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# Discovery of Insect Anti–Juvenile Hormones in Plants

## Plants yield a potential fourth-generation insecticide.

William S. Bowers, Tomihisa Ohta,
Jeanne S. Cleere, Patricia A. Marsella

Insect hormones have been researched intensively for about 30 years. Although the genesis of these studies was purely academic, increasing attention has been focused in recent years on the potential use of the insect juvenile hormones (JH) as candidate insecticides.

After some 10 years of research on JH's and active analogs as candidate insecticides, an understanding of their potential efficacy has emerged which indicates some limited practical applications but falls short of the more optimistic predictions expressed in the earlier stages of insect hormone research (*1*). The main drawback to the usefulness of JH as an insecticide is the short duration of the developmental period during which the insect is sensitive to the application of exogenous JH. The application of excess JH can upset development only during the brief period of metamorphosis that takes place when the immature insect molts to the adult stage; therefore, the application of JH to mixed developmental stages as they occur in most field situations is not sufficiently effective to provide acceptable insect control. The immature and adult stages are not controlled by excess JH and are able to cause damage such as crop destruction, disease transmission, and the like. Conversely, since JH is necessary throughout most stages of insect life, a hormone antagonist or antihormone would be a more efficacious insecticide. In order to understand the potential utility of such an antihormone, a brief summary of the importance of JH to the growth, development, reproduction, and diapause of insects is necessary.

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### Chemistry and Biological Activity of Juvenile Hormone

After the discovery of the JH activity of farnesol (Fig. 1, **1**) and farnesal (Fig. 1, **2**) by Schmialek (*2*), Bowers *et al.* (*3*) obtained a profile of the necessary structural moieties of JH through chemical degradation and regeneration of the JH activity in extracts from cecropia silk moths. This structural information, when incorporated into a sesquiterpenoid framework based on farnesol, resulted in the synthesis of (*E,E*)-10,11-epoxymethylfarnesenate (Fig. 1, **3**), which was found to possess all of the biological activities of the hormone (or hormones) in the cecropia extract. Subsequently, Roller *et al.* (*4*) isolated and identified a JH from cecropia (Fig. 1, **4**) and Meyer *et al.* (*5*) isolated a second JH from cecropia (Fig. 1, **5**). The first hormone (Fig. 1, **3**) was later authenticated as a natural hormone from *Manduca* (tobacco hornworm) larval blood (*6*). After the identification of the natural JH's, many research groups began to study the potential utility of these hormones for insect control. The natural JH's were quickly found to be too labile for field applications, but the discovery of JH activity in certain commercial insecticide synergists (*7*) revealed the possibility of developing highly active JH analogs containing an aromatic nucleus. Two such aromatic terpenoid ethers (Fig. 1, **6**) (*8*) and (Fig. 1, **7**) (*9*) were developed and are at least a thousand times more active against certain insects than the natural JH's. Zoecon (*10*) developed a highly active JH analog, Methoprene (Fig. 1, **8**), which is now registered for floodwater mosquito control and for the control of flies that breed on manure. It should be made clear that the enthusiasm for developing hormonal methods of insect control is based on the understanding that JH regulates processes in insects for which there are no endocrinological counterparts in man and other so-called higher animals. Adult development in man is dependent on the secretion of certain hormones, especially hypophyseal gonadotropins; conversely, JH's prevent insects from maturing and thus must be absent during the last stages of insect metamorphosis for adult development to occur. When JH is applied to an insect at a time when it should naturally be absent, adult morphogenesis is deranged, resulting in insects with a mosaic of juvenile and adult characters, which are unable to feed, mate, or reproduce and which soon die (*11, 12*). Although the corpora allata are quiescent during the ultimate stages of metamorphosis, they reawaken in the adult stage and again secrete JH's, which are necessary for ovarian development (*13*). If the corpora allata are removed surgically, the ovaries fail to develop and the insect is sterile (*14*).

