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BioRational Approaches for Insect Control

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ABSTRACT Investigation of the environmental impact of widespread pesticide use has revealed a virtue/vice relationship. Although many pesticides perform their function and disappear without harm to the environment, others persist beyond their useful purpose and cause direct or indirect hazard to man, domestic animals and wildlife. Concurrently, many pests have rapidly adjusted to chemical control practices through changes in behavior that avoid exposure to pesticides or throuth genetic selection for populations resistant to the toxicants. The prospect of losing control over insect herbivores and desease vectors and returning to the days of global hunger and disease is unthinkable. Fortunately, from basic studies of insect and plant biology many opportunities for the development of safe, selective and environmentally pacific strategies for insect pest management are being realized.

KEY WORDS Insect growth regulator, juvenile hormone, antihormone, pheromone, repellent, chemical ecology

INTRODUCTION

The control of insect pests of plants and vectors of human animal diseases is the main preoccupation of agricultural and public health scientists. Synthetic organic chemical pesticides have successfully limited insect predation for nearly five decades permitting an abunadnce of food and a public health posture never before imagined. Not infrequently food surpluses have accumulated to the embarrassment of prosperous nations. Equally, the control of insect vectors of disease has promoted a vast increase in world population. Despite their efficacy and cost effectiveness many insecticides are toxic to both vertebrates and invertebrates. Residues of a few of these insecticides persist in the environment and have been shown to represent a threat to man, domestic animals and wildlife. At the same time, insect pests have developed resistance to many insecticides, compromising their efficacy. Agricultural scientists recognize that it is impossible to return to the practices of the past where pest competition reduced yields to near subsistence levels and diseases ravaged human and animal populations. Accordingly, research efforts are directed towards the discovery of safe and selective methods for insect control lacking hazardous impact on the enviroment while limiting pest competition. Fundamental research into insect chemical ecology, biochemistry and physiology have revealed numerous facets of insect biology from which pest specific approaches to insect control may be developed. The first successful methodology developed for selective insect control involved hormonally mediated disruption of their developmental processes. This new class of environmentally benign chemicals has come to be called "Insect Growth Regulators". Similarly, behavior modifying chemicals derived from natural chemical signals of insects, called pheromones, have emerged as useful tools for pest monitoring and mating disruption. The use of personal repellents to prevent transmission of diseassse by arthropod vectors was greatly enhanced by the discovery and application of the synthetic chemical diethyl m-toluamide (DEET). Recent studies reveal that DEET is not without toxicity and the search for safe repellents must be renewed. Studies of insect-plant chemical ecology reveal subtle defensive strategies of plants that provide a vast resource of opportunities to develop additional biorational methods for pest management.

LIMITATIONS OF SYNTHETIC CHEMICAL INSECTICIDES

The virtue/vice relationships of conventional toxicants have been well revealed during their more than forty-five years of use. They can be manufactured far from their place of use, stored and applied when needed. Chemical insecticides can be applied in anticipation of an infestation or used to rapidly clear pest insects from infested plants through direct toxic action. In general conventional insecticides are cost effective as well as efficacious. Yet, several insecticides have been shown to leave residues or toxic metabolites in the environment that pose significant hazard to human and animal populations and many of these insecticides have been eliminated or restricted in usage by governmental regulatory agencies. The high cost of registration for new insecticides with broad spectrum toxic action has diminished industrial interest in pesticide development for agricultural crops of minor economic status. Compounding the problem is the rapid development of resistance by many pest species to even the most intensely toxic pesticides. In order to maintain appropriate protection from insect pests new approaches to pest control must focus on the development of chemicals that target those unique aspects of insect behavior, biochemistry and physiology that have no counter part in man and other animals.

Most conventional insecticides target the nervous system for disruption in order to produce rapid toxicity. Unfortunately, the transmitter system most frequently affected is one shared by nearly all animals. Vertebrates and invertebrates diverged about six hundred million years ago and during this time many aspects of their biology have changed sufficiently to provide elements of behavior, communication, development and reproduction that may be disrupted exclusively without harm to vertebrates. Thus, current efforts must focus on discovering those special aspects of insect biology that have undergone divergent evolution from other animals and targeted to selective disruption. Agricultural scientists must look to the fundamental research of entomologists and chemical ecologists to enlist their aid in support of world pest control needs.

