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Trends in Development of Insect Growth Regulators in Plant Protection

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Of various chemicals affecting insect growth, juvenile hormone mimics appear to have potential for applications in agriculture. However, at present, these compounds have found a limited application for control of stored-grain pests, in sericulture, dairy and mosquito control.

Introduction

It is now becoming increasingly clear that all life processes are ultimately mediated by organic molecules. Ever since the discovery of vitamins and hormones in the late twenties, human and animal chemistry has attracted much attention and continues to be an area of intense topical interest Over the past three decades or so, much valuable information on organic compounds mediating growth, behaviour and defence of insects, has accumulated. These molecules are invariably small (as compared to biopolymers) and may be classified generally into two major groups, depending on their biological response (figure 1). While *hormones* control their growth, *semiochemicals* elicit behavioral response (Wigglesworth 1970, Law & Regnier 1971, Nordlund 1981). Interspecific semiochemicals, *allelochemicals*, cover *allomones* (which give adaptive advantage to the emitter) and *kairomones* (Brown et al. 1970, Whittaker & Feeny 1970, Nordlund 1981; which confer advantage on the receiver) Defence secretions, repellants are, thus, allowances, while attractants will be an example of kairomones. Chemical messengers governing intraspecific behaviour, i.e. *pheromones*, control their sexual responses, aggregation or cause an alarm or help lay a trail (Nordlund 1981, Karlson & Luscher 1959).

It is quite obvious that interference with the above chemical messengers by an antagonist or by compounds which elicit these very biological responses, can be exploited to disrupt insect life and thus provide a means of their control. Chemists and biologists have been quick to recognize this potential and an enormous amount of work has been carried out to evolve practical strategies aimed at harnessing such chemicals for insect control. This approach has two main advantages over use of conventional insecticides (hard insecticides) in that (i) selective insect species targeting becomes possible, and (i.) environmental pollution can be contained. Products which have attained some commercial importance are hormones,

