INSECT HORMONES AND THEIR BIOANALOGUES AS POTENTIAL INSECTICIDES*

F. ŠORM
Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Science, 166 10 Praha 6, Czechoslovakia

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Insect endocrinology and the chemical investigation of insect hormones has recently attracted considerable attention since the progress of the theoretical knowledge in this sphere may be of practical value in combating insect pests. Currently used insecticides that have been discovered merely empirically do exhibit a number of disadvantages which are becoming more and more apparent. In the first place their effect is not specific, and besides insect pests they are noxious also to beneficial insects. Massive application of these insecticides has resulted in the emergence of resistant individuals, and the necessity to use the ever-increasing doses has led to cumulation of toxic residues of these compounds in different products that are essential for nutrition of man and cattle, thus directly or indirectly endangering human health. In some of the developed countries prohibitive measures concerning the use of certain types of classical insecticides are to be expected, and in certain countries such prohibitions have already been applied.

Insects undergo a unique and in many respects specific development between the fertilized egg cell and adult form. The females usually deposit a large number of eggs which do not contain enough nutrients to bring the whole morphogenesis process to its end. In the course of embryonic development only certain parts of morphogenesis take place after which the immature larval stages hatch from the eggs. The larvae are then able to feed and grow until they accumulate a sufficient amount of nutrients essential for completion of morphogenesis. This takes place during metamorphosis when larvae are transformed into the reproductive adult stages.

During the larval stage morphological development practically ceases while growth and increase of the body is enhanced. By contrast the morphological transformation during metamorphosis is associated with rapid differentiation of tissues and it proceeds, as a rule, without further growth of the whole body.

The growth and the morphological evolution of insects as well as the synchronization with ecological conditions are regulated by hormones which begin to act during the terminal stages of embryogenesis. At that time formation and functioning of the corresponding endocrine organs has been established. Generally, there are three principal insect growth hormones. In the first place it is the *activation hormone* synthesized in the neurosecretory brain cells; it has a regulatory function of the whole insect endocrine system since it stimulates secretory activity of other endocrine glands. The *moulting hormone* is the second insect hormone secreted by the prothoracic and other homologous glands. This hormone stimulates growth during the larval stage especially by activating the epidermal tissue and germ cells necessary for development of the adult structures. The hormone is a requisite for the moulting process (hence its name) and finally for the metamorphosis itself.

The so called *juvenile hormone* is produced by the gland called the corpora allata. This third hormone does not stimulate growth in larvae; however, in the

*For the recent review relevant to these topics see: K. Sláma, M. Romanuk and F. Šorm: 'Insect hormones and bioanalogues'. Springer Verlag Wien, 1974.

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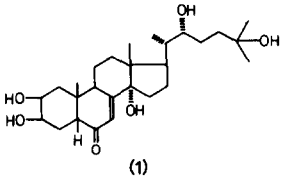
presence of the moulting hormone which is indispensible for its action it prevents morphogenetic changes associated with metamorphosis. Its function consists in keeping the insect in the larval (juvenile) stage. In adult females of certain species the hormone stimulates ovarian growth.

Present evidence usually obtained by transplanting endocrine organs indicates that insect hormones are not specific for a given species, and that all three insect hormones affect insect development by a mutual coordinated interaction. During the larval stage the moulting hormone stimulates the activity of epidermal organs, while in the presence of juvenile hormone only individual larval instars are formed. Synthesis and secretion of the latter hormone ceases at the end of larval development, and the insect is then only under the influence of activation and moulting hormone. Consequently intensive tissue differentiation and morphological changes occur resulting in the formation of pupal stages (in Endopterygotes) and ultimately adult individuals.

Progress in the development of microchemical methods leading to the isolation and identification of the compounds occurring in minute quantities in natural material enabled the elucidation of the chemical structure of the moulting and juvenile hormones. The activation hormone which seems to be either protein or polypeptide in nature has so far not been isolated in pure form.

Several compounds with the activity of the moulting hormone have been isolated from insect tissues, especially ecdysone (1) and ecdysterone (2). Many more analogous steroid compounds (so called phytoecdysones) have been isolated from plant material.



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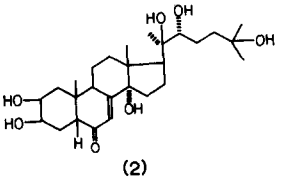
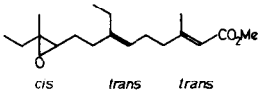


(2)

As fas as the chemical structure of juvenile hormone is concerned three compounds have been obtained from insect organisms at present. All of them are derivatives of farnesoic acid differing by the presence and localization of additional methyl groups (3,4,5). Two of these compounds have been isolated from the abdomens of the moth *Hyalophora cecropia* and originally have been designated as Cecropia hormones, the third one has been isolated from the moth *Manduca sexta.*



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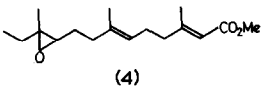

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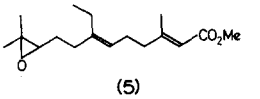

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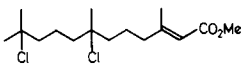
The function of individual insect hormones was conclusively demonstrated long ago when, for instance, the active corpora allata were extirpated from young larvae, metamorphosis was induced prematurely and miniature pupae and imagoes were formed. Conversely, when juvenile hormone was applied in excess to larvae at later stages of development supernumerary giant larvae were formed. Owing to this phenomenon the juvenile hormone is potentially useful as an insecticide. Thus, if a larva at terminal stages of development comes into contact with substances possessing juvenile hormone activity, it is unable to undergo further transformation into an adult individual, and only supernumerary larvae incapable of survival are formed.