Diapause is a condition of arrested activity during which insects do not feed, mate, or reproduce. The diapause state allows many insects to survive periods of climatic stress, such as winter and drought. In insects that diapause as pupae, a lack of brain hormone (prothoracotropic hormone) is responsible (*15*). In certain insects that diapause as larvae, a continuing titer of JH is necessary (*16*), whereas a lack of JH causes diapause in many adult insects (*17*). Thus, the JH's by their presence or absence are responsible for diapause during different insect stages.

It is clear that JH is necessary for multiple physiological functions throughout juvenile and adult life. Juvenile hormone secretion is somehow regulated by the insect during the physiological events described above; however, the source of this control is obscure and may differ with the species or developmental stage studied. If one could somehow terminate JH secretion, immature insects would be expected to molt precociously to adults, larval insects dependent on a high titer of JH for diapause would be unable to diapause, adult insects that require JH for ovarian development would be sterile, and those species which diapause through a lack of JH would be artificially thrust into diapause. Insects dependent on JH for production of sex pheromones would be rendered unattractive. The introduction of an antiallatotropin (anti-JH) into a colony of social insects such as ants and termites, which feed and groom their young and maintain a reproductive queen, would be disastrous. In addition to disrupting immature development and sterilizing the queen, the caste systems, which have been shown to be under JH control (*18*), should be deranged. Thus, a method of interfering with JH secretion would be, a priori, a method of insect control.

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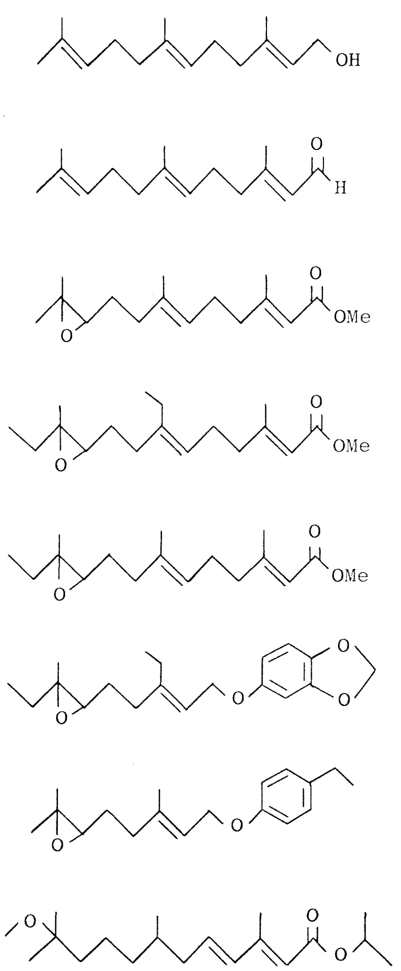


Fig. 1. Natural JH (**3–5**) and mimics.

## The Search for Anti–Juvenile Hormones

Since the idea of an anti-JH or hormone antagonist presents such attractive possibilities for insect control (*12, 19*), aside from the utility of such a tool for uncovering as yet unknown functions of JH, it seemed reasonable to us that an inhibitor of JH biosynthesis, release transport, or action might be found in sources quite apart from the insect itself. We turned to plants, a natural resource of compounds that have proved to be important in biology and medicine. Insects and plants have undergone coevolution at least since the Lower Carboniferous and some of the allelochemic relationships between insects and plants are well understood. Many chemicals in plants are known to determine host plant preference of insects and to stimulate insect feeding (*20*). Other compounds serve as lures for parasitic insects or are repellent. Some juvenile hormonally active compounds in plants have been discovered (*21*). The powerful compound 2,4-dihydroxy-7-methoxy-1,4-(2*H*)benzoxazin-3-one, which inhibits insect feeding, has been shown to be an important factor in the resistance of dent corn to the European corn borer (*22*). Gossypol and related compounds in cotton inhibit larval growth of many cotton insects (*23*). Hundreds of such interactions between insects and plants are well known and documented. Plants have been extracted by many investigators in the search for insecticides (*24*). However, in most of these studies the extracts were prepared by extraction with polar solvents (such as water or alcohol) in an attempt to find polar toxins like rotenone and ryanodine. Most of the biological testing was done with adult insects and the major criterion was death or moribundity within 24 to 48 hours. Such a criterion would be sufficient to uncover indifferent toxicants of the conventional sort but would not reveal an anti-JH. Our approach was to extract plants with a mixture of ether and acetone to obtain the less polar organosoluble plant compounds, and to test these extracts on immature insects by continuous contact throughout their development until successful metamorphosis and reproduction ensued. If metamorphosis occurred and reproduction was successful, with the production of viable offspring, the tests were terminated.