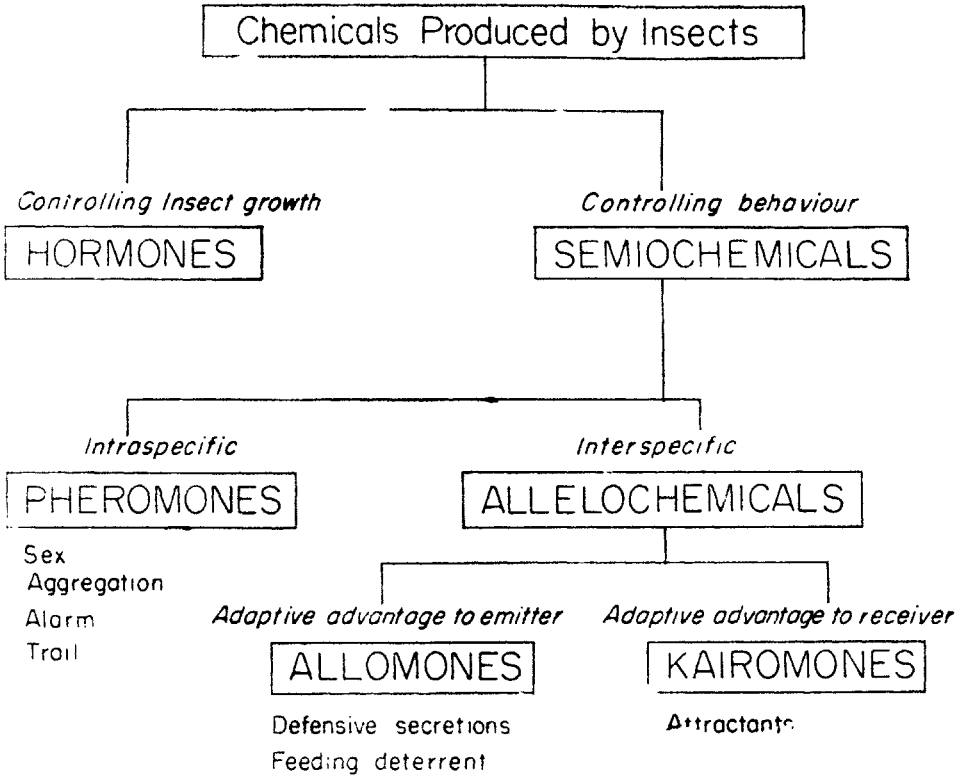


Figure 1 Classification of chemicals produced by insects

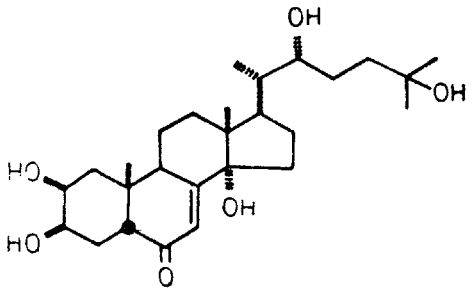
pheromones, antifeedants and repellents.

Insect Hormones

Growth and moulting of insects is governed by several hormones, of which the five major ones are: brain hormone, juvenile hormone, moulting hormone, eclosion hormone and diapause hormone (Wigglesworth 1970, Reynolds & Truman 1980, Chippendale 1977). Of these, juvenile hormone and moulting hormone have received most attention for insect control (Slama et al. 1974) since growth of an insect through various stages is governed by the timing and rate of synthesis of these two hormones.

Two moulting hormones are known. The first compound α-ecdysone(**1**), was isolated by Butenandt and Karlson in 1954 from pupae of silkworm, *Bombyx mori*. The second compound, β-ecdysone (**2**; ecdysterone, crustecdysone) was later isolated from different sources (Berkoff 1969). Since then, related compounds have been found to be widely distributed in the plant kingdom (Prakash & Ghosal 1979). Since, ecdysones and related compounds are highly polar in character, they have difficulty in penetrating the cuticle layer of the insect, thus making their field application beset with many difficulties. Moreover, they exhibit several pharmacological activities on mammals, including humans. Because of these two handicaps, moulting hormones or their bioanalogues have found little application for insect population control (Slama et al. 1974). However, it is believed that ecdysones have found application in sericulture in Japan (Nakanishi).

On the other hand, juvenile hormones and their bioanalogues offer much scope for insect control.



∝-ECDYSONE

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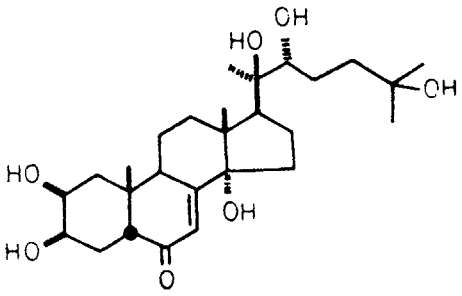

β-ECDYSONE

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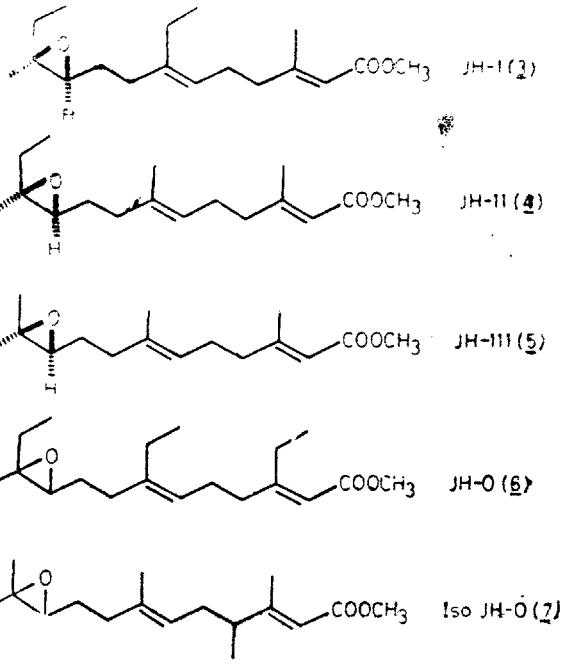


