tury (*22*). The concept of the series has evolved greatly during this time. However, changes in the concept of the soil series have been discussed elsewhere (*22*) and have not been considered in this article. The concept of the soil series and the relationship of that category to the higher categories in the scheme are discussed in the monograph on the 7th Approximation (*19*).

Concluding Remarks

The scheme of soil classification now being developed in the United States differs from earlier schemes prepared in this country and elsewhere in several ways which are important. This scheme reflects evolution in the concept of soil itself. Basic to the scheme is the concept that soil comprises a continuum on the land surface, one which can be subdivided into classes in a variety of ways. Also basic to the scheme is an effort to achieve more quantitative definitions than have been devised heretofore. Definitions of classes at every categoric level are expressed in terms of properties that can be observed or measured. These are important departures from schemes developed earlier for classifying soils.

The basic objectives of the classification scheme are essentially the same as those of earlier schemes, despite the differences in approach. The scheme must first of all organize, define, and name classes in the lowest category, and it must group these classes into progressively broader classes in higher categories and provide names for these classes. Its general purpose is to make the characteristics of soils easier to remember, to bring out relationships among soils and between the soils and other elements of the environment, and to provide a basis for developing principles of soil genesis and soil behavior that have prediction value. It is hoped that these purposes may be served better by the new scheme than by earlier ones, though only time will tell whether this hope has been realized.

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Sexual Sterilization of Insects by Chemicals

Eradication of harmful insects may be achieved with analogs of cancer chemotherapeutic agents.

Alexej B. Bořkovec

The successful eradication of the screw-worm, *Cochliomyia hominivorax* (Cqrl.), a serious pest of livestock, from the island of Curaçao, and subsequently from Florida and other states of the Southeast, by the systematic release of large numbers of male insects rendered sterile through irradiation (*1*) has attracted worldwide attention. Knipling (*2*), who originated this idea, has recently pointed out that chemically produced sterility has great potential compared with conventional insecticides for insect eradication. The irradiation technique has some obvious limitations. It requires mass release of the sterilized males, and this may often be undesirable or not even feasible. It requires a rather expensive, uniquely designed plant with specialized equipment to rear, transport, and irradiate the insects (irradiation is usually most effective on the pupal stage), and then it demands airplanes to dispense the packaged, sterilized insects. In some species (for example, the boll weevil, *Anthonomus grandis* Boh.) the irradiation dosage required for sterilization is so high that it drastically reduces the competitiveness of the insects or even kills them. The radiation-sterilization approach has other disadvantages, but the difficulties mentioned are sufficient to point up the desirability of developing a less costly and more practical method to achieve the same end with greater efficiency and flexibility. An effective male chemosterilant could be used to achieve the same result far more cheaply than irradiation. The prospects of developing effective chemosterilants which can be used safely under field conditions appear to be very good and are worthy of thorough investigation.

An insect chemosterilant may be defined as a chemical compound which, when administered to the insect, will deprive it of its ability to reproduce.

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This definition does not imply or specify the mechanism by which the compound operates; it simply classifies the compound by its final biological effect, which can be observed either in the laboratory or in the field. It is desirable to reserve the term *chemosterilant* for compounds which reduce or entirely destroy the fertility of the male ("male chemosterilants"), the female ("female chemosterilants"), or both sexes ("male-female chemosterilants"). Compounds which may interfere with the mating process are not included in this discussion.

It seems certain that most chemosterilants have some degree of species specificity and, therefore, that no compound would strictly deserve the general designation of, say, "male insect chemosterilant." Nevertheless, this point should present no problem as long as the specificity limitations are taken for granted.

Selection and Screening

In 1960 the Entomology Research Division of the Agricultural Research Service, U.S. Department of Agriculture, initiated a program of screening tests to find effective and safe insect chemosterilants. From the beginning of this program an attempt has been made to correlate the activity and the structure of each effective compound in order to select most efficiently the chemicals to be screened. Both theory and experimental data indicate a relationship between chemosterilants and so-called antitumor compounds used in cancer chemotherapy. The reproductive system always contains components with rapidly dividing cells which are in some respects similar to those in a growing tumor. It is conceivable that a compound effective in one system could also affect the other. This is an obvious oversimplification, but the experimental data (*3, 4*) have shown that most of the chemosterilants discovered thus far belong to one of the classes of compounds which are generally recognized as potentially carcinostatic.