HOW CAN ECOLOGICALLY ACCEPTABLE PEST MANAGEMENT CHEMICALS BE DEVELOPED?

Many conventional toxicants were been developed from existing war gases and through the random screening of industrical chemicals. The principal screening techniques were established to find chemicals with rapid knockdown and broad spectrum toxicity to insects. This methodology will seldom uncover selective chemicals that may require a more lengthy time of observation to demonstrate biological activity. Indeed, an action that disrupts feeding and / or reproduction can be equally efficacious for the purpose of plant protection as a direct poison. Increasingly, new methods for the evaluation of prospective insect control chemicals are being employed. The development of target selective biological assays will demand much more effort by biologists and require of them a signifcant background in fundamental studies of insect biology. In general the basic biochemistry of insects and other animals has changed very little and a poison that attacks shared processes will be toxic to man as well. However, it is recognized that the control systems that regulate the basic biochemistry have undergone signifiicant divergent evolution and we can focus our attention on ways to interfere with these regulators in anticipation of finding selective control procedures. One successful approach has been to utilize the way insects regulate their development, growth and reproduction with hormones as a means of controlling insects without hazard to other animals. Similarly, the chemical language on which insects depend for reproduction, aggregation, alarm and resource discovery can be used to control specific pest species. The natural repellents of plants, gained through eons of evolutionary resistance to insect herbivory, represents an important resource for the discovery of safe personal repellents. Thus, although we are resource rich, we must generate the ingenuity to: find the weaknesses of our insect adversaries, anticipate the subtle defensive strategies of plants in order to discover their secrets, and construct the appropriate assay systems to test for new biorational mangement toolsss.

BIORATIONAL RESOURCES FOR INSECT CONTROL

Hormonal Insect Growth Regulators

In 1917 Kopec discovered that the brain contained a hormonal center that directed insect molting. Wigglesworth(1934) discovered another center in the insect head called the corpus allatum that controlled metamorphosis. The latter gland was also shown to control reproduction by Holmgren(1909) and diapause by Bowers and Blickenstaff(1966) as well as other important aspects of insect biology. A gland in the thorax producing a molting hormone was revealed by Fukuda(1940). In 1956 Williams reported that an ethereal extract of the abdomina of male Cecropia moths would, on application to insects in the pupal stage, scramble their developmental progression and induce them to form intermediates possessing both immature and adult characters. He correctly anticipated that the active ingredient was the metamorphosis controlling hormone of the corpus allatum and called it the juvenile hormone(JH). Williams also predicted that

