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Chemistry and Biological Activity of Morphogenetic Agents

W. S. BOWERS

As the chemistry of insect hormones has been developed over the past six or seven years increasing attention has been directed toward their potential use in insect control.

In the Insect Physiology Laboratory we have pursued our studies with insect hormones with a view toward understanding their structure-biological activity relationships, ultimately to use this knowledge to cope with the burgeoning demands of our agronomic and public health needs. To this end we are actively involved in the isolation and identification of existing natural hormones, as well as active materials from other animals and plants and the synthesis of more potent and/or specific hormonal analogs. Throughout these studies we have directed our efforts toward the development of chemicals which we hope to be 1) effective in insect control ; 2) without environmental hazard to man, domestic animals and wildlife ; 3) safe and economical alternatives to conventional pesticides.

My report today deals with the development of the chemistry of the juvenile hormones, a variety of active synthetic analogs and their participation in the regulation of several biological phenomena.

Survey of Biological Phenomena Regulated by Juvenile Hormones

In Figure 1 we see detailed the life cycle of the holometabolous insect, *Tenebrio molitor*, a pest of stored grain. With *Tenebrio* as in most insects, develop-

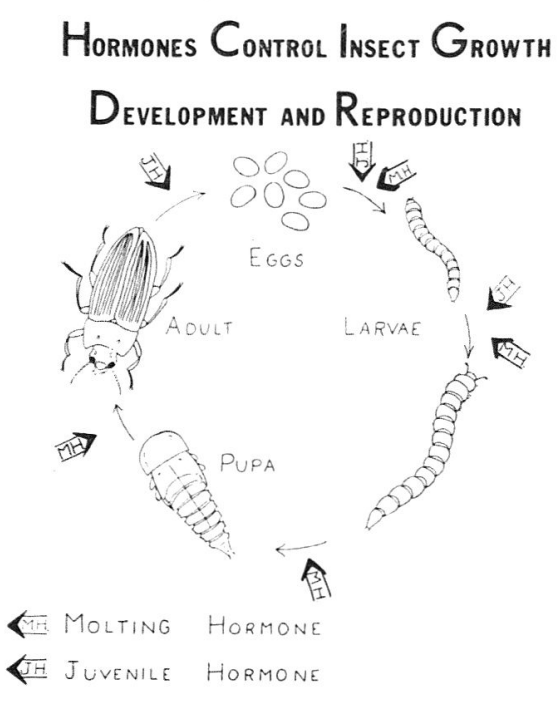


Fig. 1

ment is a stepwise process carefully regulated by hormones. Four distinct stages are recognized egg, larval, pupal and adult. The endocrinological events occurring within the egg are poorly understood, however this stage of insect development has proven one of the most sensitive with respect to susceptibility to the lethal effects of juvenile hormones (1, 2, 3). The next stage is the larval period which is characterized principally by growth and increase in mass. Insects wear their skeleton or cuticle externally and thus as they increase in size and mass they must periodically shed their old cuticle and develop a new more elastic one to permit continued growth. In the larval stage the hormones which control the molting process are the juvenile hormones, and the molting hormones or ecdysones. During larval growth no substantial changes in differentiation occur even though the genetic capacity for differentiation exists within the immature insect. Each insect species has an optimal size range which is most favorable for its ecological survival and reproductive capacity. In order to achieve this size, differentiation or development toward the reproductive stage must be subverted or controlled during larval growth and this control is provided by the juvenile hormones during each larval molt. Thus, the presence of the juvenile hormones at each molt ensures that the molt will not be accompanied by any net differentiation and that the type of new cuticle produced will be larval. In some mysterious way each insect species is able to count its molts, and at the proper time the glands which produce the juvenile hormones cease production and now in the relative absence of the juvenile hormones the next molt is accompanied by an enormous amount of differentiation which results in the development of the pupal stage. In most insects the pupal stage is outwardly a non-feeding inactive period. In fact, the pupal stage is a period of extensive tissue differentiation, during which the adult tissues are defined. The complete assumption of the adult form is acquired at the last molt which likewise occurs in the relative absence of juvenile hormones.

In addition to these four stages of insect development, other important aspects of insect life are recognized to be under the influence of the juvenile hormones. Noteworthy among these are reproduction, sex pheromone production and diapause. In many adult female insects the glands which produced the juvenile hormones during larval life begin to secrete the same or similar hormones soon after the last molt. These hormones are now necessary for ovarian development, and the production of sex pheromones. Experimental removal of the glands which produce the juvenile hormones renders the female unattractive to males and incapable of ovarian maturation.