In the course of our studies we found several plant extracts that inhibited feeding, interfered with molting, and were generally toxic. Finally, a plant extract was discovered that induced precocious metamorphosis in immature hemipterans and prevented ovarian development in several adult insects. Subsequent testing has revealed a full range of antiallatotropic activities, including the induction of diapause in Coleoptera. The antiallato-

Table 1. Induction of precocious metamorphosis in the milkweed bug with anti-JH.

| Hormone | Concentration* ($\mu$g/cm$^2$) | Percent precocious adults |
|---|---|---|
| Precocene 1 | 3.9 | 100 |
| Precocene 1 | 1.9 | 0.0 |
| Precocene 2 | 0.7 | 90.0 |
| Precocene 2 | 0.4 | 15.0 |
| Control | | 0.0 |

*Twenty 2nd-stage nymphs were confined to a 9-cm petri dish coated with the precocene residue.

Table 2. Sterilization of insects with precocene 2.

| Concentration | Insect |
|---|---|
| 7.0 $\mu$g/cm$^2$* | Milkweed bug (*Oncopeltus fasciatus*) |
| 7.0 $\mu$g/cm$^2$† | Cotton stainer (*Dysdercus cingulatus*) |
| 1.5 $\mu$g/cm$^2$‡ | Apple maggot (*Rhagoletis pomonella*) |
| 1000-ppm spray§ | Mexican bean beetle (*Epilachna varivestis*) |

*Eight newly emerged females were confined to a treated 9-cm petri dish for 48 hours. Ovaries were examined for development after 6 days. †Ten newly emerged females were confined to a treated 9-cm petri dish for 72 hours. Ovaries were examined for development after 13 days. ‡Forty-five newly emerged apple maggot females were confined to a 9-cm petri dish containing a residue of the test compound for 30 hours. After treatment, flies were held in oviposition cages and examined for ovarian development when control insects began oviposition. §Ten newly emerged Mexican bean beetle females were sprayed while feeding on a bean plant with emulsified precocene 2. Ovaries were dissected out and examined for development when controls began oviposition.

Table 3. Induction of diapause in Colorado potato beetles with precocene 2.

| Concentration topical ($\mu$g)* | Percent of beetles entering diapause† |
|---|---|
| 500 | 40 |
| 200 | 38 |
| 100 | 75 |
| Control | 0 |

*Beetles were treated topically on the abdomen with precocene 2 in 1 $\mu$l of acetone and held on potato plants growing in soil. †After 21 days beetles remaining on the plants were judged nondiapausing. Insects which had entered the soil were judged to be diapausing.

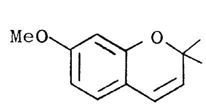
tropic extract was prepared from the common bedding plant *Ageratum houstonianum*. From 72 grams of fresh plants 1 gram of highly active oil was obtained. The scheme of purification that resulted in the isolation and identification of two active compounds, 7-methoxy-2,2-dimethylchromene and 6,7-dimethoxy-2,2-dimethylchromene, is shown in Fig. 2. In view of their induction of precocious metamorphosis, we have named them precocene 1 and 2. A synthetic method of general utility is given in Fig. 3. Subsequently, we found that precocenes 1 and 2 have previously been identified as natural products and synthesized (*25*).

