THE HISTORY AND CURRENT STATUS OF JUVENOIDS

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Abstract - The history of natural and synthetic bioanalogues of insect juvenile hormone (JH), juvenoids is more than 40 years old. The first JH-active lipid extracts prepared from the cecropia moths in 1956. The first JH-active was an isoprenoid farnesol isolated in 1961, then "pseudojuvenilizing" or JH-mimetic effects of lipids were described; after 1965, JH-active isoprenoids were isolated from natural sources. A sesquiterpenoid ester, juvabione, was isolated from paper products, and a isoprenoid compound with JH activity was isolated from the lipid extracts of cecropia. It was an acyclic sesquiterpenoid ester known as the true JH of insects, the JH-I. Major achievements of 1965-1975 this epoch were registrations and practical applications of the isoprenoid juvenoids, hydroprene, methoprene and epofenonane. They were used against mosquitoes, synanthropic flies, pharaoh's ants and cockroaches. Since 1980, commercial interests in juvenoids moved from isoprenoids to the polycyclic juvenoids, which were characterized by the presence of 4-phenoxyphenyl structure. The first juvenoid of the 4-phenoxyphenoxy series registered for practical use was fenoxycarb. This juvenoid has been successfully used against various insect pests. Another juvenoid of this series, pyriproxyfen which like fenoxycarb exhibits very high JH activity. In certain species it is more effective than fenoxycarb, but in other species the proportions may be reversed. Data concerning the action of methoprene, fenoxycarb and pyriproxyfen are provided. There may be thousands of synthetic juvenoids which mimic the action of insect hormones. The authentic JH of insects interacts with the genome of insect cells and produces the qualitative, "all-or-nothing" effect. This enables the hormone to act in concentrations close to 10^{-10} M, first recorded in peptidic juvenoids in 1973. The 10^{-10} M limits of JH activity were again found in the modern juvenoids containing the bicyclic, phenoxy-phenyl groups; fenoxycarb, pyriproxyfen and other structurally related juvenoids. At 10^{-10} M concentrations the endogenous JH and the most potent juvenoids are protected from and uninfluenced by esterase and other hydrolytic enzymes. The isoprenoid compounds, JH-I or JH-III, are mostly 10000-times less active than synthetic juvenoids. JH-I, JH-II and JH-III are not the true JH of insects, but misinterpretations of physiologically inert prenol metabolites. The true JH of insects is probably a small peptide.
Key words - Juvenile hormone, juvenoids, methoprene, fenoxycarb, pyriproxyfen

INTRODUCTION

The juvenile hormone (JH) of insects is secreted from endocrine glands called corpora allata. The principal developmental function of JH is a programmed suspension of morphogenesis and installation of larval somatic growth. This is usually associated with a fascinating indirect development, which is characaterized by a variety of diversified larval forms. At the end of larval period, the production of JH is physiologically inhibited and the interrupted morphogenetic schedule can continue on towards the fully differentiated adult forms. In adult stage of certain insect species, the JH is again used for regulation of reproduction, especially during the cycles of somatic growth in reproducing females. The JH of insects is never produced in a nonfeeding stage, except for the final part of embryonic development. These basic endocrinological features of JH were first recognized and described by Wigglesworth (1936) on *Rhodnius prolixus* (Novák, 1966).

Williams (1956) obtained the first exogenous JH effects without necessity to transplant the active corpora allata. He developed a simple JH assay for the lipid extracts and predicted that materials with JH activity could be used for controlling harmful pests. At present, synthetic analogues of JH, juvenoids, are among the most commonly employed agents for controlling noxious insects. In 1985, the amount of synthetic JH analogues, juvenoids, was estimated to more than 4000 compounds (Sláma, 1985) and this number is certainly much higher today. The industrial companies supply large amounts of very potent synthetic juvenoids, which are still carelessly disseminated throughout environment in the hope that they are nothing else but an insect hormone. Beneficial properties of juvenoids depend on extremely high effectiveness, minimum environmental contamination and absence of direct toxicity. The mode of action of insect JH, or ideal juvenoid, depends on selective binding with the genome of insect cells. Let us hope that tissue and cells of other organisms will not be the targets of JH.

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Recent researchers working with juvenoids are mainly interested in practical effectiveness of some commercial preparations, with a very superficial knowledge about physiological or endocrine conditions associated with the hormonal action. There are repeated inconsistencies in interpretation of results obtained with juvenoids. There is a general tendency to ascribe toxicity, antifeedant, antimetabolic and other adverse side effects of the purely synthetic juvenoids to JH. Certain commercial juvenoids evidently do exhibit some lethal toxic side effects, but this should be distinguished from the true pharmacokinetic action of the hormone. There are biochemical studies related to the effects of esterase enzymes on JH activity, not realizing that hormones in general become enzyme substrates only in excessive, nonphysiological quantities. In this contribution I should like to refresh some old facts in JH research, indicating the source of references and reviews. There are also a few original, physiological and endocrinological observations acquired during more than 40 years of JH research.

Initial stage of JH research

The history of juvenoids really begins in 1956 when Williams prepared the first JH-active lipid extracts from the abdomens of male adult cecropia moths (Williams, 1956). The extracts caused retention of pupal characters when injected into pupae before initiation of adult development. The extracts were also effective when applied on the surface of pupal body. This fact led Williams to conclude that similar preparations with JH activivity might be used as nontoxic and selectively acting future pesticides. Further investigations revealed that certain materials with positive JH responses were present also in the lipid extracts prepared from different Phylla of invertebrates (Schneiderman and Gilbert, 1958), from various vertebrate organs (Williams *et al.*, 1959; Schneiderman and Gilbert, 1959) and they were also present in lipid extracts from certain microorganisms and plants (Schneiderman *et al.*, 1960). The first JH-active compound with the defined chemical structure was a sesquiterpenoid alcohol farnesol (No. 1 in Fig. 1), which was previously known as a common constituent of plant oils. It was isolated from the excrements of yellow mealworm and from the yeasts by Schmialek in 1961. Originally, farnesol was believed to be the true JH of insects (Schmialek, 1961), but this conclusion was almost immediately questioned by endocrinologists, who determined existence of nonspecific, "pseudojuvenilizing" effects in JH bioassays (Sláma, 1961). The principles of this JH-mimetic action were further elaborated by Sláma (1962), who produced the false JH effects with free fatty acids or fatty alcohols that were commonly present in lipid extracts from animals and plants. In 1964, Schneiderman and Gilbert (1964) still expressed doubts about JH-mimetic effects, although later development in the field fully substantiated the principles of JH-mimetic action elaborated by Sláma (1961, 1962) at real beginning of the future juvenoid era.