Diapause is a condition of physiological arrest during which there is little or no feeding, mating or reproduction. In this condition insects are able to survive periods of inclement weather, such as heat, cold drought, etc. In many adult insects which diapause, this condition

supervenes when the production of juvenile hormones is decreased or stopped. When the period of environmental stress ends, the production of juvenile hormones resumes and normal feeding, mating and reproduction proceed.

Lethal Effects of Juvenile Hormones

In the foregoing, brief description of the biological phenomena regulated by juvenile hormones, it is clear that the juvenile hormones by their presence or absence control important aspects of biochemistry and physiology in every stage of insect life. It is upon this understanding that much of the hope of a hormonal-based insecticide is founded. Clearly, if we supply a juvenile hormone to a stage in which development normally is programmed to proceed in the absence of these hormones, it is possible to disrupt or interfere with development. Thus, exposure of a last stage larva, pupa or nymph to juvenile hormone, or an active chemical mimic, sidetracks the expected process of maturation and so modifies the subsequent molt that a supernumerary immature form or an intermediate form results which combines mature and immature characters. Such morphogenetic mixtures are incapable of further development and soon die.

The eggs of many insects fail to complete embryogenesis or are unable to hatch when exposed to morphogenetic chemicals, such as the juvenile hormones and other chemicals with similar hormonal activity. Ovicidal effects are produced by treating the eggs directly by contact or fumigation or by exposing the adult female to juvenile hormonal chemicals. In the latter case a peculiar type of sterility is obtained. Thus, in most insects normal numbers of eggs are produced, but successful embryogenetic development is prevented.

In insects which diapause as adults, such as the alfalfa weevil, *Hypera postica* and the cereal leaf beetle *Oulema melanopus*, treatment with juvenile hormone active chemicals terminates diapause rapidly and the insect is forced into an awakened state in which it must feed, mate and reproduce (4, 5). If the protective state of diapause is removed during periods of environmental stress, such as during winter or drought, the insect cannot survive.

Thus, several stages of insect development (i.e., egg, larval and pupal) are susceptible to the untimely presence of juvenile hormones, including the important protective state of diapause.

Biological Assays for Morphogenetic Chemicals

In order to relate biological activity and chemical structure relationships, rapid, sensitive and reproducible biological assays are of paramount importance. Two assays which we developed in our laboratory are the *Tenebrio* genitalia assay (6) and the milkweed bug assay (7). In the

Tenebrio assay shown in Figure 2 advantage is taken of the fact that several distinctive morphological characters of the pupa have no apparent counterpart in the normal adult insect. Treatment of a pupa

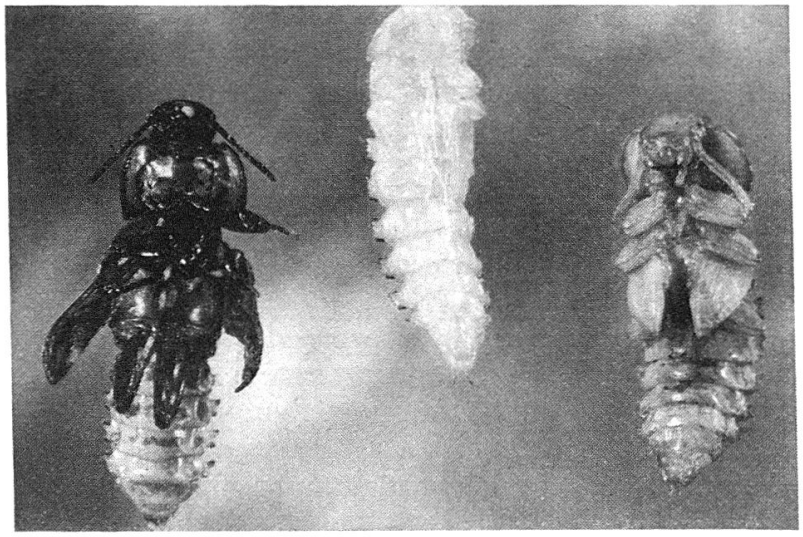


Fig. 2

with a juvenile hormonal chemical induces the development of a pupal-adult intermediate in which these pupal characters are retained in the intermediate ; unequivocal proof of juvenile hormone activity. The milkweed bug assay (Fig. 3) involves treatment of a last stage nymph with a hormonal chemical and depends upon the development of a nymphal-adult intermediate or supernumerary nymph as a sign of juvenile hormone activity.