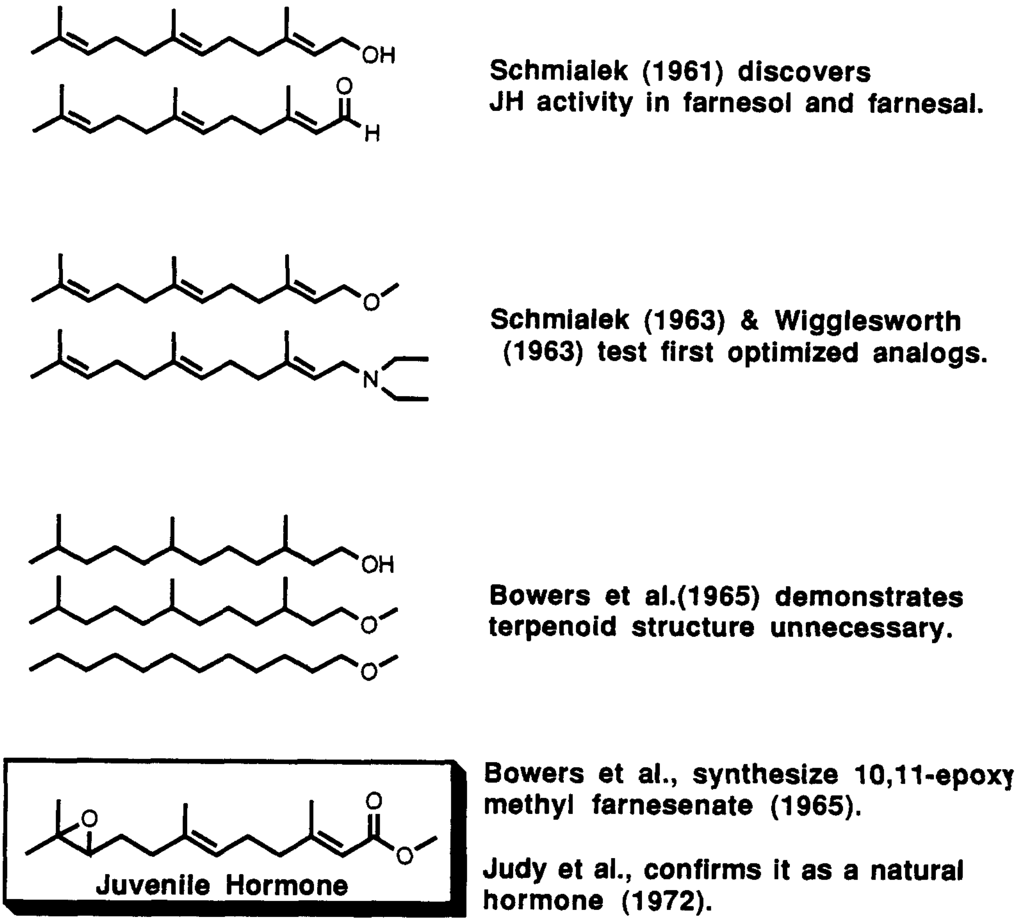

Fig. 1. Evolution of juvenile hormone chemistry.

the hormone, when isolated and identified, would constitute a safe insecticide because of it's unique action in insects for which no counterpart action exists in vertebrates. In 1961 Schmialek reported that an extract of insect frass possessed JH activity and identified the sesquiterpenoid alcohol farnesol and its aldehyde as the active compounds. Collaborating with industrial associates and Wigglesworth, Schmialek(1963) demonstrated that JH active analogs of farnesol could be prepared. Bowers and Thompson (1963) synthesized non-terpenoid compounds with JH activity, and in 1965 Bowers et al., published the structure of 10,11-epoxy, methyl farnesenate which was synthesized as a result of chemical prospecting for the active hormonal chemical in the Cecropia extract. The synthetic hormone was vastly more active than farnesol and or any of its' optimized analogs. Eight years later Judy et al.(1973) authenticated the epoxy methyl farnesenate as the principal juvenile hormone of insects(Fig. 1).

Additional, homologous JHs unique to Lepidoptera and Diptera were subsequently identified (Roller et al. 1967, Meyer et al. 1968, Bergot et al. 1980, and Richard et al. 1989). Industrial

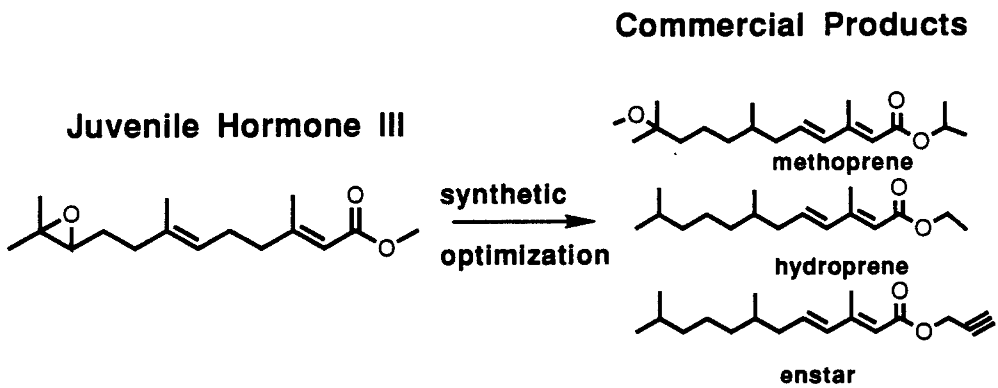

Fig. 2. Synthetic optimization of JH Ⅲ into commercial growth regulator products.

optimization efforts to provide a stable hormone of high activity focused on modification of the hormone, discovered by Bowers et al.(1965), and resulted in several insect control products developed by the Zoecon Corporation (Henrick et al. 1973)(Fig. 2). The hormonal products initially targeted mosquitoes as a larvacide and later additional products for the control of flies, fleas, ants, cockroaches, stored product pests and greenhouse insects emerged. The principal action of the hormone analog was to disrupt metamorphosis preventing the emergence of the adult reproductive stages.