Juvenile Hormones

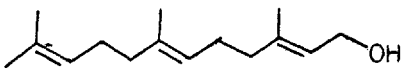
Though, the presence of a juvenile hormone was demonstrated by Wigglesworth as early as 1935, it was not until 1967 that Röller and co-workers succeeded in obtaining a pure preparation of this hormone from the lipid extract of abdomens of the male Silkworm, *Hyalophora cecropia*. Williams (1956) was the first to discover that these abdomens are an exceptionally rich source (3 μg/10 g tissue) of juvenile hormone. By 1968 structure of JH-1 (3) was known in all detail, except absolute stereochemistry (Röller & Dahm 1968, Trost 1970), which was subsequently established by Nakanishi et al. (1971). A second juvenile hormone. JH-II (**4**), was obtained from the cecropia extract by Meyer et al. (1968). Judy et al. (1973) isolated a related compound JH-III (**5**), from organ-cultured corpora allata of adult females of the tobacco hornworm, *Manduca sexta*. This compound was known synthetically earlier. Since then, it has been isolated from the larval blood of *M. sexta*, the adult *Melolantha melolantha* insects, and the organ culture of yellow mealworm, *Tenebrio molitor* (Bowers 1976). Organ tissue culture represents a powerful tool for biosynthesis of such compounds even though in trace quantities, since isolation from such media is considerably simpler. These three insect juvenile hormones have now been isolated from various species, representing different insect orders (Trautmann et al. 1976). Recently, two more juvenile hormones, JH-0 (**6**) and Iso JH-0 (**7**), have been isolated from developing embryos of the tobacco hornworm, *M. sexta* (Bergot et al. 1980, 1981).

Even though, our knowledge of the nature of insect juvenile hormones has become

impressive, much remains to be accomplished with regard to individual role of these hormones and the precise mechanism by which JHs control metamorphosis and reproduction. However, it is now generally believed that JH-I and JH-II are responsible for controlling metamorphosis, whereas JH-III may play a purely gonadotropic role. Though, these roles have not been demonstrated in many insect orders, they certainly hold true for Lepidoptera.

Juvenile Hormone Mimics

Even before natural insect juvenile hormone could be isolated in a pure form, Schmailek (1961) had succeeded in obtaining from faeces of yellow mealworm, *Tenebrio molitor*, two compounds with juvenile hormone activity. These compounds were readily identified as the well-known farnesol (**8**) and the corresponding aldehyde farnesal (**9**) (Schmailek 1961). This finding was exploited by Bowers et al. (1965), in synthesising all-*trans* methyl 10, 11-epoxyfarnesate (**10**), incorporating known features of the natural cecropia JH, which had still not been fully characterized, in this acyclic sesquiterpene framework. This compound displayed all the biological activities of the cecropia hormone (Bowers 1976). Continued synthetic activity in this area led to synthesis of several analogues displaying JH activity. Hydrochlorination in ethyl alcochol of farnesic acid resulted in a material rich in **11**, and 1000 times more potent than JH-I against Hymenoptera (Williams 1970). Around the same time, Slama and Williams identified the so-called "paper factor" as the sesquiterpenoid **12** (juvabione), a constituent of the balsam fir, *Abies balsamea*, the chief source of the American paper pulp. Juvabione elicits in several test insects, biological response typical of JH (Williams 1970). Compounds mimicking juvenile hormone activity have since been isolated from a number of plants; recently juvabione-type compounds were isolation from the wood of *Cedrus deodara* in our laboratory (Bhan et al.



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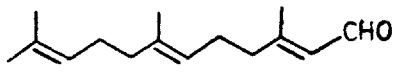

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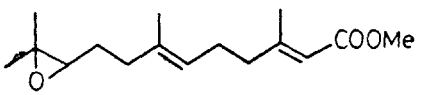

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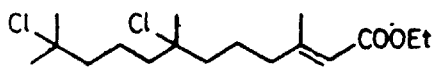

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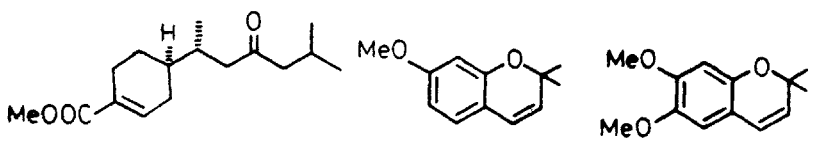

(+)–JUVABIONE
12

PRECOCENE-I
13

PRECOCENE-II
14

1984). The number of purely synthetic compounds exhibiting JH activity is indeed very large and a listing of such compounds is available. The generic name juvenoid has been proposed and is being used to describe true naturally occurring juvenile hormones (e.g. JH-I) and other compounds showing JH activity (Slama et al. 1974).