Since 1962, chemists launched intensive search for new terpenoid materials with JH-activity. Farnesylmethylether and farnesyldiethylamine, for instance, appeared to be more active than farnesol (Schmialek, 1963; Bowers *et al.*, 1963; see Schneiderman and Gilbert, 1964 for a review). When Röller and his colleagues identified the JH-active principle from the lipid extracts of cecropia (Röller and Bjerke, 1965; Röller *et al.*, 1965, 1967), they actually did not come out with some unknown structural type, because essential structural features of the future JH-I (i.e. the 3,7,11-trialkyl-2,6,10-tridecatrienoate backbone; see Schmialek, 1963) as well as the 10,11-epoxyfarnesoate function (Bowers *et al.*, 1965) were already known. It was actually predicted by Bowers that future JH, when discovered, should be structurally related to the 10,11-epoxyfarnesoate (see No. 3 in Fig. 1). Indeed, the active fraction of the lipid extracts from cecropia was identified by Röller *et al.* (1967) as a methyl cis-10,11-epoxy-3,11-dimethyl-7-ethyl-trans, trans-2,6-tridecadienoate (see No. 4 in Fig. 1). This compound has been glorified and declared to be the true JH of insects (JH-I). The closely related derivative, 10,11-epoxyfarnesoate of Bowers (No. 3 in Fig. 1) was later recognized as the most common JH-active compound in the lipid extracts from various insects and became generally known as JH-III. The authors isolating JH-I did not realize at that time that there might be hundreds of nonspecific JH-active mimics, such as other isoprenoids, fatty acids, peptides or polycyclic aromatic compounds, which were discovered much later. As the biological activity of JH-I was higher in comparison to farnesol and other compounds, it was generally accepted that the JH-I was the true JH of insects.

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In addition to structure-activity investigations among the derivatives of JH-I (cf. Röller *et al.*, 1967; Westermann *et al.*, 1969; Wigglesworth, 1969; Pfiffner, 1971), a new competition for synthetic juvenoids was stimulated by rather uncommon finding of materials with insect JH activity in certain American paper products (Sláma and Williams, 1965, 1966; Williams and Sláma, 1966). This finding manifested in practice that an insect population could be selectively destroyed without direct intoxication, just as a consequence of developmental failures. This vision of alternative insect control by means of nontoxic, hormonally acting pesticides, was generally favoured by the ongoing discrimination of neurotoxic insecticides when Rachel Carson published the book Silent Spring in 1962. The "paper factor" contained in the wooden pulp of the Canadian balsam fir was identified by Bowers *et al.* (1966) as a methyl ester of an alicyclic sesquiterpenoid acid, called juvabione (No. 2 in Fig. 1). A similar, structurally related compound, dehydrojuvabione, was find in a balsam fir growing in Europe (Cerný *et al.*, 1967), but the common European evergreen trees did not contain JH activity at all.

Virtual absence of juvabione-sensitive pyrrhocorid bugs in forests containing the Canadian balsam fir led us to speculate (Sláma and Williams, 1965, 1966) that certain plants might perhaps develop resistance against insect herbivores by evolutionary adaptations leading to synthesis of compounds with insect JH activity. The hormonally based animal-plant interactions of ecological importance were known in mammals. Serious reproductive disfunctions or complete sterility of sheep grazing on Australian clover pastures can be used as an example. The sheep were sterilized by estrogenically active isoflavones or benzofurocoumarins present in some fodder plants (Sláma, 1980). The indicated hormonal theory of insect-plant interactions has been often criticized, although experimental arguments in favour or against the theory were lacking. More recently, however, the hormonal insect-plant relationships have been reinvestigated experimentally, using plants with very high ecdysteroid content as a model (Zelený *et al.*, 1997). As far as JH activity is concerned, however, the screenings of plants for JH activity revealed only a few compounds (cf. Bowers and Nishida, 1980; Bowers, 1991), suggesting that the presence of topically active, lipid soluble, JH mimics in plants can be viewed rather as an exception (reviews by Bowers, 1991; Sláma, 1969, 1979, 1985, 1987; Staal, 1967; Williams, 1970). The plants commonly contain slightly polar sesquiterpenoid compounds (alcohols, acids) with a very low JH activity, but certain plants, like *Cyperus iria* contain JH-III (Schwartz *et al.*, 1998).

The boom of synthetic isoprenoid juvenoids, 1965 - 1975

The synthetic preparation of isoprenoid juvenoids culminated between 1965 and 1970 (Williams and Robbins, 1968). Special role at initial stage of juvenoid research was played by a synthetic preparation of farnesoates by Law *et al.* (1966). This preparation was generally known as Law and Williams mixture. The most active compound of this preparation was identified as an ester of 3,7,11-trimethyl-7,11-dichloro-2-dodecenic acid (Romaòuk *et al.*, 1967). In certain insects, this dihydrochloride was considerably more effective than JH-I. It was practically used in a number of physiological, dose-response juvenoid investigations. Increased synthetic efforts were naturally also stimulated by structures of the natural products, like juvabione (Sláma *et al.*, 1968; Mori and Matsui, 1970) and JH-I (Wigglesworth, 1969; review by Pfiffner, 1971).

In addition to large number of new acyclic or alicyclic sesquiterpenoid juvenoids which were prepared before 1971 (reviews by Bowers, 1971; Cruickshank, 1971; Šorm, 1971; Sláma, 1971; Wakabayashi *et al.*, 1971), one particular type of the acyclic isoprenoid juvenoids revealed outstanding laboratory as well as field effectiveness. This type was represented by dodecadienoate juvenoids developed by Zoecon Corp. in USA as the best candidate for future insect control (Henrick *et al.*, 1973; Henrick, 1982). The structure of dodecadienoates was relatively simple, closely related to naturally occurring isoprenoid compounds, biodegradable and environmentally friendly. The dodecadienoates hydroprene and methoprene (5 in Fig. 1) were historically the first juvenoids registered for practical use. They have been successfully used against a number of different urban and field pests (Henrick, 1882) and they are still favoured as the least toxic, biodegradable, environmentally safe juvenoids until this time.