### Biological Activities of the Precocenes

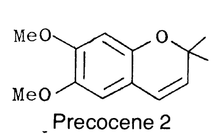
*Precocious metamorphosis*. The initial discovery of the anti-JH activity of the precocenes was made by treatment of 2nd-instar milkweed bug nymphs by contact with the crude lipid extract of *Ageratum*. Miniature adults were formed after molts to apparently normal 3rd- and 4th-instar nymphs. Under these circumstances the 5th instar was omitted. With the pure compounds we found that precocene 2 was about tenfold more active than precocene 1 (Table 1). After purification of the precocenes, we found that with the pure compounds we could induce precocious maturation (Fig. 4) from 2nd-, 3rd-, and 4th-instar nymphs by treatment of the 1st, 2nd, and 3rd instars, respectively. Thus, in order to induce precocious metamorphosis we were obliged to treat the previous instar. In Fig. 4 it can be seen that a treated nymphal stage gives rise to an additional nymphal instar which then molts to the precocious adult. Apparently an intercalary instar is necessary after the induced cessation of JH, which allows the expression of genetic information intermediate between the nymphal progression and the genetic information requisite to adult development. In this respect the intercalary instar that succeeds the treated stage may assume the function of the normal 5th-stage nymph, which by analogy must functionally resemble the pupal stage of the Holometabola. Alternatively, a period of time exceeding the normal length of an instar may be required for the precocene to sufficiently lower the JH titer to permit precocious metamorphosis. Although the morphology and coloration of the precocious adults is identical with that of normal adults, the wings of precocious adults do not expand as fully as do those of normal adults. The degree of wing cell multiplication is apparently prescribed by the

72-gram whole plants: *Ageratum houstonianum*

1. Extraction.
   Homogenized in diethyl ether and acetone (1:1).
   Yield 1 gram of crude lipid.
2. Florisil column chromatography of 0.7 gram of crude lipid.
   Stepwise elution with increasing concentration of diethyl ether in petroleum ether.
   Two active fractions.
3. Thin-layer chromatography of active fractions with petroleum ether, diethyl ether, acetic acid (90 : 10 : 1).
   Two active substances obtained in pure form.
   Substance 1: 16 mg (Rf 0.71)
   Substance 2: 20.3 mg (Rf 0.17)
4. Nuclear magnetic resonance and mass spectrometry.




Precocene 1




Precocene 2

Fig. 2. Isolation and identification of antiallatotropins from *Ageratum houstonianum*.

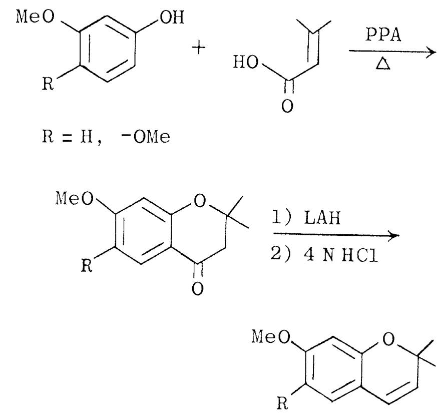



Fig. 3. Synthesis of antiallatotropins (*28*).

number of molts. The color and venation of the wings, however, are definitely adultoid, proving that adult differentiation has been accomplished. Another interesting developmental characteristic of Hemiptera is the possession of two segmented tarsi during the nymphal stages, which give rise to three segmented tarsi in the adult stage. If the precocious molt occurs from the 4th instar (omitting the 5th instar), precocious adults with three segmented tarsi are formed. Precocious adults arising from 2nd- and 3rd-instar nymphs, however, retain two segmented tarsi, indicating that certain morphological features require a fixed minimum number of developmental stages. We have also been able to induce precocious metamorphosis by fumigation of milkweed bug eggs with the precocenes. The eggs were removed from the fumigation chamber just prior to hatching, and the empty chorions were removed immediately after hatching to minimize contamination. The normal 1st, 2nd, and 3rd instars that developed gave rise to precocious adults, omitting the 4th and 5th stages. The progression through three normal nymphal instars before undergoing precocious metamorphosis might be explained by considering that very little of the compound actually penetrated into the embryo and therefore required a much longer time to be effective than did contact or direct topical treatment of a nymphal stage. Other Hemiptera are also quite sensitive to the precocenes; we have been able to induce precocious metamorphosis in *Lygaeus kalmii* Stål and in *Dysdercus cingulatus* (F.) (Fig. 5).