Compounds with Anti-juvenile Hormone Activity

The occurrence of juvenoids in the plant kingdom led Bowers to search for an antagonist in nature. This search was motivated by the consideration that since juvenile hormone is essential in the early stages of growth of the insect, any compound inhibiting its secretion may provide a useful method for insect control. Screening of a number of plants for such an activity, finally led to isolation of two compounds, named precocene-I **(13)** and precocene-II **(14)**, with powerful anti-juvenile hormone activity, from *Ageratum houstonianum*. Exposure to these compounds induced, for example, the cotton stainer (*Dysdercus cingulatus*) nymphs to moult to tiny adults, which failed to reproduce and died. Various other typical anti-juvenile hormone activities were noted (Bowers 1977, 1983). However, it would appear that the precocenes are antagonistic only to JH-III, and have little effect on species or stages where the more potent JH-I and JH-II are important (Siddall 1977).

Juvenoids in Pest Management: Current Status

As a result of these discoveries, a picture slowly started emerging where pest management with juvenoids, at least in some situations, appeared practical. This concept was first advanced by Williams (1956), who later referred to such hormonal agents as third generation pesticides (Williams 1967). Exogenous application of juvenoids can retard or disrupt insect growth in several ways (table 1) Since, exogenous application of juvenoids to larval insects can prolong the larval stage, and since in agriculture larval stage does the maximum damage to crops, it had become quite clear in the early stages itself that juvenoids will be of little value for such applications. However, where the damage is caused mostly by the adult insects, juvenoids appeared to offer much scope, such as for the control of stored-grain pests and disease vectors.

Though, the areas of possible application for juvenoids were quite in focus, it had become evident that natural insect juvenile hormones, which were now readily available through synthesis, are too unstable and possess too low an activity for any practical application. Although a number of efforts have been made to synthesize the JH-mimics for commercial use (Slama et al. 1974, Menn & Beroza 1972, Gilbert 1976, Siddall 1977), the task of taking a compound from the laboratory to the market is a very specialised

Table 1 *Effects of exogenous application of juvenoids*

Insect stage	Effect
Eggs	Disruption of embryogenesis; ovicidal effect.
Larval	Disruption of post-embryonic development; application at the final instar stage may lead to formation of perfect supernumerary larvae or give rise to insects with adult features.
Pupal/Adults	May affect reproductive system in some species; induce sterility or reduce fertility; reduce secretion of sex pheromones. May disrupt diapause. Affect colour polymorphism. May change caste bias.

one, in which pharmaceutical and pesticide companies have the right expertise. The chief requirements of a juvenoid suitable for field application would be:

(*i*) high biological activity,
(*ii*) reasonably good photo-and chemical stability,
(*iii*) biological activity against a range of harmful insects,
(*iv*) low toxicity to natural parasites of these insects,
(*v*) low mammalian toxicity,
(*vi*) non-phytotoxicity, and
(*vii*) reasonably easy to be synthesised or isolated.

Requirement (*iii*) is essentially dictated by the tremendous expense involved in generating safety data for any new compound meant for field application, as perstatutory requirement in most countries. Compounds which have received US governmental registration (compounds 15, 16, 17) or have undergone field trials are shown in figure 2. The commercial success achieved by methoprene is chiefly due to its several appropriate formulation