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The structures of juvenoids known before 1974 revealed several predominating structural types, mostly derived from acyclic or alicyclic sesquiterpenoids (Suchý *et al.*, 1968; Sláma, 1971; Sláma *et al.*, 1974). In addition, there was a large and well established group of aromatic-terpenoid ethers originally found by Bowers (see Bowers, 1969; review by Bowers, 1971), and a group of aromatic terpenoid juvenoids related to juvabione (Suchý *et al.*, 1968; Mori and Matsui, 1970). However, there was also one atypical type of nonisoprenoid juvenoids, which were really strange and absolutely unrelated to isoprenoid structure of JH-I. These juvenoids were peptides, similar to the tripeptide L-isoleucyl-L-alanyl-p-aminobenzoate shown in Fig. 1, 10 **(**Zaoral and Sláma, 1970). This compound with amidic bonds and peptidic branching was more active than juvabione in *Pyrrhocoris apterus* assays. With further modifications at the -NH_2 terminus, we obtained further peptide juvenoids with enormously high JH-activity (Poduška *et al.*, 1971).

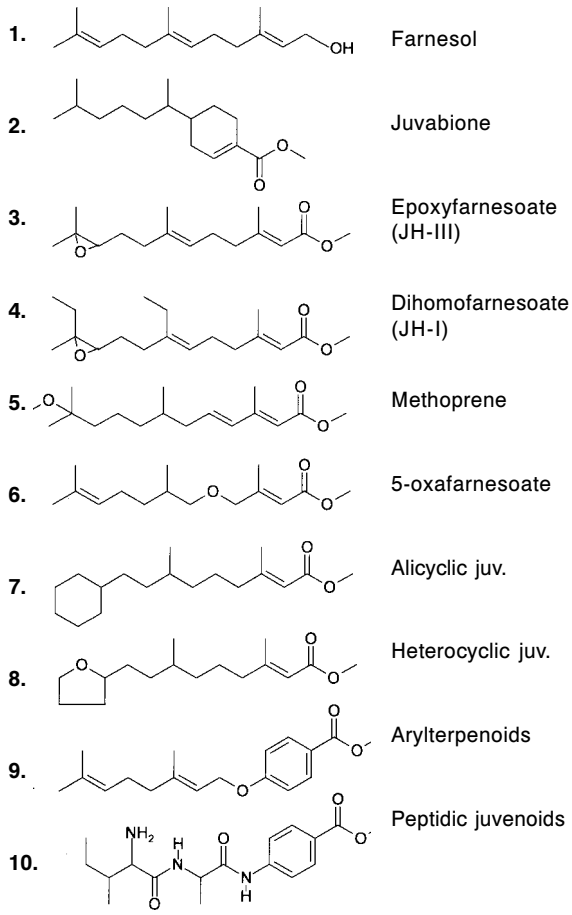

Figure 1. Some natural and synthetic isoprenoid juvenoids and juvenoid types known before 1980.

Increasing types and quantities of the synthetic juvenoids

In 1971 the first comprehensive juvenoid review estimated the total amount of synthetic juvenoids to some 500 active molecules, which were distributed into 8 structural categories (Sláma, 1971): 1. Acyclic terpenoids; 2. Acyclic terpenoids with heteroatoms in the chain; 3. Cecropia JH-I type; 4. Juvabione type; 5. Aromatic terpenoid ethers, thioethers and amines; 6. Peptidic analogues of JH ; 7. Other nonterpenic analogues, and; 8. Insecticide synergists related to sesamex. The most potent and also most selective JH analogue of that time was a peptide derivative, pivaloyl-L-alanyl-*p*-aminobenzoate,

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which exhibited 10000-fold higher JH activity than JH-I in pyrrhocorids, but was completely inactive after topical application in all other insect species studied (Sláma, 1971).

In the book on insect hormones and bioanalogues (Sláma *et al.*, 1974), the structures of juvenoids were classified into: A. Acyclic juvenoids (1. Farnesol and derivatives, 2. Geraniol and derivatives, 3. Farnesoic acid and derivatives, 4. Cecropia juvenile hormones, and 5. Other acyclic juvenoids); and, B. Cyclic juvenoids (1. Juvabione and dehydrojuvabione, 2. Derivatives of benzoic acid and acetophenone, 3. Phenyl ethers and aniline derivatives, 4. Nitrophenols, halophenols and nitroanilines, 5. Benzenesulphonic acid derivatives and, 6. Peptide juvenoids). The extensive juvenoid review from 1982 (Henrick, 1982) presented extensive structure-activity data for acyclic sesquiterpenoid juvenoids, with special attention of the dodecadienoate type. This review classified the so far existing juvenoid structures into: 1. Alkyl 3,7,11-Trimethyl-2,6,10-dodecatrienoates (farnesoates), 2. Alkyl (2E,4E)-3,7,11-trimethyl-2,4-dodecadienoates, 3. Terpenoid phenyl ethers, 4. Aryl terpenoids, and 5. General analogues. The last group contained description of all nonterpenoid juvenoids, including the 4-phenoxyphenyl or 4-benzylphenyl juvenoids. In 1985, the total amount of biologically active juvenoids was estimated to more than 4000 compounds, which were separated into 9 structural categories: 1. Natural juvenoids from animals and plants; 2. Farnesoates and 2,4-dodecadienoates; 3. Oxa-, thia- and aza-farnesoates; 4. Alicyclic (terpenoid) juvenoids; 5. Heterocyclic juvenoids; 6. Arylterpenoid juvenoids; 7. Simple non-isoprenoid juvenoids; 8. Polycyclic non-isoprenoid juvenoids, and a new category; 9. Juvenogens (Sláma, 1985).