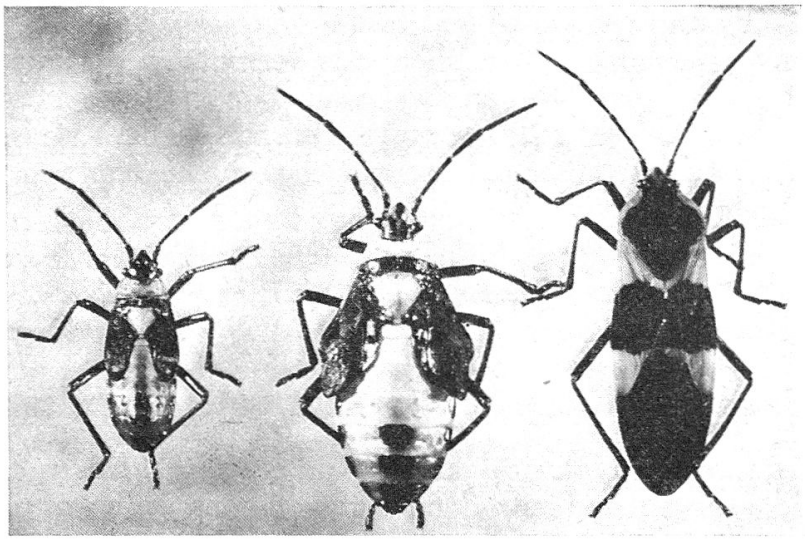


Fig. 3

These two assays fulfill the need for rapid evaluation of candidate hormonal chemicals, although they do not allow a complete projection of activity relationships for a great variety of insect pests. Indeed we evaluate the biological activity of morphogenetic agents on a variety of insect pests as these insects are available to us. Among those pests for which we have developed satisfactory bioassays are the housefly, yellow fever mosquito, tobacco hornworm, corn earworm, alfalfa weevil, confused flour beetle, German cockroach, black carpet beetle, Mexican bean beetle, Colorado potato beetle and the cotton stainer. In these assays, interference with morphogenetic development is the principal criteria of activity. Another biological assay (Fig. 4) developed in our

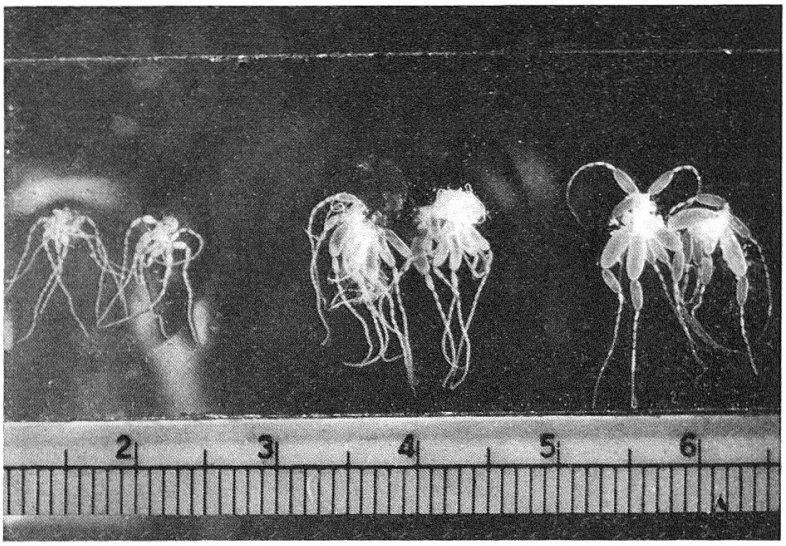


Fig. 4

laboratory is the cockroach ovarian assay (8, 9). This test is highly specific for natural juvenile hormones and discriminates severely against many of the very active synthetic morphogenetic chemicals. In this assay the glands (corpora allata) responsible for production of the juvenile and/or gonadotropic hormones are removed from young mated female American cockroaches. In the absence of these glands the ovaries are unable to develop and reproduction is impossible. Treatment of these cockroaches with an active juvenile hormone by topical application or by injection causes rapid growth and development of the terminal oocytes and allows successful reproduction. This is no less than classical replacement therapy.

By now it is abundantly clear that a wide variety of chemical structures are able to induce morphogenetic effects in insects indistinguishable from the biological activities of the *Cecropia* juvenile hormones. Indeed a great number of chemicals with relatively high juvenile hormonal activities were developed prior to the identification of the