The juvenile hormone and its bioanalogues are also considered to be of practical value for the control of insect pests because, contrary to moulting hormones, they may be applied topically in analogy to classical insecticides. Furthermore, it is most significant that recently a large number of compounds with the action of juvenile hormone have been prepared; synthetically they are easily accessible although chemically their structure is different. These so called bioanalogues of juvenile hormone are not only highly biologically active in some cases, but their effect against individual insect species is in many cases specific.

The investigation of juvenile hormone bioanalogues has in fact preceded the determination of the structures of *Hyalophora cecropia* juvenile hormones. It has been established for some time that the sesquiterpenic alcohol farnesol possesses similar effects on insect development to those of corpora allata

extracts. The biological effects of farnesol have been very considerably surpassed by the artificial mixture of compounds formed by the introduction of gaseous hydrogen chloride into solutions of farnesoic acid in methyl alcohol. Later on the active principle itself has been isolated from that mixture, and it proved to be the dihydrochloride of methyl farnesoate (6). This substance had extremely high juvenile hormone-like action in bugs of the family *Pyrrhocoridae* (0.001 μg per individual) and is somewhat similar in structure to the juvenile hormones from *Hyalophora cecropia.* Further impetus for the investigation of juvenile hormone bioanalogues was the so called 'paper factor'. Dr. Sláma working in the laboratory of Professor Williams found that the larvae of the hemipteran bug *Pyrrhocoris apterus* failed to metamorphose into adults, while those cultured in Prague developed normally. It was shown that this effect was caused by a compound mimicking juvenile hormone present in the paper manufactured from the Canadian balsam fir (*Abies balsamea*). Later it was established that the active principle itself is the so called (+) juvabione (7) identical with methylester of the known sesquiterpenic todomatuic acid. The second factor responsible for the biological effects of the paper from the *Abies* is dehydrojuvabione (8).



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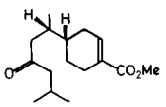

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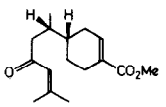


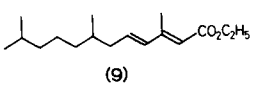
(8)

One may say that the first models for the synthesis of juvenile hormone bioanalogues were the hormones obtained from *Hyalophora cecropia* (3,4,5), the dihydrochloride (6) of methyl farnesoate, and finally (+) juvabione (7). At the present time probably some thousand or so juvenile hormone bioanalogues have been prepared, and have mostly been described in patent specifications. In this short review only a few basic types of these compounds will be mentioned, especially those with a high biological effect against some insect pests.

The juvenile hormones from the Lepidopterans *Hyalophora cecropia* and *Manduta sexta* are the only natural hormones that have been isolated from insects until now. All three compounds possess a high activity and a relatively low specificity. A series of synthetic methods have been proposed which make it possible to prepare the desired compound of the corresponding stereochemical structure. However, all the known synthetic processes are relatively complicated and expensive; which is one of the reasons why for the time being we cannot think of the practical application of these hormones. Thus attention at present is directed to their more stable and synthetically more feasible analogues.

Acyclic juvenoids

Some derivatives of farnesoic acid are very interesting, and structurally closely related to Cecropia hormones. They contain a conjugated diene grouping with an esterified carboxyl. Two of these compounds (protected by a series of patents) are produced by the firm Zoecon under the designation No 512 (9) and No 515 (10). Both substances show a high biological activity and their practical application is directed mainly to the control of mosquitoes and aphids.



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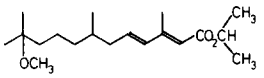
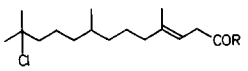


(10)

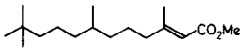
A simple analogue derived from the methyl farnesoate dihydrochloride (6) is the methyl 11-chloro-3,7,11-trimethyldodecene-2-oate (11). The relevant diethylamide (12) is very active against the beetle *Tenebrio molitor* (0.0005 μg).



(11) R = OMe
(12) R = $N(C_2H_5)_2$

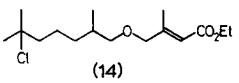
The chloro atom bound to the quaternary carbon is known to be rather unstable, as is the epoxide grouping which forms part of the molecule of natural hormones. For this reason analogues have been prepared in which the chloro atom was replaced by the sterically similar methyl group. Some of these com-

pounds as e.g. (13) have a relatively high biological activity against certain species of insects.