For easier orientation over structural types of isoprenoid juvenoids, some of their representative structures can be found in Fig. 1. We can see that chemical structure of the dodecadienoate methoprene (5) fits very well to structures of the naturally occurring isoprenoids from animals and plants (1-4). The dodecadienoates actually represent a single group of commercial juvenoids that are structurally related to natural products. The structure of 5-oxafarnesoate (6) represents a large group of the isoprenoid-like juvenoids containing various heteroatoms (O, N, S) in the basic chain. The presence of cyclohexane moiety in the molecule (7**)** exemplifies the group of alicyclic sesquiterpenoids, similar to juvabione (2). The tetrahydrofurane compound (8) shows basic type of the heterocyclic isoprenoid juvenoids. Large numbers of the structurally related bioanalogues of these representatiave juvenoid types have been prepared and tested for JH activity in various insect species (reviews by Henrick, 1982; Sláma, 1985).

The arylterpenoid group of juvenoids (9) was extensively investigated since the discovery of JH activity of aromatic insecticide synergists in 1968 (Bowers, 1968, 1969). Fig. 1 (9) shows a common representative juvenoid, the geranyl ether of p-hydroxybenzoate. These juvenoid derivatives of aromatic terpenoid ethers represented in the late 1970s perhaps the largest group, including several hundreds of JH-active compounds. They were considered as hot candidates for practical use. The most successfull, epophenonane, was registered by Hoffmann-LaRoche Co. and it was successfully used against some pests, especially in the fields and orchards (see below). Certain aromatic terpenoid alcohols were used in form of their fatty acid esters as the biologically activated juvenogen complexes (Sláma *et al.*, 1978a). Fig. 1 (10) shows chemical structure of the peptidic juvenoid, L-isoleucyl, L-alanyl, p-aminobenzoate (Zaoral and Sláma, 1970) for its easier comparison with the isoprenoids. The slightly polar properties and extremely high activity of the peptidic juvenoids enabled Babu and Sláma (1972) the first utilization of juvenoids as systemic agents, affecting insect feeders through the plant system.

A superficial examination of the structures presented in Fig. 1 indicates a relative conformity in all these juvenoid structures with respect to size of the basic chain, similar position of branching radicals and occasionally similar location of the functional groups. The highly lipophilic physico-chemical properties make these compounds to be ideal ligands for binding with receptor sites of the JH. It is beyond the scope of this contribution to go into the details of structure-activity relationships among the isoprenoid juvenoids. These relationships have been described in previous review articles (Henrick, 1982, 1995; Sláma, 1985; Sláma *et al.*, 1974).

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Synthetic juvenoids after 1975

In contrast to continuously increasing quantities of new juvenoid structures, the essential biological and physiological features associated with JH action were mostly found before 1975. Further investigations of juvenoids were directed towards selection and development of suitable candidate compounds for practical use. The first officially registered juvenoids, hydroprene and methoprene (Fig. 1, 5) were successfully used in the control of mosquitoes, ants and flies (review by Henrick, 1982). Retrospective view would show that methoprene marked a culmination in the efforts to use biodegradable, selectively acting, and ecologically friendly natural-like structures, whose action would be based on JH activity without toxic side-effects. Unfortunately, disadvantages of methoprene and other "clean" juvenoids is that they do not cause immediate knockdown and assanation of the infested areas. Its use requires professional skill and knowledge of suitable periods and optimum modes of their application. This handicap of methoprene as a safe biorational product has never been fully restrained. The chemists of insecticide companies therefore tried to avoid this handicap by combination of JH activity with some lethal side effects or even with immediate toxicity. The common chemical manoeuver how to achieve this goal was incorporation into the juvenoid molecule structural characters prerequisite for high toxicity. They introduced the bicyclic 4-phenoxyphenoxy group, which was once used for the synthesis of highly toxic pyrethroids.

The rate of JH activity of the best isoprenoid juvenoids, including methoprene, is usually in the range of concentrations between 10^{-6} M and 10^{-7}M (related to living body mass). The exceptionally high rates of JH activity were previously found only with juvenoids of the peptidic type. They were effective in standard ID-50 dosages of a few picograms per specimen, which was equivalent to concentrations of 5×10^{-9} M (Sláma, 1971), 5×10^{-10} M in topical application or 2.5×10^{-10} M in oral application (cf. Sláma, 1981). Such enormously high rates of bilogical activity are known for the peptidic hormone proctolin in insects and the peptidic hormones oxytocine and vasopressine in the mammals. The most frustrating feature of the peptidic juvenoids is limitation of their activity to just one family of insects, the Pyrrhocoridae. Moreover, in contrast to isoprenoid juvenoids, the JH activity of the peptides is strictly limited by geometrical and optical conformations. For example, the enormously high JH activity is all completely lost by replacement of the central L-amino acid by its unnatural, D-optical antipod (Poduška *et al.,* 1971, 1973). We tried to find a superactive peptide juvenoid for other species than only pyrrhocorid bugs (Poduška *et al.,* 1971, 1973; Sláma *et al.,* 1974; Hlaváèek *et al.,* 1976a, 1976b), but all our efforts were unsuccessful. Only one single compound of the peptidic type (11 in Fig. 2) showed slight but definite JH activity also in pupae of *T. molitor.*

Organic chemists working in juvenoid research were always concerned more about the isoprenoid juvenoids, because they were active in all insects. Some of them did not consider the peptidic types as real juvenoids. Henrick (1982) speculated, for example, that peptidic juvenoids might probably exert JH activity indirectly, via stimulation of endogenous JH production in the corpora allata. Unfortunately, it was not so. The peptidic juvenoids positively act in allatectomized specimens and they show direct, localized epidermal JH effects.

The recent era of 4-phenoxyphenyl juvenoids

Shortly after registration of methoprene, another terpenoid aromatic juvenoid was registered for practical use, epofenonane. Its chemical structure was derived from the structural type indicated by (9) in Fig.1 (Hangartner *et al.,* 1976). Epofenonane had somewhat better effects than methoprene in certain field applications but, basically, its range of JH activity was more or less similar to methoprene. In 1981, however, the researchers of Hoffmann-LaRoche laboratories reported on the discovery of quite exceptional, highly effective, nonisoprenoid type of new juvenoids (Masner *et al.,* 1981). The range of biological activity of these new juvenoids was extraordinarily high, the standard ID-50 dosages reached values close to picograms per specimen, i. e. close to 10^{-9} M or 10^{-10} M concentrations in the body.