Cecropia hormones, and several of these might be said to have predicted the eventual structure of the Cecropia hormones (9, 10). Not only are many of these chemicals of purely synthetic origin but a few are completely unrelated to the *Cecropia* hormones chemically (6, 7). With such a diverse array of active chemicals it is understandable that nomenclatural problems arise. Some investigators object, and perhaps properly, to the use of juvenile hormone "analogs" or "homologs" as a generic description for these chemicals, since they are not natural products and many are indeed not analogs or homologs of the *Cecropia* juvenile hormones. Since several of these compounds are as active, and some are as much as a thousand times more active than the natural juvenile hormones, use of the term "mimic" seems altogether inadequate. It might be recalled that the *Cecropia* juvenile hormones were isolated and identified from the adult male *Cecropia* moth and not from the immature stages. Thus, a reasonable doubt must exist concerning their actual role in the immature insect and their proper designation as juvenile hormones. Assuming that the hormones from the *Cecropia* moth are indeed its authentic juvenile hormones and that all Lepidoptera share the same hormonal structure, many additional orders of insects exist which may have somewhat different natural juvenile hormones. Indeed the low order of activity of the *Cecropia* juvenile hormones for Diptera and Hemiptera suggest that the concept of other juvenile hormones should be entertained unless and/or until further research clarifies the present uncertainty. It does not therefore seem unreasonable to use the terms analogs, homologs, or juvenile hormonal chemicals etc. where adequate chemical names and/or structures are provided to define the compounds under discussion. I make this plea not for a loose usage of nomenclature but because of the need for an adequate generically descriptive terminology with which to deal with the many compounds now available and to prevent the development of an inflexible terminology which makes no allowance for the possibility of other juvenile hormones from natural sources.

Development of the Chemistry of Morphogenetic Chemicals

Perhaps one of the most exciting discoveries in the chemistry of juvenile hormones was discovery of the juvenile hormone activity of farnesol (10) (Fig. 5). Isolated from the feces of *Tenebrio* this sesquiterpenoid alcohol was found to mimic the juvenile hormone in *Cecropia* extract in a wide variety of insects. This discovery provided great impetus to the subsequent development of additional morphogenetic chemicals and laid down much of the chemical structure information with which we are presently working. Few of the serious students of insect endocrinology believed that farnesol was the *Cecropia* hormone because of its low biological activity and chromatographic behavior

when compared to the active principle in *Cecropia* extract. Many however shared our belief that the secret to the structure of the juvenile hormone lay within the sesquiterpenoid framework of farnesol. Support of this theory was forthcoming when the methyl ether and diethyl amine of farnesol were found to possess much higher activity than the parent alcohol (11). We were also engaged in structural modification of farnesol and at first sought to determine the contribution of the double bonds toward activity. Selective saturation of each of the double bonds decreased activity although even hexahydrofarnesol possessed some activity. Our next intended steps were to synthesize nor farnesols

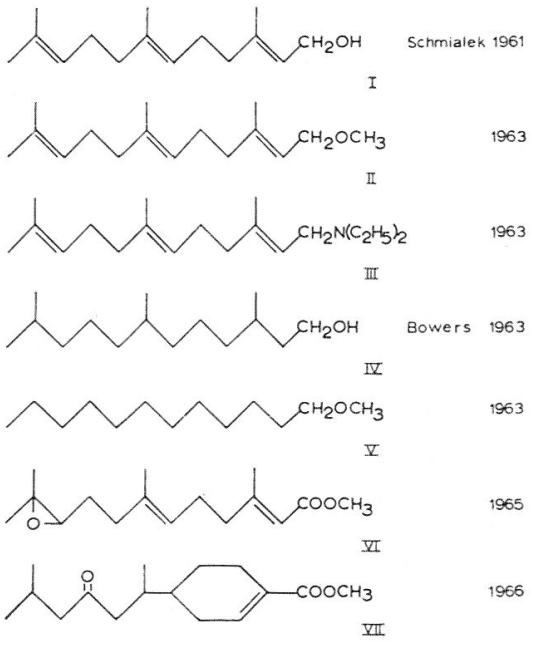


Fig. 5

lacking one or more methyl branches. In view of the activity of hexahydrofarnesol we decided instead to test some saturated unbranched alcohols. We selected a series of such alcohols from octanol to tetradecanol and found that all of these had some juvenile hormone activity on *Tenebrio*. The most active of the series was dodecanol ; a twelve carbon alcohol having the same carbon skeleton as farnesol, albeit lacking the three olefinic bonds and methyl branches. Since the methyl ether of farnesol was more active than the parent alcohol we prepared the methyl ethers of these alcohols and were quite surprised to discover that activity of each compound was greatly enhanced, especially the twelve carbon dodecyl methyl ether (6). However interesting and exciting these findings were, there was little that could be done in the way of structural modification of a saturated straight chain alcohol or