A brief review of the most important classes of potential antitumor compounds follows (*5*).

Alkylating agents. Alkylating agents (*6, 7*) are chemically related materials which are thought to replace an active hydrogen in a biologically significant compound by an alkyl group. It is important to note, however, that from a chemical point of view a true alkylating agent introduces an alkyl group (a hydrocarbon residue) into a molecule, whereas the chemotherapeutic alkylating agents introduce a substituted alkyl group (aminoalkyl, hydroxyalkyl, thioalkyl, or even more complex radicals). The common chemical alkylating agents (for example, alkyl halides, alcohols, olefins), with the possible exception of alkyl sulfates, cannot be used under physiological conditions. Typical examples of chemotherapeutic alkylating agents are chloroethylamines and sulfides (nitrogen and sulfur mustards), aziridine derivatives (ethylenimines), and alkyl sulfates or sulfonates.

Antimetabolites. Compounds which are chemically and structurally similar to important metabolites are thought to be able to replace or displace these metabolites and thus render the metabolic process inoperative. Since the term *metabolite* itself is somewhat arbitrary, it is impossible to classify antimetabolites (*6, 8*) according to their chemical characteristics. There are certain structurally similar groups which serve as a basis for classification (for example, amino acids, purines, pyrimidines, and hormones). Sometimes compounds which can interfere with the in vivo synthesis or utilization of a metabolite are included. Such compounds may be entirely different from the metabolite chemically.

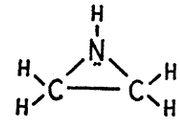
Radiomimetic compounds. Materials which have an effect seemingly similar to that of ionizing radiation (x-rays, gamma rays) are referred to as radiomimetic or radiation-simulating (*9, 10*). Their principal characteristic, supposedly, is an ability to attack directly the genetic material of a cell. Most alkylating agents are thought to belong to this class. Unfortunately, quite a number of entirely unrelated compounds may affect the genetic material directly or indirectly, and the decision as to whether the attack is direct or indirect is difficult to make.

Mitotic poisons. Compounds which are thought to interfere with the division of a cell nucleus are classified as mitotic poisons or antimitotic compounds (*9, 11, 12*). There is little general agreement as to the scope of this class. Loosely applied, the term *antimitotics* includes radiomimetics and practically all other compounds used in cancer therapy. The term is sometimes specifically applied to colchicine and its derivatives and to a group of biologically active quinones.

Miscellaneous agents. It is apparent that these various classes overlap to a considerable degree and that the usefulness of such a classification is very limited. Often, to avoid confusion, compounds which are neither alkylating agents nor obvious antimetabolites are classified as miscellaneous.

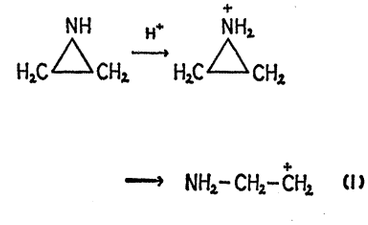
Chemistry

Aziridine derivatives. The most numerous and important of the chemosterilants known at present are aziridine derivatives. Aziridine (ethylenimine) is a nitrogen-containing heterocyclic compound with a three-membered ring (I), and most of its chemical properties can be understood in terms of its structure.



(I)

An excellent review of the chemistry of aziridine and its derivatives has been published by Bestian (*12*), hence only a few of the more important features are discussed here. The free pair of electrons on the nitrogen atom in the ring is responsible for the basicity of the compound and its consequent reactivity with nucleophilic reagents. The three-membered ring is a highly strained structure of low thermochemical stability (*13*), and a reactive ionic intermediate (II) is easily formed.