Phytochemical Resources. In basic research laboratories studies of insect endocrinology revealed the presence of juvenile hormonally active substances in the balsam fir tree by Slama and Williams in 1965. Bowers et al. (1966) identified the active substance and called it juvabione(Fig. 3).

Aromatic Analogs. Releated to the natural JH, this discovery prompted additional studies of plants as a possible resource of new chemistry that might target the insect endocrine system as a natural defensive artifice of plants against insect predators. Several plant compounds used as insecticide and drug synergists were found to possess JH activity by Bowers(1968)(Fig. 3). Bowers and Nishida(1980) discovered additional phytochemicals with very high JH activity in the sweet

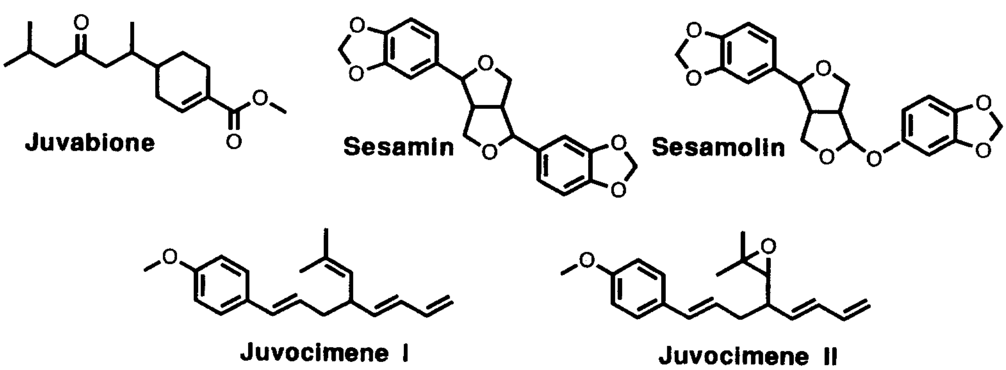

Fig. 3. Discovery of phytochemicals with insect juvenile hormone activity.

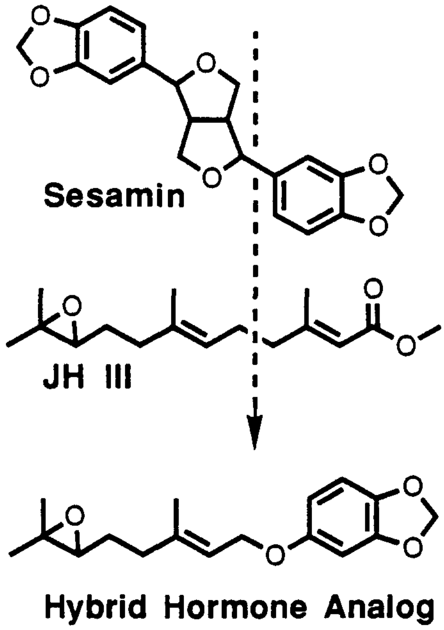

Fig. 4. Early synthetic studies combined structural information from phytojuvenoids with elements of the natural juvenile hormone to yield analogs 10,000 times more active than the natural hormone.

basil plant which they called juvocimenes(Fig. 3). Synthetic optimization studies combining structural information from the JH active phytochemicals with that of the natural hormone yielded very active aromatic-terpenoid hybrid analogs with vastly superior JH activity(Bowers 1969)(Fig. 4).

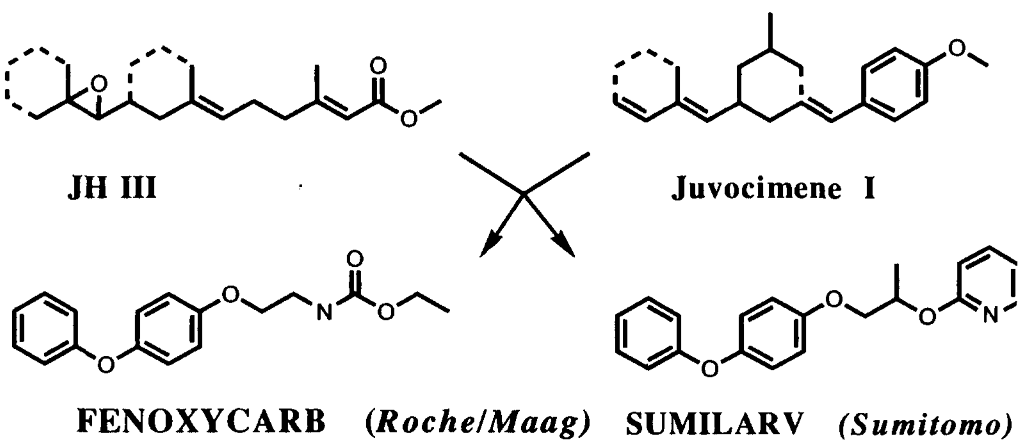

Fig. 5. Phytochemical and natural JH as models for optimization ultimately yielded a 2nd generation of growth regulator products.