methyl ether. Instead of pursuing this line of study we sought to learn more about the chemistry of the active principle in the *Cecropia* extract by standard chemical techniques. Although we had very little of the extract and recognized that this amount was insufficient to permit isolation and identification of the hormones ; its high biological activity allowed extensive chemical study. By column chromatography the active principle behaved like a sterol on silicic acid (8) and on Florisil. Mild saponification at room temperature did not destroy activity although strong alcoholic base did reduce or destroy activity altogether at reflux temperatures. We felt that if an ester were possible it must be some sort of a hindered ester. We found further, that treatment of the free acids derived from the saponified *Cecropia* extract with diazomethane regenerated in part the biological activity of the original extract. We were confident of the presence of olefinic bonds since catalytic reduction eliminated activity as did treatment with bromine. Reduction with sodium borohydride did not affect activity although treatment with lithium aluminium hydride destroyed activity. These facts taken together suggested a hindered ester perhaps even a simple ester, since a methyl ester would serve. With farnesol as a constant model it seemed to us that the methyl ester of its corresponding acid (farnesenic acid) would be hindered by the conjugated double bond and thus fulfill these tentative requirements. Synthesis and biological evaluation of methyl farnesenate yielded a compound of considerable activity, but lacked the polarity by column chromatography in comparison with the *Cecropia* principle. Some additional polar function seemed necessary. A ketonic function was ruled out by the lack of effect of treatment with sodium borohydride although a hydroxyl group seemed possible. Exhaustive attempts to acetylate and methylate or otherwise derivatize a hydroxyl function in the *Cecropia* extract and thus modify the biological activity or alter its chromatographic characteristics failed. We determined quite early that two double bonds were necessary for maximum activity in methyl farnesenate namely in the 2 and 6 positions and moreover that the *trans trans* isomers were the most active. We sought to modify the double bond in the 10, 11 position by introducing various groups which we felt might confer the desired polarity. Finally, epoxidation of the 10,11-olefinic double bond gave a compound with exceedingly high biological activity in all assays including the cockroach gonodatropic assay and by topical treatment we could terminate diapause in several adult insects. This compound also possessed the desired chromatographic behavior. In reporting our study (9) we stated that "Its high biological activity ; chromatographic behavior, destruction by saponification, lithium aluminum hydride reduction, hydrogenation and activity by topical application in a variety of assays, is very characteristic of the *Cecropia* extract activity, and it is believed that this compound will be found to be very similar chemically to the natural hormone when the latter is isolated and characterized."

Our interest in structure-biological activity relationships led us to isolate and identify the so called "paper factor" from balsam fir wood which we called "juvabione". It was the first cyclic structure with juvenile hormone activity to be found (12). It is an α-β, unsaturated methyl ester and its structure leaves no doubt as to its terpenoid origin. Its unique chemical structure and activity spectrum, restricted to insects in the family Pyrrhocoridae, provided a hopeful glimpse for the sought after selective hormonal pesticide.

Subsequent investigators discovered another compound in fir wood which possessed an additional double bond, which was called dehydrojuvabione (Fig. 6) and found to have about one-tenth of the

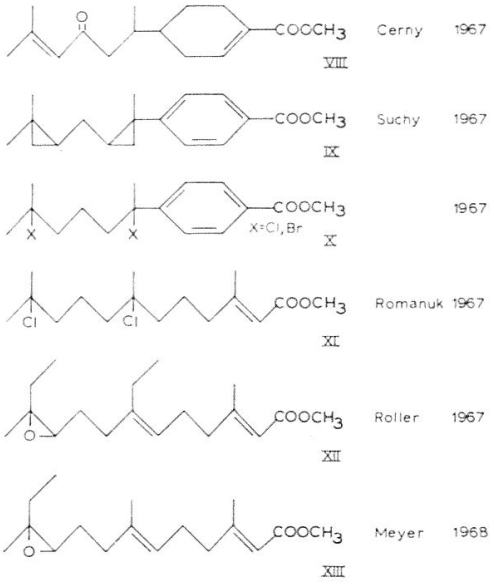


Fig. 6

biological activity of juvabione (13). Synthesis of aromatic analogs of juvabione provided compounds also specifically active on Pyrrhocorids but with activity several magnitudes higher than the plant derived compounds (14). Several elegant stereospecific syntheses of these compounds have been published (15, 16, 17).

The report of a hydrochlorination reaction mixture of farnesenic acid with high biological activity (18) stimulated a great deal of interest and finally one of the active components was isolated and identified (19) as the 7,11-dichloro methyl farnesenate. This compound was active on Pyrrhocorids at nanogram levels although much less active on other insects. The other active principle(s) in the original reaction mixture has proven refractory to identification (18).

In 1967 a team of investigators isolated one of the cecropia juvenile hormones (20) and characterized it as methyl 10,11-epoxy-7-ethyl-3,11-dimethyl-2,6-tridecadienoate. The sterochemistry of the natural

hormone was found to be *trans trans* for the olefinic bonds in the 2 and 6 position and the 10,11-epoxide was assigned a cis configuration. The ethyl branches increase the hormonal activity over *trans trans*-10,11-epoxy methyl farnesenate especially in Coleoptera and Lepidoptera resulting in 5 to 10X increase in activity. In Diptera and Hemiptera no differences in activity could be observed. Another team in 1968 working independently isolated and identified a second juvenile hormone methyl 10,11-epoxy-3,7,11-trimethyl-2,6-tridecadienoate (21). Its stereochemistry and biological activity were equivalent to the other *Cecropia* hormone.