The most important structural innovation was incorporation of the bicyclic, 4-phenoxyphenyl group into the juvenoid molecule. This was made exactly in a similar manner as it was previously made in the

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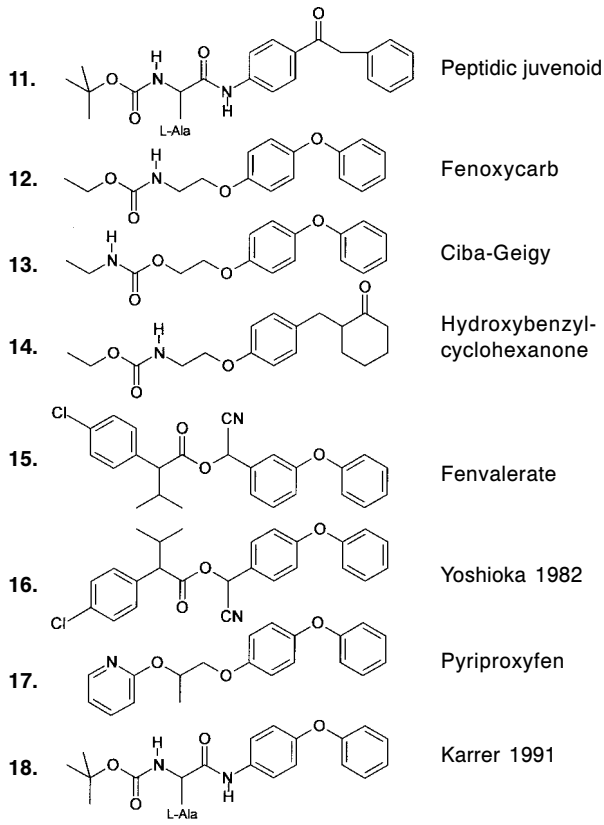

Figure 2. Polycyclic nonisoprenoid types of juvenoids developed mostly after 1981.

field of highly toxic synthetic pyrethroids. In the case of juvenoids, however, the pharmacological effectiveness of these unnatural compounds was not toxicity but real JH-activity. The first juvenoid of this 4-phenoxyphenyl series registered for practical use was fenoxycarb (Fig. 2, 12). This compound completely violated the old strategies for juvenoids as the safe "third generation pesticides" (see Williams and Robbins, 1968), because the molecule of this juvenoid has been composed from two most pernicious toxic elements, i. e. carbamate on one side and pyrethroid on the opposite side of the molecule.

The inventors of fenoxycarb confessed that it was discovered by chance during random screenings for JH activity (Masner *et al.*,1981). Regardless whether this was true or not, the side chain of fenoxycarb shows some structural similarities with the juvenoid peptides (compare structures 11 and 12 in Fig. 2). One can notice, especially, that the oxygen or nitrogen atoms occur at similar locations as the -NH- imino groups and carbonyl groups of the peptides. The JH activity of fenoxycarb is really enormous (Dorn *et al.*, 1981), the ID-50 dosages reach the values of picograms per specimen, matching the previously established records by the peptide juvenoids. Unlike the peptides, however, fenoxycarb is effective in representatives of unrelated insect groups, including economically important pests like mosquitoes and tortricids (Masner *et al.*, 1981; 1987). The commercial preparation of fenoxycarb has been successfully used against various urban and field pests under the name Insegar (against orchard pests), Logic (fire ants), Torus (fleas, cockroaches), Pictyl (mosquitoes) and Varikill for many years (Dorn *et al.*, 1981; Masner *et al.*, 1981, 1987; review by Grenier and Grenier, 1993).

The chemists of Ciba-Geigy had always an original approach to juvenoid synthesis. According to Karrer and Farooq (1981), each of the three isoprene units of the acyclic sesquiterpenoid JH-I could be replaced by an aromatic benzene ring without losing the biological activiy. They prepared and tested a number of remarkable juvenoid structures (Scheurer and Ruzette, 1974; Franke *et al.*, 1975) including the strange tricyclic polyphenoxyphenoxy juvenoids composed of 3 benzene rings (Karrer and Farooq,

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1981). The 4-phenoxyphenyl compound shown in Fig. 2 (13) was again classified among the most active JH mimics (Karrer and Farooq, 1981). A juvenoid of this series, diofenolan (CGA 59205), similar but not exactly identical with 13 in Fig. 2 has been commercialized under the name Aware (Sachser *et al.*, 1994).

The above indicated theory based on substitution of individual isoprene units by benzene rings (Karrer and Farooq, 1981) is very attractive, but not fully specific to the benzene rings. Incorporation of alicyclic, cyclopentane or cyclohexane, rings into olefinic chains of isoprenoid as well as nonisoprenoid juvenoids has similar effect on JH activity as in case of the phenyl (Sláma *et al.*, 1974; Henrick, 1982). In 1978, we prepared a series of juvenogen glycosides derived from the bicyclic, 2-(4-hydroxybenzyl)-1-cyclohexanone (Sláma *et al.*, 1978b). These compounds were extremely selective. They were absolutely inactive as JH mimics in contact application, but became very active when swallowed with food. This was due to internal liberation of JH-active aglycone by intestinal glycosidase enzymes. The basic structure of the parent juvenoids, the 2-(4-hydroxybenzyl)-1-cyclohexanones, has been successively modified during the last two decades by Wimmer and his co-workers (Wimmer and Romaãuk, 1981; Wimmer *et al.*, 1981, 1997). The carbamate analogue with the side chain of fenoxycarb (14 in Fig. 2; Wimmer *et al.*, 1997) was again found to be the most active juvenoid of this series. Its maximum range of JH activity also reached the critical levels of 10^{-8} M or 10^{-10} M concentrations in the body. Moreover, analogous highly effective juvenoids of this bicyclic series were obtained by replacement of the cyclohexanone by cyclopentanone; 2-(4-hydroxybenzyl)-1-cyclopentanone (Rejzek *et al.*, 1998).