*Antigonadotropic activity*. All of the precocious adult female insects possessed well-formed ovaries that remained essentially undeveloped throughout their short lives. This result gave conclusive proof that the corpora allata were inactive, since the allata are known to be the source of the gonadotropic (juvenile) hormone (*13*). Treatment of a variety of adult insects with the precocenes (especially precocene 2) soon after their emergence prevented ovarian development. Table 2 shows the antigonadotropic activity of precocene 2 on a variety of insects. In addition to preventing ovarian development, precocene 2 applied to inseminated gravid milkweed bugs caused yolk resorption and regression of the ovaries back to the undeveloped condition. Interestingly, the eggs deposited within a few hours after treatment with precocene 2 (prior to resorption of the remaining eggs) hatched and developed to the 3rd instar and then molted into precocious adults. A small amount of the antihormone must have reached the eggs and induced precocious metamorphosis later in development. This result parallels the effect of fumigation of eggs with precocene 2 as described above.

*Diapause induction*. Diapause in adult Coleoptera has been shown to depend on the cessation of JH secretion (*17*), which, in the case of the Colorado potato beetle, is induced by exposure of the larvae to short-day photoperiod. We found that topical treatment of normal, nondiapausing Colorado potato beetles with precocene 2 induced a substantial percentage of the beetles to leave their food plants, burrow into the soil, and construct diapause cells. During 4 months of observation none of these beetles reemerged from the soil. In Table 3 the most effective concentration was 100 μg, which was the lowest dosage applied. Activity and feeding were severely depressed at the higher concentrations and it is possible that these beetles were forced into diapause so rapidly that they were unable to crawl from the plant and burrow into the soil.

*Ovicidal activity*. A number of reports indicate that JH and analogous mimetic compounds block embryogenesis (are ovicidal) when applied to eggs in a solvent carrier (*26*). The results detailed in Table 4 show that the precocenes are ovicidal by fumigant action on the eggs of the milkweed bug and the Mexican bean beetle, as well as by contact spray to the Mexican bean beetle. The ovicidal action seems to occur rather late in embryogenesis, since most of the eggs contained fully developed embryos and a few nymphs or larvae did emerge; however, all of these died within a few hours. Since very little is known about the endocrinological events during insect embryogenesis it is inappropriate to speculate on the mode of ovicidal action.

## Reversal of Antiallatotropic Activity

If the precocenes actually inhibit secretion of the corpora allata, by action directly on the gland itself or indirectly by way of mediation of some other control center (brain, corpora cardiaca ?), it should be possible to reverse the antiallatotropic activities at the target level by treatment with exogenous JH. Although we have not yet attempted to reverse all of the antiallatotropic activities, we have prevented precocious maturation of milkweed bug nymphs by combined treatment with precocene 2 and JH **3**. We have similarly treated adult milkweed bugs with precocene 2 and JH **3** (Fig. 1, **3**), and observe that mating, ovarian development, oviposition, and embryogenesis proceed normally. The undeveloped ovaries of milkweed bugs sterilized by treatment with precocene 2 are shown in Fig. 6 and contrasted with ovaries that develop normally when precocene 2 and JH **3** treatments are combined, effecting complete reversal. As noted previously, the ovaries of precocious females do not develop. Further, these females refuse to