These phytojuvenoids suggested the possibility of incorporating additional aromatic structures into the optimization efforts to produce superior JH analogs and led to the eventual emergence of a second generation of commercial products (Fig. 5) of vastly improved activity, albeit with chemical structures bearing little relationship to the natural JHs.

Insect molting inhibitors

Molting in insects is a process permitting the developing immature stage to shed its old exoskeleton and put on a new looser, baggier one in order to grow in size and to mature into the adult reproductive stage. A method of interfering with the molting process would provide insect control free of hazard to other animals. The first molt inhibitor was a benzoylphenyl urea discovered by the Phillips-Duphar Company and called variously, dimilin, diflubenzuron or TH 60-40. Soon other industrial products with similar chemistry appeared.

These compounds are intrinsically ineffective by contact and must be ingested to prevent molting. Nevertheless, they are highly effective against many plant feeding insects and herald a new insect growth regulator for selective insect control. Although the molting inhibitors were discovered as a result of random screening rather than by study of a biological model they are still considered as biorational since they affect an arthropod specific target site and are essentially harmless to other animals.

Future insect growth regulator candidates

Despite their efficacy and safety the JHs are mainly useful for the control of insect pests that do their damage in the adult stage. Thus, mosquito and fly larvae are unimportant as pests but the adults represent the economically important stage that can be conveniently and specifically controlled with JH containing products. JH based IGRs do not affect the immature stages and these are often the most active feeding pests in agriculture. Clearly new methods of attack are needed to stop or prevent the development of the immature feeding stages. It was visualized that the hormone antagonists, especially of the juvenile hormone, would stop the development of immature stages and cause them to molt very early into sterile, diminutive adults. Classical research showed that extirpation of the corpora allata removed the source of JH and induced the early formation of adults that were sterile. A method of performing a chemical allatectomy might offer a new approach to selective insect control of those immature stages most damaging to plants. Continuing to research plants as a resource of defensive chemistry focused on the insect endocrine system Bowers et al.(1976 a & b) discovered compounds in the *Ageratum* plant that induced precocious metamorphosis and sterilized many insects. The natural anti-juvenile hormones (AJH) shown in Figure 6 were called precocene 1 and 2. Subsequently, Binder et al.(1991) found the precocenes in the herbivore-resistant species, *Nama rothrockii*, a member of the plant family Hydrophilaceae. Thus, the precocenes have arisen independently in widely separated plant families as protective secondary plant chemicals.

Mode of action studies established that the precocenes destroy the corpus allatum by an oxidative activation process (Bowers & Martinez-Pardo 1977, Pratt et al. 1980, Soderlund et al.