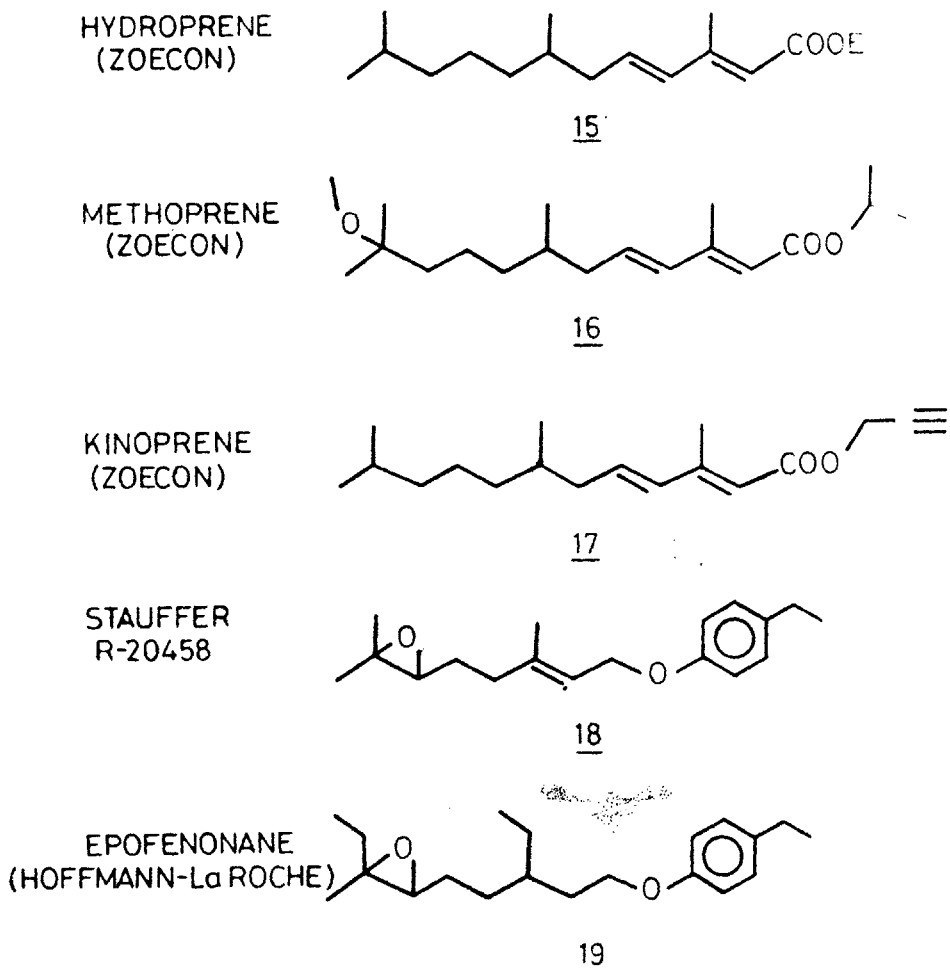

Figure 2 Juvenoids commercialised

Table 2 *Commercial products based on juvenoids*

Juvenoid	Trade name	Pest species
Methoprene	Altosid SR-10	Mosquitoes
,,	Altosid 10F	Flies
,,	Altosid CP-10	Manure breeding flies
,,	Pharogone	Pharaoh ant
,,	Kabat	Cigarette beetle
,,	Apex	Fungus gnat
,,	Precor	Fleas
,,	Altosid SE	Stored grains, nuts
Kinoprene	Enstar	Greenhouse Homoptera

(Young et al. 1977), some of which are given in table 2. A micro-encapsulated formulation of methoprene (Altosid SR-10) for mosquito control was registered in USA in 1973 and is now used worldwide. Several species of mosquitoes can be effectively controlled using 0.06 to 0.12 lb/acre. The horn-fly, *Haematobia irritans* and the stable-fly in the dung could be effectively controlled by giving ~100 mg feed of methoprene/animal. Another formulation of methoprene (Kabat) is being marketed worldwide for beetle control; 2–100 ppm of methoprene effectively control this pest. A formulation of kinoprene, under the trade name 'Enstar' has been registered for control of greenhouse Homoptera (Bowers 1983).

Since exogenous application of juvenoids to larvae at the final instar stage may lead to bigger larvae (table 1), this effect can be exploited to advantage where larval stage is economically productive, as in sericulture. A product (Manta) based on methoprene has been registered in Japan, which has increased silk productivity.

Future Prospects and Conclusions

Juvenoids have severe limitations as far as the usual pests of agricultural crops are concerned, as here it is the larval stage that does the maximum damage, and juvenoids only prolong this stage. Forestry pests too have not shown fairly enough response to juvenoids. However, where damage is done by the adult insects (e.g., stored products pests; flood-water mosquitoes; manure-breeding flies) there appears to be good scope for juvenoids.

The present use of juvenoids in pest management, although small, provides an excellent example of rapid conversion of major breakthroughs in basic research into innovations of practical utility. Various aspects of insect endocrinology still remain to be explored and the new findings are bound to further the prospects of use of insect growth regulators (IGR) in agriculture. The present day juvenoids have a rather short life both in the field and on the insect; half-life of exogenously applied juvenoids in insects is usually less than an hour. More potent and more persistent juvenoids will have to be synthesised and new formulation technology and delivery systems evolved.

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