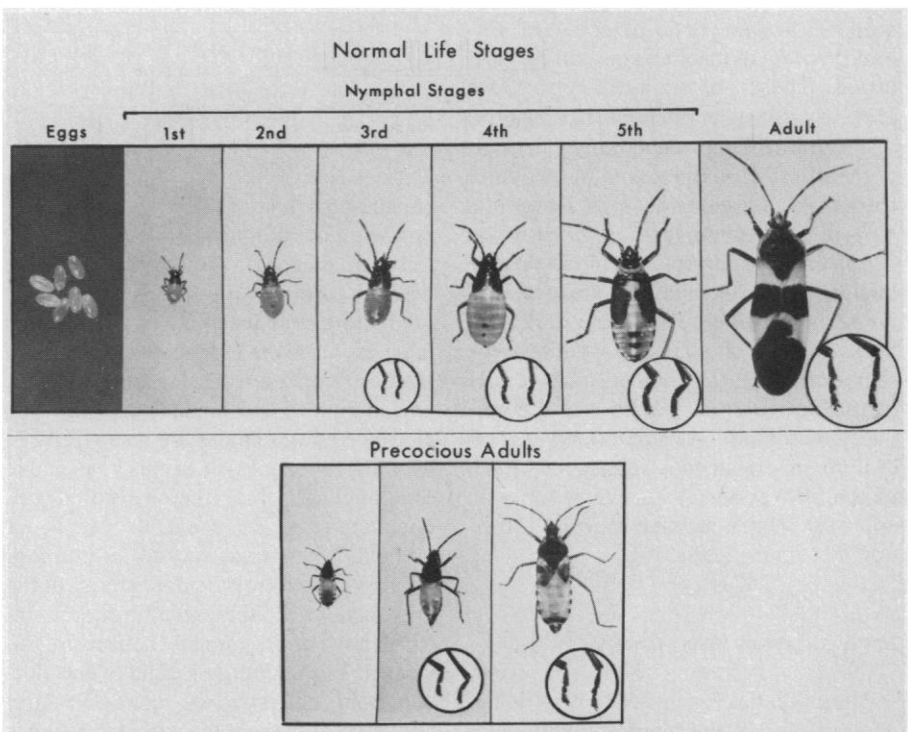



Fig. 4. Induction of precocious metamorphosis in the milkweed bug *Oncopeltus fasciatus*. Treatment of 1st, 2nd, and 3rd nymphal stages induces precocious metamorphosis from the succeeding 2nd, 3rd, and 4th stages.

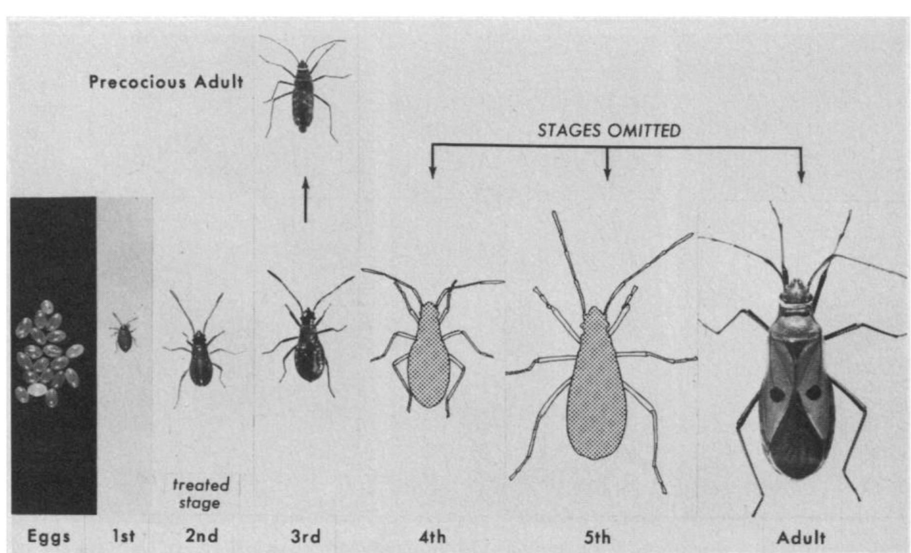



Fig. 5. Induction of precocious metamorphosis in the cotton stainer *Dysdercus cingulatus*. A treated 2nd-stage nymph underwent development in an apparently normal 3rd-stage nymph, and then molted into a precocious adult.

mate with either precocious or normal males, thereby demonstrating their lack of sexual behavior. After topical treatment with JH 3 precocious females undergo ovarian development and have been observed to mate, although oviposition has never occurred.

## Mode of Action of Anti-Juvenile Hormones

It is clear from the reversal experiments that the precocenes depress the JH titer. Although we are ignorant of the mode of action of the precocenes, several theoretical mechanisms can be visualized. These are (i) interference with JH biosynthesis in the corpora allata; (ii) disruption of brain regulation of the corpora allata; (iii) induction of enzymes responsible for metabolism of JH (or of a biosynthetic precursor); (iv) disruption of, or competition for, hormone protein binding (*27*); (v) mimicry of some hormone metabolite responsible for feedback control of allatal biosynthesis or secretion; and (vi) competition with JH at the active sites. Additional theories will undoubtedly be generated as research on precocenes intensifies. Each of the above suggestions represents an approach that is amenable to investigation by existing technology.

