtedly, the final selection of the most advantageous technique will be made when the effectiveness, safety, and cost of each procedure are fully assessed.

The leading role of arizidinyl chemosterilants in the SIRM is still unchallenged. No other group of structurally related compounds contains such a large selection of sterilants active in both sexes of a variety of insects. Although the toxicological properties of aziridines are a serious problem that must be considered in any practical application, past experience shows that it can be overcome and that effective and safe utilization of these compounds is a distinct possibility.

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