(13)

For a better understanding of the relationship between the structure and the biological activity, the synthesis of compounds where one or more methylene groups ($-CH_2$) of the isoprenoid chain present in the farnesoic acid have been replaced by oxygen atom, was of some importance. Many of these so called oxa-analogues of juvenile hormones have been prepared, for example the 5-oxa-compounds (14 and 15). These substances retain practically all of the biological activity of the respective model compounds.



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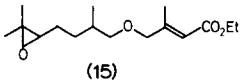
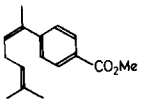


(15)

Cyclic juvenoids

As mentioned already the model compounds for the bioanalogues of the juvenile hormone containing a benzene ring were juvabione and dehydrojuvabione. A relatively easily accessible analogue of these substances was the aromatic compound (16) and its dichloro-derivative (17).



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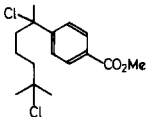
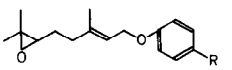


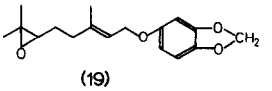
(17)

Important aromatic bioanalogues have been prepared by Bowers. The epoxygeranyl ether derived from methyl *p*-hydroxybenzoate (18) and the compound (19) analogically derived from 3,4-methylendioxyphenol have considerable activity.

Aromatic ethers derived from geraniol are generally very interesting. Thus the epoxygeranyl *p*-chlorophenylether (20) as well as the relevant *p*-nitro-derivative (21) show a high activity against a dangerous pest of wheat, *Eurygaster intergriceps*; the compound (22) is highly active against certain insects of the order Coleoptera.



(18) R = CO_2Me
(20) R = Cl
(21) R = NO_2



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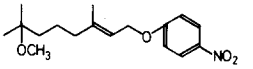
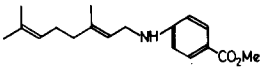


(22)

The relatively low specificity of juvenile hormone is demonstrated by the fact that many compounds derived from the *p*-aminobenzoic acid also mimic the activity of this hormone. Methyl *N*-geranyl-*p*-aminobenzoate (23) and the corresponding chloro-derivative (24) are able to influence the larval development of the bugs of the family *Reduviidae*, especially *Rhodnius prolixus* and above all *Triatome infestans* which transmits the Chagas diseases in South America and is a serious insect pest from the sanitary point of view. Active are also *N,N*-digeranyl derivatives (25,26).



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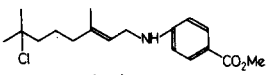

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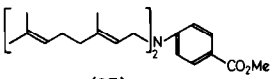

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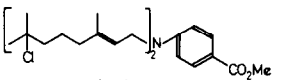
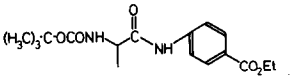


(26)

Some peptidic derivatives of *p*-aminobenzoic acid which do not contain an isoprenoid chain show a remarkable biological activity even though only against certain hemipteran species. Thus ethyl *tert*-butyloxy-carbonyl-L-alanyl-*p*-aminobenzoate (27) is active against *Pyrrhocoris apterus* at a dose of 0.001 µg per individual, and the compound (28) with an activity of 0.000002 µg per individual is probably the most highly active substance known up to now, exceeding considerably the activity of natural Cecropia hormones against these insects.



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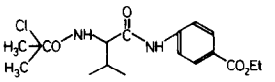

(28)

It is interesting that in the case of these peptide derivatives the biological activity is related to the optical configuration of the middle amino acid (e.g.

of the alanine moiety); the analogous compound (27) derived from D-alanine being practically inactive.

Some analogues of the juvenile hormone mentioned above have already been tested in small field experiments. Not much is known about the results up to now; however, according to our own experience the practical application of these compounds as insecticides of the so called third generation requires not only high biological activity against a certain species of insects but also a considerable stability when applied in field experiments. In contrast to classical insecticides that are immediately toxic to all the developmental stages of insect, the bioanalogues of juvenile hormones affect only a certain critical period of the development (e.g. the last larval instar). Since the development of insect is usually not closely synchronized in Nature, i.e. insects mature gradually in accordance with the ecological conditions, it is necessary to use the bioanalogues during certain seasonal periods, and to apply the compounds that are stable for at least 1–2 weeks under field conditions. Many of the compounds prepared hitherto, especially some derivatives of 3,4-methylendioxyphenol and compounds containing an oxirane grouping, are highly active but they have relatively low chemical stability. This disadvantage can be partially compensated by using suitable chemical stabilizers or by modifying the method of application of the drug, e.g. by microincapsulation.

While it is probable that the application of the bioanalogues on a large scale will not be realized in the very near future, their investigation, however, has resulted in a series of new theoretical findings as well as hopeful perspectives for their practical use in the future.