## Implications for Insect Control

The potential for insect control is implicit in each of the biological actions of the precocenes. The induction of precocious metamorphosis not only shortens the life cycle of the immature stages, but results in diminished feeding (that is, less crop damage). Although a few of the precocious males are capable of successful mating and insemination of normal females, all of the precocious females are sterile. Successful mating between precocious males and females is exceptional. Since adult females are also sterilized by the precocenes, it seems reasonable to conclude that the mixed developmental stages of insects as they occur in field populations would be susceptible. Whether the ovicidal activity of the precocenes is the result of an intrinsically antihormonal action is unknown. The endocrinological events during embryogenesis are quite obscure; however, at present the ovicidal action is fortuitous and complimentary to the overall pesticide potential.

Table 4. Ovicidal action of precocene 2.

| Dose | Percent to hatch | Percent dead larvae within 24 hours | Insect |
|---|---|---|---|
| *Treated by fumigation** | | | |
| 0.5 mg | 2 | 100 | Milkweed bug |
| 0.2 mg | 0 | 0 | Mexican bean beetle |
| *Treated by contact spray†* | | | |
| 100 ppm | 2.7 | 100 | Mexican bean beetle |
| 10 ppm | 18.4 | 76.7 | Mexican bean beetle |
| Control | 80.0 | 0 | Mexican bean beetle |

*Newly laid eggs were confined in watch glasses and exposed to the vapors of precocene 2 deposited on the lid of the watch glass. †Four-day-old eggs were sprayed with precocene 2 in an emulsion formulation.

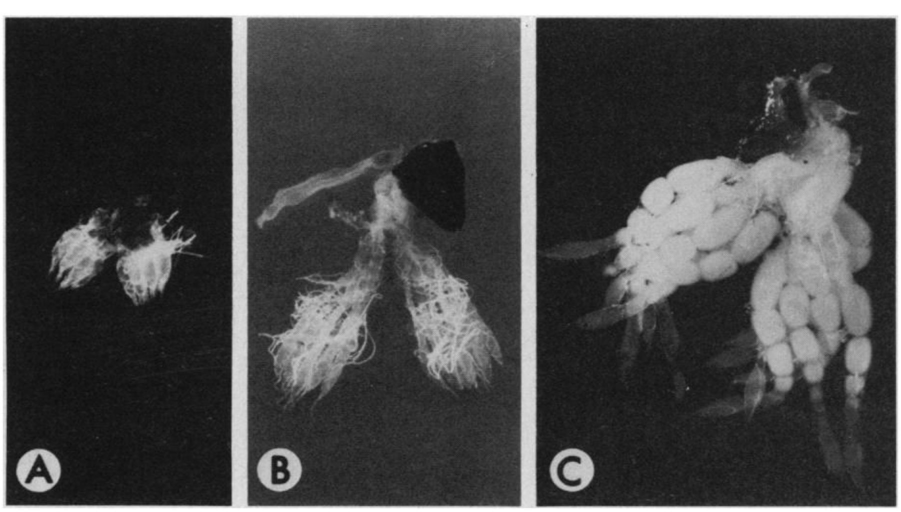



Fig. 6. Effect of precocene 2 on ovarian development of milkweed bugs. (A) Ovaries of precocious adult developing from 4th-stage nymph. (B) Undeveloped ovaries of 5-day-old adult treated with precocene 2 on the day of eclosion. (C) Fully developed ovaries of 5-day-old adult treated with precocene 2 and JH3 on the day of eclosion.

The facile induction of diapause in the Colorado potato beetle illustrates an additional exciting possibility for insect control. Since diapausing insects do not feed, mate, or reproduce, damage to crops and livestock would be eliminated.