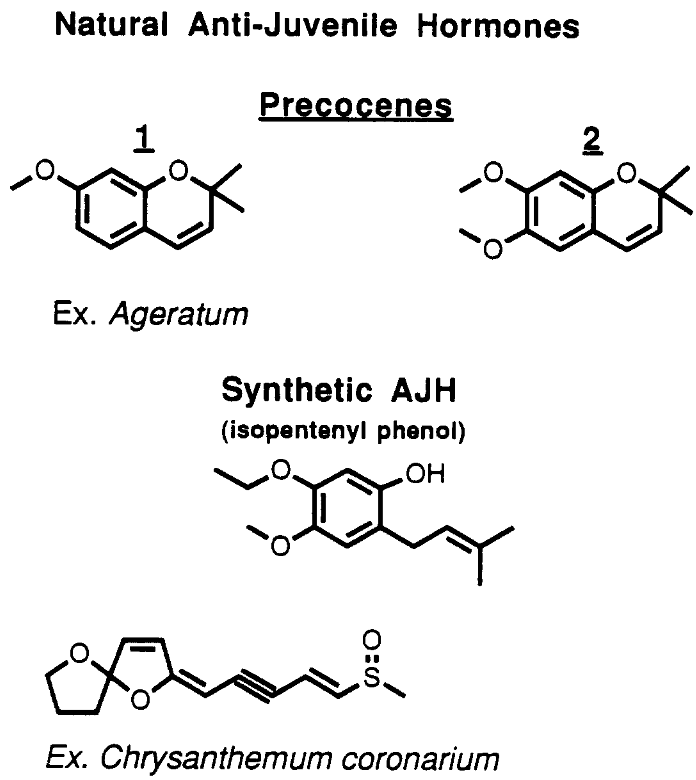

Fig. 6. Natural and synthetic anti-juvenile hormonal compounds.

1980). Non-chromene analogs were also developed that undergo a similar oxidation / activation and possess activity identical to that of the precocenes (Bowers et al. 1982). Bowers and Aregullin(1987) discovered a polyacetylenic phytochemical with insect anti-juvenile hormone activity in *Chrysanthemum coronarium* (Fig. 7) thereby sustaining interest in plants as a continuing resource for new insect growth regulator models. Commercial efforts have revealed additional antihormonal chemistry (Staal 1986, Wing et al. 1988), but as yet none have demonstrated the broad spectrum of activity needed to justify the high development and registration costs.

Insect pheromones

Insects are dependent on many chemicals with communicative significance. Chemical messengers, called pheromones are used to signal for sexual availability, courtship, resource making, colonization, alarm, social recognition, orientation etc. [for reviews see : Chemical Ecology of Insects (1984), W. J. Bell & Carde, R.T., eds., Handbook of National Pesticides Vol. 1, Mandava, N.V. ed.]. Since many of the signals are entirely specific to a single species highly directed control efforts, free of hazard to non-target species, can be devised.

Sex Phermones. Perhaps the most studied are the sex pheromones and several methods for their use in pest management have been devised. Butenandt et al.(1959) characterized the first

INSECT PHEROMONES

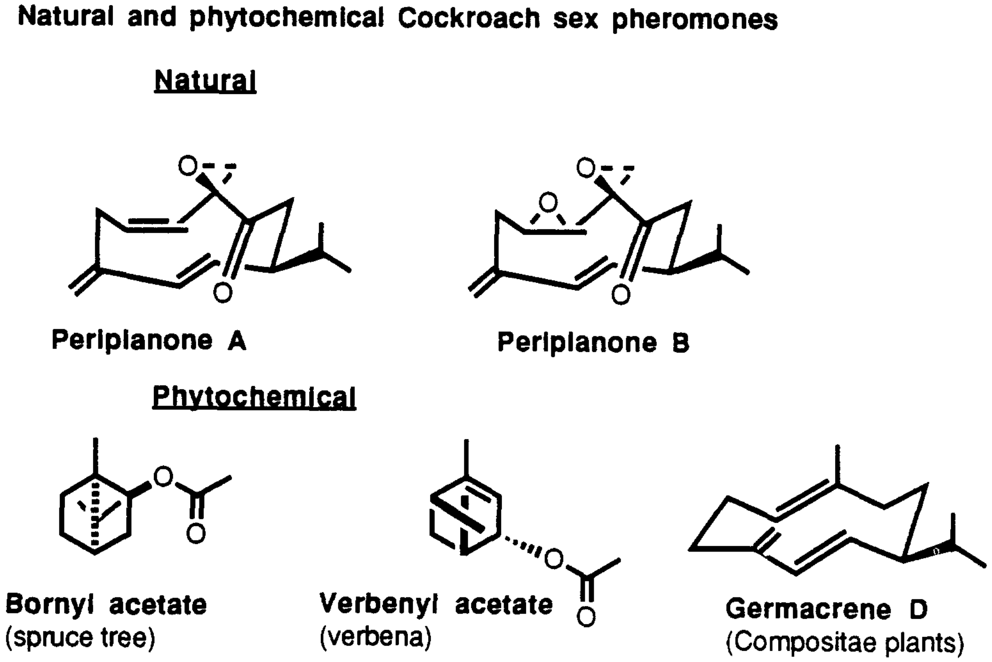

Fig. 7. Natural sex pheromones of the American cockroach, *Periplaneta americana* and phytochemical minics.