The isolation and identification of the *Cecropia* juvenile hormones have stimulated an intense amount of interest in insect endocrinology and physiology as well in economic entomology. A host of novel and innovative syntheses of these juvenile hormones has appeared, far too many to mention here. Much of the chemistry developed to satisfy the unique structure of these hormones has been new chemistry and thus the spin off value to science in general has been substantial.

At this time in the Insect Physiology Laboratory we were seeking means of increasing the activities of our synthetic hormonal compounds. We tried without success several combinations of different hormonal agents to see if any synergism was possible. Since most insecticide synergists are effective because they inhibit inactivation of the insecticide within the insect, it seemed reasonable to see if synergists would likewise increase hormonal activity in insects. It has already been established that insects are able to inactivate the *Cecropia* hormones (22). Treatment of *Tenebrio* pupae with a threshold amount of *trans trans* 10,11-epoxy methyl farnesenate and piperonyl butoxide resulted in a slight increase in activity over hormone treated controls, but the increase was not sufficient to warrant further interest. The control group which had been treated with piperonyl butoxide alone, however, also revealed a substantial degree of morphogenetic damage indistinguishable from that of the hormonal treatments. After determining the purity of the piperonyl butoxide and ruling out accidental contamination with any known hormonal analogs the tests were repeated with a series of graded dosages of the synergist. The results left no doubt that the piperonyl butoxide had juvenile hormonal activity. Additional synergists were tested and several were found to possess moderate to good activity (Fig. 7). The most active synergist was Sesoxane (sesamex) a methylenedioxy phenoxy acetal which was active in *Tenebrio* at submicrogram levels (7). It is worthy of mention that Sesoxane is a better synergist for pyrethrum than piperonyl butoxide and past studies have shown that in general phenoxy compounds are better synergists than the corresponding benzyloxy analogs (23). Another synergist, propyl 2-propynyl phenyl phosphonate (Niagara 16388) which is completely unrelated to piperonyl butoxide or Sesoxane was found to have moderate activity in *Tenebrio* but was completely inactive on Hemiptera. Two

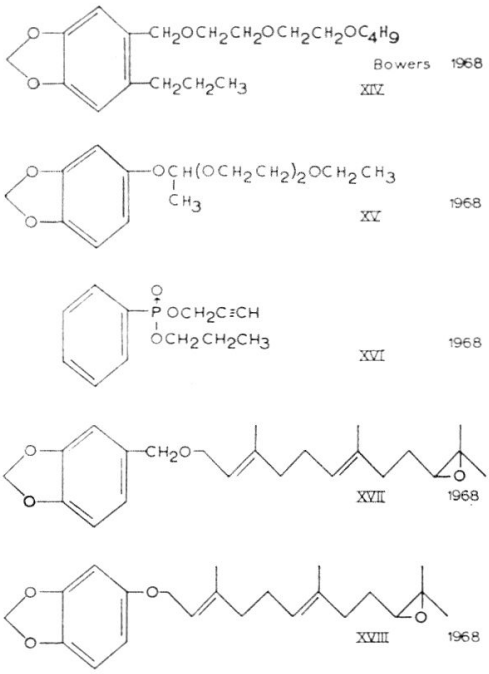


Fig. 7

natural synergistic compounds, sesamin and sesamolin were isolated in pure form from sesame oil and found to have only slight juvenile hormone activity. Most of the synergists with activity were methylenedioxy phenyl (MDP) derivatives which differed principally with respect to the side chain substituents. Numerous MDP derivatives lacking side chain substituents were tested without success. Several polyethers similar to the synergist side chain substituents were likewise inactive. Clearly no single feature of the synergists was responsible for activity. Although the chemical structures of the synergists were completely unlike the natural *Cecropia* hormone or any of the heretofore known "mimics", a common mode of action or site of activity in the insect seemed a reasonable hypothesis. How could our understanding of juvenile hormone chemistry be combined with or related to the synergists. One of the first attempts to combine the features of synergist and hormonal chemicals was the synthesis of piperonyl-farnesyl ether. This hybrid compound was only slightly active on *Tenebrio* but quite active on milkweed bugs (7). Introduction of an epoxide across the terminal double bond of the farnesyl side chain increased activity in both assays. Synthesis and testing of sesamyl-farnesyl ether epoxide resulted in an increase in activity of about one magnitude. In this study of these hybrid molecules the phenoxy derivatives were uniformly more active than the corresponding benzyloxy homologs. Continued study resulted in the synthesis of the corresponding epoxy geranyl ether of 3,4-methylenedioxyphenol (Sesamol) which was active in the nanogram

range on all species of insects tested (Fig. 8). It was also found that the allylic olefinic bond in the geranyl moeity should be *trans* for maximum activity. Since the ethyl branches of the *Cecropia* hormone contribute increased activity over the normal sesquiterpenoid analogs the