An additional effect of the precocenes, which we have observed in Hemiptera, is that a few treated nymphs are unable to molt and remain as nymphs until death. The secretion of molting hormones (ecdysones) must have been blocked directly or indirectly by the precocenes. One can hypothesize that the precocenes have somehow prevented the synthesis or release of ecdysiotropin (brain hormone), which is necessary for the secretion of molting hormones. In partial support of this theory, we find that blocked nymphs are induced to molt by injection of $\beta$-ecdysone. Alternatively, the precocenes may interfere directly with ecdysone synthesis. It should be emphasized that inhibition of molting occurs in less than 10 percent of treated 4th- and 5th-instar nymphs and then only at near-toxic concentrations of precocene 2. If this biological activity can be improved and extended to earlier instars through chemical structure optimization studies, an additional, unique mode of insect control would be possible.

Our most successful studies with the precocenes have been carried out on Hemiptera, especially on milkweed bugs and cotton stainers. In these species we have demonstrated the full range of antiallatotropic activities—precocious metamorphosis, sterilization, and reversal of these by treatment with JH. While we have sterilized representative insects in the orders Diptera and Coleoptera and induced diapause in Coleoptera, we have not succeeded in inducing precocious metamorphosis in Holometabola. In order to realize the full potential of the use of antiallatotropins in insect control, a breakthrough in chemical structure must be made to extend the full range of biological activities to other insects. The partial specificity of the precocenes may foreshadow the discovery or development of antiallatotropins specific to selected pest species.

The efficacy of anti-JH against various developmental stages highlights the potential superiority of this approach in contrast to the use of the JH's or analogs that are generally effective only against insects during the ultimate stages of metamorphosis. Since JH's have not been demonstrated in arthropods other than insects, the development of an insect control process based on the use of antiallatotropic compounds should represent an insect-specific approach to safe and selective insecticides.


### Summary

Two simple chromenes with anti-JH activity have been isolated and identified from the bedding plant *Ageratum houstonianum*. By contact and fumigation these compounds induce precocious metamorphosis and sterilization in several hemipteran species of insects. Certain holometabolous species are sterilized, forced into diapause, or both. Each of these biological actions is equivalent to removal of the corpora allata, which produce the JH's, and is reversible by treatment with exogenous JH. Thus, the action of these compounds is to stop the production or depress the titer of the JH's. To our knowledge, this is the first discovery of anti-JH, and we hope it will guide the way to the emergence of a fourth generation of safe and insect-specific pesticides.



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28. Reaction of an appropriate phenol with excess dimethylacrylic acid in polyphosphoric acid (PPA) on the steam bath gives the crystalline chromanone in nearly quantitative yield. The chromanone is reduced with lithium aluminum hydride in ether and then stirred briefly with 4*N* HCl to effect dehydration to the chromene. Overall yield is about 80 percent.



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# Criminality in XYY and XXY Men

## The elevated crime rate of XYY males is not related to aggression. It may be related to low intelligence.


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Few issues in behavior genetics have received more public and scientific attention than that given to the possible role of an extra Y chromosome in human aggression. Soon after the literature began to suggest an elevated frequency of the XYY genotype among inmates of institutions for criminals and delinquents, interest in this issue had a meteoric rise; and it has been sustained ever since. This happened for several reasons. Stories about a few men who had or were presumed to have an extra Y chromosome and who had committed serious crimes were given prominent attention in the press, suggesting the intriguing idea that the single Y chromosome normally found in males contributes to "aggressive tendencies" in that sex and that an extra Y carries these tendencies beyond their usual bounds. Reports of antisocial behavior in XYY men, often based on a single case, soon began to appear in the scientific literature (*1*) and were taken as evidence of an XYY-aggression linkage. The serious moral and legal implications of such a linkage attracted the interest of social scientists and legal groups to the XYY phenomenon (*2*), and students of genetics and psychology saw in it, as Lederberg (*3*) has said, "one of the most tangible leads for connecting genetic constitution with behavior in man."

A number of studies have supported the earlier finding of an elevated frequency of cases with an XYY complement among men in institutions, particularly in penal-mental institutions (*4*–


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