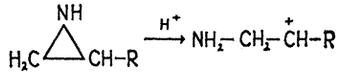


(II)

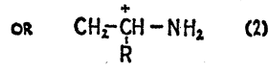
The ease with which the nitrogen accepts a proton, the ease with which the ring opens, and the reactivity of the carbonium ion II are all influenced by the substituents on the aziridine ring. Any one of the five hydrogens in aziridine can be substituted, and the effects of the substitution can be fairly well predicted if the position of the substituent, as well as its nature, is considered. If more than one of the hydrogens are substituted, the prediction becomes considerably more difficult and often only a qualitatively significant guess can be made. For discussion of the general

principles, it is sufficient to consider the case where there is only one substituent.

The substituent can be attached either to a carbon or to a nitrogen atom. Since the two carbons in the aziridine ring are equivalent, only two possibilities of nonequivalent substitution exist. A substitution on the nitrogen will either increase or decrease the availability of the free electron pair and thus govern the rate of the first reaction step in reaction 1. The main effect of substitution on a carbon, on the other hand, will be the decrease or increase of the electron density on that carbon and a subsequent increase or decrease of the reactivity of the carbonium ion II, especially if the substituent is attached to the electron-deficient carbon. It must be kept in mind that once a carbon in the aziridine ring is substituted (III), the two carbons cease to be equivalent and formation of two isomeric carbonium ions (IV and V) can occur.



(III) (IV)



(V)

It is not known whether this possibility has any effect on the biological activity of the aziridine derivative, but it may well influence the steric requirements of the alkylating moiety and the reaction mechanism.

A detailed discussion of this problem must include consideration of the two possible reaction mechanisms, S_{N_1} and S_{N_2}, according to which the alkylation can proceed. Clapp and his co-workers (*14*), Cromwell and his co-workers (*15*), and others have published a number of studies concerned with aziridine ring cleavage, and review of this work would be beyond the scope of this discussion. It appears that in biological systems the hydrolytical S_{N_1} process may be the main obstacle to the biochemically significant S_{N_2} process (nucleophilic attack by a physiologically significant molecule), and that an active compound must possess a proper balance of resistance (to the S_{N_1} hydrolysis) and reactivity (in an S_{N_2} reaction).

The substituent affects the behavior of the aziridine ring by virtue of its electronic and steric characteristics. The electronic inductive effects are easiest to interpret, and, fortunately, they seem to be of decisive importance in most monosubstituted aziridines. Nucleophilic substitution on the ring nitrogen or on one of the ring carbons could be expected to reduce the reactivity of the compound toward nucleophilic reagents, while electrophilic substitution should produce the opposite result. It is quite difficult, however, to predict the relative contribution of the S_{N_1} and the S_{N_2} processes to the overall reaction purely on a theoretical basis. From the assumption that the S_{N_1} process is of no biological importance and that only the S_{N_2} process gives rise to a physiologically significant reaction product, it follows that a desirable substitution would be the one which favors a direct nucleophilic attack on the ring rather than formation of an ionic intermediate. The general reactivity of the compound would then be only of secondary importance. The lack of chemosterilant activity of many 2,2-dimethylaziridines seems to support this assumption.

There are two other major factors which may be of importance. It is reasonable to suppose that the eventual sterilizing effect is a direct or even an indirect consequence of a reaction in which a molecule of the chemosterilant interacts with the physiologically significant moiety. The ability of the chemosterilant to reach the site of action is clearly essential to its proper function. It is conceivable that the carrier portion of the molecule (that is, the substituents on the aziridine ring) and its steric and solubility properties are critical and just as important as the rate at which it finally reacts. It is also apparent that the ease of transfer may vary from one species to another, and it may be that herein lies the main clue to the specificity of action of most chemosterilants. In spite of these complexities there are some simple generalizations which are useful in predicting and estimating the chemosterilant's activity. It was mentioned earlier that a nucleophilic substitution on a ring-carbon will decrease the alkylating ability of the compound. Complex aziridine derivatives as compared with similar 2-methylaziridine and 2,2-dimethylaziridine derivatives, show a progressive decrease in sterilizing activity which parallels the decrease in reactivity. There are some notable exceptions to this generalization, but as a rough estimate it is very useful.

Attempts at correlating structure and activity must include consideration of the possible relationship between the number of aziridine groups in a molecule and its sterilant activity. This problem is closely connected with the mode of action, and it is mentioned again later. Suffice it to say that effective sterilants have been found among the mono- and the oligoaziridinyl compounds but that the proportion of active to inactive compounds is lower in the monoaziridines than in the oligoaziridines.