sex pheromone from the commercial silkworm, *Bombyx mori* after a 30 year research effort. The sex pheromone complex of the Boll Weevil, arguably one of the most devastating insect pests of agriculture, is routinely used to monitor field infestations as a guide to the application of control measures. The structures of the pheromone components were characterized from the extractives of four million weevils and fifty-four kilograms of fecal material(Tumlinson et al. 1969). Perhaps the greatest stimulus to sex pheromone research resulted from the development of the electroantennogram method of discovery and identification of lepidopteran pheromones developed by Roelofs(1979). This method was used to identify submicrogram quantities of pheromones extracted directly from the pheromone gland itself. Often an initial identification could be tentatively made on only one insect. Subsequent synthesis of the estimated structure provided the ultimate proof. Although some species use a single compound for sexual attraction the greater number require a precise blend of components for full response(Silverstein et al. 1966). Thus, the beetles *Ips paraconfusus* use a mixture of three compounds (-)-ipsenol, (+)-ispdienol, and (+)-cis-verbenol. Taken individually the components are inactive.

Use in Pest Mangement. The most successful application of sex pheromones in pest management has been for monitoring the presence and density of pest populations. The utility of the pheromone monitoring procedure is that it ensures the most prompt and conservative use of chemicals thereby limiting the pesticide load on the environment and reducing the overall cost of plant protection. Successful application of pheromones in monitoring for pests in apple orchards can reduce insecticide and miticide usage up to 50%(Roelofs 1981). In many cases it is not feasible to try to mass trap insects using sex lures because of the high density of traps and overall cost of operation. However, the use of pheromones to permeate the atmosphere has been demonstrated to reduce mating success and effect successful control of certain insect pests ie., cabbage looper, pink bollworm etc.(Roelofs 1981)

The sex pheromones of cockroaches have attracted widespread interest for over two decades following the initial investigations of Roth and Willis (1952). Although great efforts were ongoing to characterize the structures of the natural pheromones of the American cockroach, *Periplaneta americana* Bowers and Bodenstein(1971) and Nishino et al.(1977) were able to discover plant compounds in spruce and verbena oil that induced the mating display in these cockroaches indistinguishable from that elicited by the natural pheromones. The plant compounds eliciting the response were (+)-bornyl acetate, (+)-E-verbenyl acetate, Alpha- and Beta- santalol and a $C_{15}H_{24}$ Plant hydrocarbon isolated from *Liquidambar styraciflua* and *Liriodendron tuplipifera*(Fig. 7). The hydrocarbon structure was later identified by Tahara et al.(1975) and Kitamura et al.(1976) as germacrene D, a sesquiterpenoid hydrocarbon later found to compose the skeleton of the natural pheromones which were eventually fully characterized by Persoons et al.(1979) and Nishino et al.(1988). The cockroach sex pheromones have been used successfully in household traps for the German cockroach(*Blatella germanica*), and the American cockroach(*Periplaneta americana*).

Alarm Pheromones. Many species respond to attack by elaborating alarm pheromones that signal to siblings the presence of a predator or parasite. The alarm pheromones of aphids are perhaps the best characterized. After Dahl(1971) and Kislow and Edwards(1972) demonstrated that aphids released alarm pheromones in their cornicle secretions, Bowers et al. (1972) isolated and characterized the alarm pheromone of aphid species belonging to 19 genera in three aphid subfamilies (Aphidinae, Chaitophorinae, and Callaphidinae) as the sesquiterpene hydrocarbon (E)-β-farnesene(Fig. 8). This pheromone is the broadest interspecific pheromone known. Subsequently Bower et al.(1977) and Nishino et al.(1977) identified another sesquiterpene hydrocarbon (-)-germacrene A as the alarm pheromone of aphids in the genus *Therioaphis* (Callaphidinae) (Fig. 8). The anticipated utility of the alarm pheromones as natural repellents to prevent aphid attack of plants is limited by the lability of the pheromones to light and air. Rapid breakdown diminishes the efficacy of the alarm pheromones. Nevertheless, Griffiths and Pickett (1980) demonstrate that combination of alarm pheromones with insecticides improves efficacy presumably by the induction of increased activity of the aphids who contact more insecticide. Synthetic optimization of the alarm pheromones has revealed several analogs with superior stability (Nishino & Bowers 1976, Nishino et al. 1976) and the development of slow release formulations (Dawson et al. 1982) increases the possibility for their eventual use in aphid pest management. Propheromones that release pheromonal carbonyl compounds in light offers additional promise for application (Liu et al. 1984). Gibson and Pickett (1983) have also shown that the wild aphid-resistant to