The juvenoid-pyrethroid paradox

It has been already indicated that the bicyclic phenoxyphenoxy structure forms essential component in most synthetic pyrethroids (permethrin, decis, cypermethrin, phenothrin, fenvalerate). The synthetic pyrethroids are for insects the most neurotoxic compounds ever known. They paralyse functions of insect nervous system in dosages of a few nanograms per specimen. This rate of toxicity can be compared with that of the medium active juvenoids. It is difficult to comprehend that the two absolutely different pharmacological actions, direct neurotoxicity and hormonal activity, could be at all accomplished by so similar structures. Synthetic pyrethroids are also peculiar by gradual absence of structural features of the natural chrysanthemic acid. The completely unrelated to chrysanthemic acid, though very effective pyrethroid, is fenvalerate developed by Sumitomo (see 15 in Fig. 2). By comparing chemical structures of fenvalearate (15) with the juvenoids 11-14, we find that the most toxic and the most hormonally active molecules have similar dimensions, similar length of the side chain and both contain the phenoxyphenoxy group. However, the synthetic pyrethroids have a 1,3-phenoxyphenyl (*meta)* junction of the side chain, whereas this is always 1,4- (*para*) in all active juvenoids.

The above indicated pyrethroid-juvenoid similarities inspired me a long time ago to ask a specialist in fenvalerate synthesis, Dr. Yoshioka, for preparation of a fenvalerate analogue with the "juvenoid-like", 1,4-phenoxyphenyl substitution of the side chain. Dr. Yoshioka was kind enough to synthesize such compound (16 in Fig. 2) and make it available for bioassays of JH activity in various insect species. Unfortunately, the compound (16) had neither pyrethroid nor juvenoid activity.

Pyriproxyfen

Since 1975, Japanese chemists were very active in preparation of new isoprenoid juvenoids. They investigated effects of chain length on JH activity (Mori *et al.*, 1975), effects of pyridyl structures in the terpenoid molecules (Kramer *et al.*, 1979; Ichikawa *et al.*, 1980), effects of phenoxy propyl ether structures (Niwa *et al.*, 1989) and effects of 4-alkylphenyl aralkyl ethers (Hyashi *et al.*, 1990). As the most successful Japanese juvenoid for practical use the Sumitomo researchers finally selected also a 4-phenoxyphenoxy type compound with a pyridyl structure in the side chain. This juvenoid, pyriproxyfen (17 in Fig. 2) fulfilled all criteria and requirements for a highly effective juvenoid. It has been commercialized under the name Knack, Amiral or Sumilarv (Hatakoshi *et al.*, 1986, 1991; Miyamoto *et al.*, 1993). At present, the juvenoid pyriproxyfen is among the most frequently used pesticides. The effects

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of pyriproxyfen have been assayed on a wide range of different insect species, including some important urban pests like mosquitoes (Okazawa *et al.*, 1991), ants (Banks and Lofgren, 1991), or cockroaches (Koehler and Patterson, 1991). Similarly like in the case of fenoxycarb, the rate of JH activity of pyriproxyfen is also very high. In certain cases, the JH activity of pyriproxyfen is higher than that of fenoxycarb, in other cases it is somewhat smaller, depending on species, developmental stage and the mode of application (review by Grenier and Grenier, 1993; Miyamoto *et al.*, 1993).

With the first highly effective 4-phenoxyphenoxy juvenoids in 1981 (Karrer and Farooq, 1981; Masner *et al.*, 1981), I recalled our unattained dreams of having some peptidic juvenoid with a broad spectrum of action. There was an idea that this could be perhaps achieved by replacement of *p*-aminobenzoate by phenoxyphenoxy or phenoxyaniline structures, which was also motivated by juvenoid (11) in Fig. 2, which was slightly active in *T. molitor*. As our juvenoid research was at that time suppressed, I asked Dr. F. Karrer of Ciba-Geigy for his help in preparation of 4- phenoxyaniline juvenoid with aminoacids in the side chain (*tert*-butyloxycarbonyl, L-alanyl; see 18 in Fig. 2). Our mutual satisfaction was, that this compound had indeed a reasonably high JH activity in several insect species, although it was almost inactive in the pyrrhocorids. This shows, that the barrier limiting JH activity of the peptidic juvenoids to one pyrrhocorid family of insects was evidently in position of the *p*-aminobenzoic acid. The bicyclic phenoxyphenoxy as well as phenoxyaniline are not natural chemical structures. The responsive endogenous receptor sites for JH on the genome of insect cells therefore cannot be directly tuned to these artificial synthetic structures, which evidently imitate some other, natural biosynthetic products, perhaps pteridines or the like.

The mode of JH action

Physiological and endocrinological conditions associated with the mechanism of JH action in insect developoment were extensively reviewed by Sláma *et al.*, 1974. Pharmacological analysis of JH action revealed that the hormone can exert its action only during rather short critical periods of tissue susceptibility to the hormone (Wigglesworth, 1969). After termination of the JH-sensitive period, application of a juvenoid in quantities 500 million times over the regular ID-50 proved to be ineffective (Sláma, 1985). During the last two decades, physiological problems of JH action were moved aside due to predominating interests in practical utility of juvenoids as pesticides (Henrick, 1982, 1995; Grenier and Grenier, 1993; Miyamoto *et al.*, 1993; Dhadialla *et al.*, 1998). The purely morphological criteria for juvenoid effectiveness have been exchanged for rates of death or percentage reduction of the whole populations after the treatment. These data cannot be undermined because they significantly improved our knowledge concerning the action of selected juvenoids in different species and different developmental stages of insects. They also helped to develop the best juvenoid pesticides. However, these evaluations of JH activity are very variable with respect to different authors and different industrial companies. The informations like: “this juvenoid is more active in this or that species”, do not provide satisfactory information what the “more active” exactly means (cf. Henrick, 1982; Grenier and Grenier, 1993; Dhadialla *et al.*, 1998). The “activity” often includes a mixture of real JH activity with a complex of pharmacological side effects, including antifeeding, antimetabolic action or toxicity. In this case some authors took advantage of the discredited commercial term IGR (Insect Growth Regulators) for mixing all kinds of biological activities together.