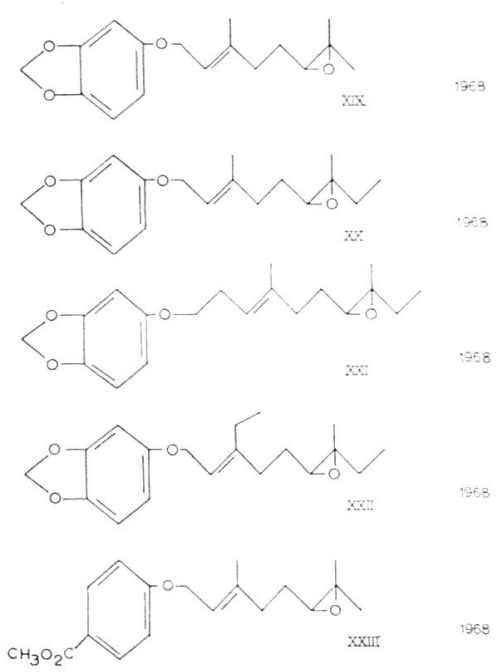


Fig. 8

corresponding MDP epoxy geranyl homologs were synthesized. Biological evaluation of these compounds revealed exceedingly high juvenile hormone activity (24) in Lepidoptera, Coleoptera, Hemiptera and Diptera. With especially sensitive insects, development could be arrested with dosages in the picogram range. Until the biological activity of these compounds was fully realized, working with them in the laboratory presented several unique problems. Thin-layer chromatography plates exposed for only brief intervals in the laboratory concentrated sufficient of the hormone vapors to render them useless. Insects reared in the same laboratory room where synthesis or biological testing was performed, unaccountably molted into morphological monsters and died ; an effect subsequently put to good use by developing assays based upon fumigation. A study was now made of the contribution of the aromatic portion of the hybrid compounds to biological activity. The unsubstituted phenoxy ethers were only slightly active in most assays. Numerous substituted phenoxy ethers were prepared and many of these were moderately active. Para substitution with methyl, ethyl, propyl, isopropyl, chlorine and bromine groups gave compounds active on *Tenebrio* in the microgram to nanogram range. Of these, methyl, ethyl and isopropyl were the most active

(Fig. 9) (25). Meta substituted hybrids were less active whereas other substituted compounds were inactive. None of these compounds possessed the broad spectrum or extremely high biological activity of the corresponding methylenedioxy "hybrids". All of the good aromatic

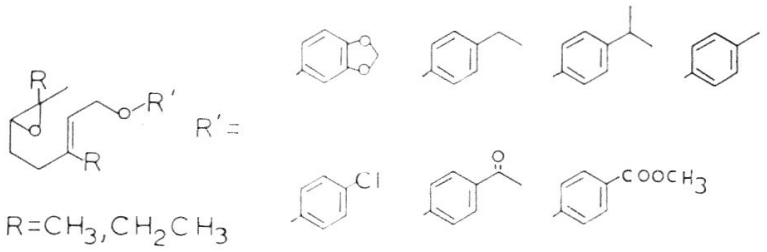


Fig. 9

terpenoid ethers are more active than the *Cecropia* juvenile hormones by several magnitudes when assayed on the yellow mealworm, milkweed bug and tobacco hornworm. For purposes of comparison of the biological activities of several of these hormonal agents on a single pest species Figure 10 shows the amounts of compound in terms of nano-

EFFECT OF JUVENILE HORMONE COMPOUNDS
ON CONFUSED FLOUR BEETLE

Compound	Topical * (ng/pupae)	Diet ** (ppm)
10,11-Epoxy FAME	500	1000
Synthetic Cecropia JH	250	100
SGEE	100	10
Ethyl SGEE	10	1
Diethyl SGEE	1	0.1-1.0

* All pupal-adult intermediates or second pupae

** No normal adults produced

Fig. 10

grams by topical application and parts per million in the diet required to kill 100% of the treated insects. The sesamyl geranyl ether epoxides (SGEE) and ethyl branched homologs (Ethyl SGEE, Diethyl SGEE) are by far the most effective. In Figure 11 the susceptibility of a variety of insect pests to the sesamyl "hybrids" is shown. The high degree of effectiveness against such important pests as the confused flour beetle and yellow fever mosquito indicate the barely realized potential of such compounds for insect control.