Many aziridines are male-female sterilants, but it is not always easy to translate the experimental data into a clear statement which would classify a given compound unequivocally. The effect of 2,2,4,4,6,6-hexakis(1-aziridinyl)-1,3,5,2,4,6-triazatriphosphorine (apholate) on stable flies, *Stomoxys calcitrans* (L.), illustrates this problem (*4*). The compound affects both males and females. Mating of treated males with untreated females yielded a normal number of eggs which had a low viability. Mating of treated females with untreated males yielded an abnormally low number of eggs which had a normal viability. Only the mating of treated males with treated females, however, yielded a low number of eggs none of which hatched.

Chemosterilants other than aziridines. Most of the active compounds which do not contain the aziridine ring are female sterilants. There seems to be no chemical relationship which would make possible a useful classification. About 100 nonaziridine alkylating agents were tested on house flies (*Musca domestica* L.), screw-worm flies, or Mexican fruit flies [*Anastrepha ludens* (Loew)], but only a few showed sterilizing activity, and this was highly erratic and difficult to reproduce. In many of these compounds the sterilizing level and the toxic level were very nearly the same, and this may account for their erratic behavior. From more than 100 antimetabolites tested, two can be selected as good examples of compounds with clear-cut sterilizing activity. 5-Fluorouracil is an effective female sterilant for house flies, screw-worm flies, Mexican fruit flies, and oriental fruit flies (*Dacus dorsalis* Hendel); methotrexate (4-amino-N^{10}-methyl pteroylglutamic acid) is a female sterilant for house flies and screw-worm flies.

Mode of Action

Almost no experimental data are available concerning the interaction of chemosterilants with the insect organism, and the remarks which follow are strictly in the realm of speculation. Because the alkylating agents, and specifically the aziridines, are at present the most promising chemosterilants, only this class of compounds is considered here. It seems certain that the aziridine ring is the essential carrier of the sterilizing activity and that it interacts at some point with a biologically significant molecule which is responsible for the success or failure of the reproductive process. The most important, and still unresolved, question concerns the identity of this biologically significant molecule. The mode of action of some antimetabolites (for example, 5-fluorouracil) has been elucidated to a considerable extent (*8*), and it appears that with these compounds the biologically significant molecule is an enzyme which is normally required for the in vivo synthesis of nucleic acids. There seems to be no reason to believe that the same mechanism is not applicable to an insect organism. Unfortunately, no such evidence is available regarding the aziridines or any other alkylating agents. The crosslinkage hypothesis of Stacey and others (*16*), in which the biologically significant moiety was assumed to be a chromosome, cannot account for the activity of monofunctional aziridines unless one makes the dubious assumption that the monoaziridines react differently from the oligoaziridines. A recent suggestion by Timmis (*8*) is of interest in this connection. He speculates on the possibility that the action of alkylating agents is essentially similar to that of the antimetabolites although the blocking of the important enzyme may not be accomplished by the alkylating agent itself but rather by an antimetabolite which the agent forms *in situ* with an available metabolite. A second alkylating function would be an added advantage because the newly formed antimetabolite would be able to react irreversibly with the enzyme and its efficiency would be thus increased. It is interesting to note that this hypothesis not only would explain the apparently higher activity of the *bis*-aziridines as compared with monoaziridines but would account also for the lack of difference between *bis*-, *tris*-, and other oligoaziridines.

Application

It is apparent that the practical application of insect chemosterilants under other than strictly controlled laboratory conditions will present some problems. The main problem with some of the early chemosterilants was their potential toxicity to beneficial species of insects, wildlife, and plants and, most importantly, to man. In principle, the same difficulties were encountered previously with highly toxic insecticides and fumigants. Although chemosterilants may present some serious complications in the form of possible genetic effects which may not be immediately observable, it may be expected that methods of application will be ultimately devised which will obviate or eliminate the toxicity hazards. It should be emphasized, however, that at present we are in the initial stages of research on chemosterilants and that only continuation and intensification of this work will bring about fulfillment of the promise which this approach offers.

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