A survey of juvenoid literature during the past few years has shown, paradoxically, that papers dealing with the JH-esterase enzymes are more numerous than papers on juvenoids or JH. This shows that biochemists still blindly follow the old, naive chemical view (Sanburg *et al.*, 1975) that the titre of JH would be regulated by hydrolytic activity of the esterase enzymes. This primitive chemical view ignores the regulatory functions of the neuroendocrine system and neglects the facts that hydrolytic enzymes with micromolar values of the K_m cannot hydrolyse hormone molecules that occur and act in subnanomolar concentrations (cf. Sláma and Jarolím, 1980). It appears that during millions of years of insect evolution, some important regulatory substances, such as hormones, acquired ability to act at extremely low concentrations and so escape out of the influence of enzymes. Inactivation and

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catabolism of these molecules acting at 10^{-10} M concentrations depends on physical factors, spontaneous breakdown, passage through the membranes and excretion.

The old-fashioned views also persisted with regard to the mode of action of JH at tissue and cell levels. The 50 year old concept postulated by Piepho in 1951 claimed that insect JH should have a quantitative effect on development of insect tissue and cells. According to this generally accepted doctrine, the high concentrations of JH would produce larval cells, the intermediate concentrations pupal cells, while the complete absence of JH would cause secretion of the adult cuticle. This illusive misinterpretation can be still found in all textbooks of insect physiology, being used as theoretical basis in various JH investigations, including the recent studies in molecular biology (Riddiford, 1995). It took a long time to disprove the old doctrine and to provide convincing evidence that the fantastic developmental polymorphism associated with insect metamorphosis has nothing to do with different concentrations of JH. The real mode of action of JH at cellular level is actually very simple. It depends on the purely qualitative, "all-or-nothing" effects on developmental programming of individual cells; the genome of each cell receives individually the message of either being activated by JH or not, there is no intermediate way (Sláma, 1995; Sláma and Weyda, 1997).

A new look at real nature of endogenous JH

Before insect hormones became known, endorinologists noticed that the neuroendocrine complex of insects (neurosecretory cells of the brain- corpora cardiaca-corpora allata) shows apparent structural and functional analogy with the neuroendocrine complex of vertebrates (neurosecretory cells of the hypothalamus, anterior and posterior pituitary; see Novák, 1966). Since the pituitary hormones are all peptides or proteins, we expected that according to common biological rules of correlations betwen structure and function, the c. cardiaca and c. allata of insects should also produce peptidic hormones (cf. Sláma *et al.,* 1974). Unfortunately, insect endocrinology was deliberately directed to isoprenoid nature of JH by farnesol (Schmialek, 1961), epoxyfarnesoate (Bowers, 1965) juvabione (Bowers *et al.,* 1966) and, especially, by isoprenoid structure of JH-I (Röller *et al.,* 1967). Chemical arguments dominated over serious physiological inconsistencies, which showed that JH activity was present in nonfeeding adult stage, only in males and not in the females and not in the males of other saturniid species. The controversial fact and question why should the JH-I in cecropia originate exclusively in the male accessory sexual glands (Shirk *et al.,* 1976), remained unexplainead. When Röller and his coworkers elegantly synthesized active JH-I (Dahm *et al.,* 1967) and when JH-I was found directly within the c. allata (Judy *et al.,* 1973), former inconsistencies were quickly forgotten. The JH active principles previously encountered in adrenal cortex of vertebrates, thymus and human placenta or in microorganisms and plants (see above) have nevber been identified. The presence of JH-I was found in the haemolymph of other lepidopteran species *(Manduca sexta* ; Peter et al., 1975), in cockroaches (Müller *et al.,* 1975; Lanzrein *et al.,* 1976), flies (Girard *et al.,* 1976) and later in a number of other insect species. Evidently, compounds related to JH-I or epoxyfarnesoate represent ubiquitous isoprenoid metabolites. The acute oral toxicity of JH-I was very low when given to mice in a single oral dose of 5g per kg of body mass (Siddall and Slade, 1971).

In standard bioassays on *P. apterus,* ID-50 dosages of pure *cis, trans, trans*-JH-I were close to one microgram per specimen. This was quite disappointing, because the synthetic peptidic juvenoids already available showed ID-50 dosages smaller than one picogram per specimen, which shows that the synthetic peptides were million-fold more effective (Sláma, 1971). The fact that the natural JH would be million-fold less effective than a synthetic compound led me to conclude that: a) either the bug *P. apterus* used another JH molecule, perhaps a peptide; or b) that Röller *et al.,* 1965, 1967) isolated some physiologically inert, false isoprenoid present in accessory sexual glands of the male cecropia moths. In order to prove the first possibility, we started intensive search for JH in the lipid extracts from haemolymph and from the whole body of adult female *P. apterus.* After purification we obtained several unidentified lipid fractions which showed some degree of JH activity in the topical assays. However, control experiments with the extracts of allatectomized females also yielded the JH-active lipid fractions.

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Since allatectomized females were positively deprived of their legitimate source of JH, this result provided evidence that insect body contained some physiologically inert lipid materials, which may be million-fold less active than the authentic JH, but still could give some positive JH responses when extracted, concentrated and applied on the body of sensitive larvae. The real chances in extracting the true JH without intervention of the false mimetic lipids would be very small, one to a million.

The endocrinological status of insect JH is absolutely unique among animal hormones due to existence of several thousands of the synthetic, structurally profoundly different hormonomimetic molecules (Sláma, 1985). Vertebrate endocrinology knows only one such example - estrogenic hormones. Estrogens have also many natural and synthetic mimics that give positive responses in Allen-Doisy tests on ovariectomized rats. The rate of hormonal activity of the natural or synthetic estrogen mimics never surpasses that of the true estrone or estradiol. In certain cases, some nonsteroidal phytoestrogens (miroestrol) may be almost as active as estrone (Sláma, 1980). In comparison with estrogens, the situation with insect JH shows apparent absurdity in the sense that a synthetic chemist could make a superhormone with million-fold higher effectiveness than the true hormone, JH-I. We know from the field of molecular biology that the receptor-ligand interactions evolved and became optimalized during the long evolutionary process. How could a randomly synthesized molecule fit the hormone receptors better than the authentic hormone?