Effect of Sesamyl Geranyl Ether Epoxide Homologs on Insects

Insect	Dose	Effect
Housefly Pupae	0.5 ng	Pupal-Adults
Milkweed Bug Nymphs	10.0 ng	Nymphal-Adults
Tenebrio Pupae	0.5 ng	Pupal-Adults
Hornworm Larvae	0.1 ppm	No Pupation
Corn Earworm Larvae	0.5 ppm	No Adult Emergence
Mosquito Larvae	0.1 ppm	No Adult Emergence

Fig. 11

Despite the discovery of these exceedingly active compounds we have continued our search for additional active materials. We questioned the purpose of the polyether side chains of the synergists and attempted to combine similar glycol features with known active terpenoid moeities. The epoxy geranyl ethers of ethylene glycol ethyl and butyl ethers are active in the nanogram range on *Tenebrio* (Fig. 12)

Effects of Morphogenetic Agents on Tenebrio Pupae

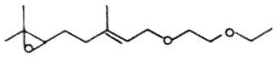
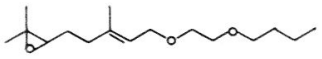
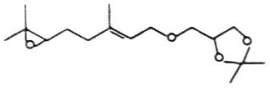
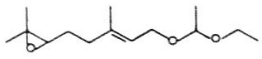
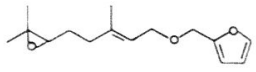
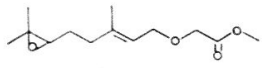
Compound	Pupal-Adult Intermediates Topical Treatment (ng)
I 	0.1
II 	0.1
III 	0.1
IV 	100.0
V 	100.0
VI 	100.0

Fig. 12

and are excellent ovicides for a variety of economic species. Longer glycol substituents are less active. Several highly oxygenated derivatives of epoxy geraniol also possess substantial juvenile hormone activity and are being tested intensively.

A sidelight to our development of the methylenedioxy hybrids is the discovery that they are effective as synergists for pyrethrum (26). In collaboration with other USDA scientists we have found that they are nearly as effective in standard Peet-grady synergism tests as the standard piperonyl butoxide (Fig. 13).

Table 1.--Effectiveness of 5 juvenile hormone compounds used with pyrethrins compared with piperonyl butoxide against susceptible house flies (by Peet-Grady method).

Synergist tested[a]	No. tests	% kill in 1 day		
		All insects	Male	Female
trans-4-[(6,7-epoxy-3,7-dimethyl-2-octenyl) oxy]-1,2-(methylenedioxy) benzene	7	74	88	58
trans-4-[(6,7-epoxy-3-ethyl-7-methyl-2-nonenyl) oxy]-1,2-(methylenedioxy) benzene	5	49	78	32
trans-2-[(6,7-epoxy-3,7-dimethyl-2-octenyl) oxy]-3,4-(methylenedioxy) toluene	4	34	66	16
trans-4-[(6,7-epoxy-3,7-dimethyl-2-octenyl) oxy/propyl]-1,2-(methylenedioxy) benzene	4	77	92	60
trans-4-[(7,8-epoxy-4,8-dimethyl-3-decenyl) oxy]-1,2-(methylenedioxy) benzene	8	72	86	57
Piperonyl butoxide	7	92	97	88
No synergist	8	6	13	1
Official Test Insecticide (pyrethrins 1 mg/ml)	8	59	85	33

[a] In Dispersol, 0.4 mg/ml pyrethrins + 2.0 mg/ml candidate synergist.

Fig. 13

Summary

There has been a limited amount of exploration of insect hormones, however intense the effort has been. We have in hand 25 or 30 compounds active on insects in the nanogram and picogram range. Our synthetic efforts have yielded compounds vastly more active than the *Cecropia* juvenile hormones, and which compte with or exceed conventional insecticidal activity. Indeed as we redouble our efforts to apply this knowledge to field application our problems multiply. Economy of synthesis, stability under field conditions, methods of application, etc. will surely complicate our present and future efforts. Clearly we need additional molecular models of natural insect hormones to build upon. This conference has offered intriguing evidence of other insect juvenile hormones. Our assays and the criteria by which we judge our data and testing procedures need reexamination. Rational study of the biosynthesis and degradation of insect hormones may provide leads to the development of antihormones. Some doubt has been expressed that juvenile hormones will be accepted by the farmers, formulators and public because they do not kill insects immediately. I believe that our growing environmental awareness requires a substantial readjustment in our approach to insect control and we must provide the missionary work to maintain and concentrate research on these fundamental approaches to insect control. Whether the ideas or compounds in hand are equal to the task is far less important than our continued search for alternative measures of insect control.

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