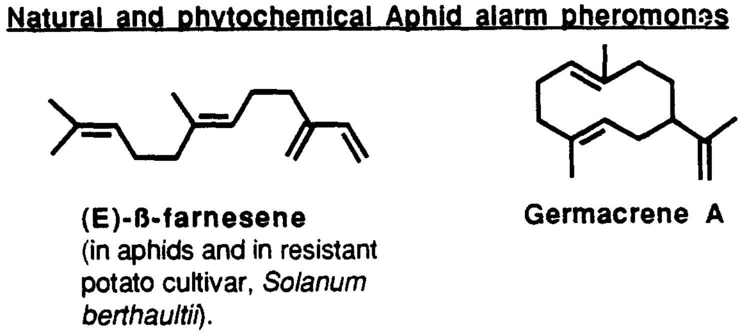

Fig. 8. Aphid alarm pheromones.

mato *Solanum berthaultii* release(E)-β- farnesene from its trichomes as a resistance mechanism against aphid attack. This is the first report of a plant using the identical chemical pheromone of an insect for protection.

Repellents

The origins of the use of personal repellents are doubtless lost in prehistory but the use of vola'ile chemicals to repel biting arthropods and ectoparasites are universal to all cultures. Repellents are commonly used by animals for protection against parasites and predators. Thus, insect defensive secretions contain a striking array of simple hydrocarbons, esters, aldehydes and alcohols used to fend off potential attack by other arthropods (Blum, M.S. 1981). Benzoquinones, naphthoquinones and phenolics are also repellent components of insects (Tschinkel 1969) Insects are the principal vectors of all of the ancient plagues and seem to conspire constantly to keep man in a perpetual state of ill health. The reproductive potential of humans appears to be a constant, but historically malignant diseases like malaria, yellow fever, typhus and trypanosomiasis have viciously checked population growth. Prior to World War II most personal repellents were derived from plant volatiles and included the well known secondary chemicals geraniol, citronellol, camphor and menthol. The need for a long lasting repellent during the war led to a massive screening effort of industrial chemicals that untimately led to the adoption of the chemical diethyl m-toluamide or DEET. DEET was quickly moved into production and can be credited with the protection of millions of soldiers from vector borne disease. Following the war DEET entered the civilian market and displaced the natural repellents. It should be noted that DEET was a patented repellent preparation and could be sold for a premium price whereas the natural repellents lacked commercial advantage and were soon pushed out of the market. Recently, re-examination of DEET has revealed that it is not an innocuous chemical and possesses significant toxicity to humans.

Our improved understanding of insect biology and of the natural chemical defenses of plants offers the possibility of discovering new natural repellents lacking the toxicity of DEET and similar synthetic chemicals. The exciting discipline of chemical ecology investigates how plants and animals interact in nature. Some of their defenses are clearly based on the deployment of repellent chemicals. We have discovered several plants that posses potentially useful natural repellents. Among the plant secondary chemical repellents we find that simple aromatics like coumarin, piperonal, piperatone and linalool are highly effective space repellents for ants, mosquitoes and blackflies (Bowers 1991 unpub. data). Their volatility is a limitation when duration is considered but modern slow release formulations and special release media promise to improve their efficacy dramatically. Beyond the use of natural repellents for personal protection it must be recognized that repellents serve their host plants well and constitute a natural mechanism to fend off herbivores. Problems of high volatility and sensitivity to light and air can now be overcome by suitable formulation. Increasingly, investigations focus on the potential application of natural repellents for the direct protection of crops.

SUMMARY

Insect growth regulators targeted to disruption of hormonally ordered processes have already made important contributions to the search for environmentally acceptable methods of insect control. Similarly, pheromones find use in integrated pest management programs as monitoring tools and for mass confusion. Molting inhibitors and repellents are now in the vanguard of additional efforts to find natural protectants for crops and for public health protection. In order to meet the continuing challenge agricultural scientists and entomologists must increasingly focus their efforts on the study of those elements of basic insect biology that will allow the development of safe and selective products for plant and animal protection.

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