The described pharmacological relationships provide a strong presumptive evidence that JH-I to JH-III are not the true JH of insects. They are common metabolites of prenol synthesis which are hormonally inert under physiological conditions. The true chemical nature of insect JH still remains to be elucidated. It does not seem to be an isoprenoid. According to the most effective synthetic juvenoids, it might be a small peptide with some L-amino acid in the middle, with amino acid of very small polarity or its apolar derivative at the N terminus and some polycyclic structure (pteroyl?) at the carbonyl end of the molecule. Its biological activity should go down to 10^{-9} M or 10^{-10} M concentrations. The true JH of insects does not need to be effective in topical application. Before the JH-I was found, L' Hélias (1964) concluded that the true chemical nature of insect JH should be related to pteridines. Certain juvenoids are suspected from stimulation of the appearance of single-gene, recessive mutations in the synthesis of pteridine pigments (Sláma, 1998). The existence of several thousands of juvenoids indicates that intracellular receptor sites of JH are opened for coincidental binding with other molecules of the determined size, determined physico-chemical properties and appropriately oriented functional groups. A simple finding that certain molecule has JH activity and therefore qualifies among juvenoids, should not provide a priviledge to regard this molecule as being related to a natural product. Chemical structure of the true JH of insects is, as we have seen, so far unknown. For the sake of environmental safety, all synthetic juvenoids, including the ones already registered and practically used, should be restrictively treated as agrochemicals unrelated to natural products. The occurrence of more than 4000 synthetic molecules which bind with the genome of insect cells, could represent a real hazard provided that similar unknown binding would take place also in some non target organisms. The potential danger does not depend on direct toxicity of juvenoids to mammals, which could be easily discerned. The danger of any such superactive chemical may be in the covert, nondiscernible long-term effects. Let us hope that this danger will not apply to the modern synthetic juvenoids.

Juvenoids and urban pests

The noxious insects of urban communities were always favourite targets for practical use of juvenoid pesticides since the very beginning of juvenoid research. Long time ago, already in 1966, the materials with JH activity were found to be effective against mosquitoes (Spielman and Williams, 1966). They were used against cockroaches already in 1968 (Emmerich and Barth jr., 1968). Relatively promising results were also obtained with some nontoxic isoprenoid juvenoids against the stable flies (Wright and Schwarz, 1972) or against some other fly species (Schwarz *et al.*, 1974; Sehnal *et al.*, 1975). There were also good ambitions for practical use of juvenoids against the triatomine parasitic bugs (Patterson, 1973) or against certain ants and stored product insects (Srivastava and Srivastava, 1974; Hoppe, 1976;

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Kramer *et al.,* 1979). The most investigated juvenoid target among urban pests were always cockroaches (Riddiford *et al.*, 1975), the widely employed juvenoid compound was methoprene and later fenoxycarb which appeared to be more effective (see review by Bennett and Reid (1995).

Due to the high biological activity and relatively low acute toxicity of juvenoids, their practical application in the control of urban pests increased to such an extent that its detailed description would run out of the scope of this contribution. The readers interested in practical effects of juvenoids are advised to find informations included in numerous review articles: Henrick (1982, 1995), Retnakaran *et al.* (1985), Sehnal (1976, 1983), Sláma *et al.* (1974), Staal (1975, 1982) and Staal *et al.* (1981). These are older reviews describing mainly the effects of isoprenoid juvenoids methoprene and epophenonane. Specific informations concerning the practical effectiveness of the more recent polycyclic nonisoprenoid juvenoids (fenoxycarb, pyriproxyfen, diofenolan) can be found in review articles by Bennett and Reid (1995), Dhadialla *et al.* (1998), Dorn *et al.* (1981), Grenier and Grenier (1993), Henrick (1995), Masner *et al.* (1981), Miyamoto *et al.* (1993).

At present, juvenoids made a real progress in their practical use in the pest control. Here the topic is reduced only to a brief, telegraphic, description of the most recent publications related to urban pest control during the past 3 years. With respect to cockroaches, there are appeared some new informations concerning the effects of fenoxycarb (Evans *et al.*,1995) and pyriproxyfen (Lim and Yap, 1966). Some new data also appeared with respect to the effects of juvenoids on mosquitoes (Pawar *et al.*, 1995), on the effects of hydroprene and methoprene in a synanthropic fly *Musca autumnalis* (Yonggyun and Kraftsur, 1995) and on the effects of juvenoids in several species of flies of veterinary importance (*Aedes, Lucilia, Musca;* Londershausen *et al.*,1996). Zhang and his co-workers recently published several articles on various aspects of pyriproxyfen action in the housefly (Zhang and Shono, 1997; Zhang *et al.*, 1998). The control of Pharaoh's ants in urban communities, which was so successfully executed for many years by methoprene (cf. Henrick, 1982), has been now reinvestigated with respect to pyriproxyfen (Vail and Williamas, 1995).

As far as the stored product pests are concerned, the effects of methoprene and fenoxycarb have been quite recently described in *Sitophilus* (Letellier *et al.*, 1995). The current status and future perspectives of the use of insect growth regulators for the control of stored product insects have been just discussed by Oberlander *et al.* (1997). Advances in hormonal insect pest control in general have been summarized by Hoffmann and Lorenz (1998). Jones (1995) has speculated about the long known fact that morphogenetic action of JH might possibly be associated with regulation of the gene expression.

In addition to articles of more or less general practical importance, we can find also reports on the interactions of juvenoids with some specific urban pests. These reports include the effects of juvenoids on parasitic arthropods like ticks (Teel *et al.*, 1996) and fleas (pyriproxyfen, see Kawada and Hirano, 1996; Meola *et al.*, 1996). The effects of fenoxycarb have been recently investigated in some beneficial insects, especially the mulberry silkworm *Bombyx mori* (Leonardi *et al.*, 1998; Monconduit and Mauchamp, 1998; Kamimura and Kiguchi, 1998) and also in the honey bee (Bitondi *et al.*, 1998). The pests of ornamental flower plants, such as whiteflies, can be successfully treated by juvenoids according to Ishaaya and Horowitz (1995). Finally, Schwarz *et al.* (1998) recently reported on lethal effects caused by a plant *Cyperus iria* in the mosquitoes. The plant contains a large amount of 10,11-epoxyfarnesoate, which was long time believed to be the most common, true JH of insects. Apparently, isoprenoids related to juvenoid structures with JH activity are ubiquitoes in nature. Their misinterpretation as the true juvenile hormones of insects was overwhelmed by practical interests in the use of synthetic juvenoids as pesticides. The problem of what is the real JH of insects remained opened.

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