# INSECT JUVENILE HORMONES AND THEIR BIOANALOGUES

Zdeněk WIMMER and Miroslav ROMAŇUK

*Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6*

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This survey supplements and up-dates review articles of other authors published in the field of substances affecting the development of the insect, juvenoids. Attention has been paid primarily to such structures as deserved more detailed investigation in the given field owing to their biological properties, further to less known structures and facts, and lastly to the most recent information from literature, mainly paying attention to the present trend in searching for structural types of substances affecting insect development. The synthetic juvenoids discussed are divided into chapters, on the basis of the skeleton of the molecule, on aliphatic juvenoids, juvenoids with one aromatic ring in the molecule and finally juvenoids with two and more cycles (aromatic as well as non-aromatic) in the molecule. Certain attention has also been paid to optically active juvenoids. Finally the role is mentioned of complex hormonogen compounds, juvenogens, in the protection of cultured plants against economically important insect pests.

## 1. INTRODUCTION

Insects are the most widespread animal class on Earth. Although the majority of insect species are useful from our point of view, many of them still exist which may be considered as serious food competitors with man, or as carriers of serious diseases. Man has always endeavoured to control such insect species. Examples of this human activity may be traced even in antiquity when man started to make use of his acquired knowledge on the toxicity of some natural compouds. This knowledge gradually increased and improved and from the second half of the last century natural substances

started to be used systematically as insecticides. With the development of science, mainly chemistry, in this century an intensive research has been done in this field, which resulted in the early synthetic insecticides. At their time they represented real progress in insect pest control. Some of them are still used – with certain restrictions – up today, even though only for laboratory use or for specific purposes of some branches of agricultural production. Present regulations for the protection of the life environment, which have become stricter and which are gradually applied in the world, actually forbid the use of many of these substances. The reason is usually their high toxicity for warm-blooded animals and also the existence and cumulation of the metabolites of primary insecticides which are frequently considerably toxic. Moreover, the losses of agricultural products caused by insect pests even before harvesting reach incredible values according to FAO data. Thus, for example, about one fourth of the wheat harvest is destroyed yearly in the world, about 45% of rice production and approximately one third of the production of maize, fruit and cotton.

Therefore methods of controlling the excessively spread populations of insect pests are still one of the goals of present common research of chemical and biological laboratories all over the world. A new and undoubtedly prospective research field was brought about by the discovery of the existence, and later the structure, of the insect juvenile hromone (JH) and natural and synthetic substances capable of perfectly imitating its effects (juvenoids). JH is synthetized and excreted by the pair gland called corpora allata and it plays an important role in the developmental periods of the individual insect, because it also inhibits the transformation of the larva to an adult insect. When JH or juvenoids are applied at these critical periods a disturbance of vitally important functions takes place in insects. This offers the possibility of utilizing these properties of JH or juvenoids for control of the population of insect pests. The methods of biological testing of the effect of JH or juvenoids have been standardized for individual species of insect pests. The methods have been described frequently by various authors and recently by Sláma and co-workers[1], Sehnal[2] or Hrdý.[3]

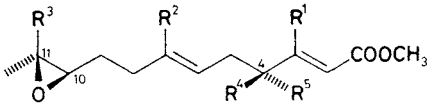
The common attention of chemists and biologists has been paid recently to the development of modern insecticides characterized by effect selectivity at high absolute values of biological activities, sufficient stability under the influence of biotic or abiotic factors, and the lowest possible level of toxicity for warm-blooded animals. The economical aspect is also important, i.e. the availability of starting raw materials and the difficulty of the synthetic procedure, as well as the potential marketing of the final product.

Juvenoids which fulfil a number of these criteria belong without doubt among prospective candidates. A number of review articles and monographs survey JH and substances imitating their effects. Among them the most important ones are men-

tioned below in the concrete contexts. A more detailed enumeration of all known structures would exceed the possibilities of this journal. The aim of this survey is thus rather the actualization of this problem by supplementing it with less known facts and recent data from literature.

## 2. NATURAL JUVENILE HORMONES

In 1936 Wigglesworth[4] demonstrated the existence of JH in insects by his experiments with the kissing bug, *Rhodnius prolixus*. However, it took more than 30 years before American scientists were able to isolate and finally identify[5] the first JH (JH-I, *I*) from the pair gland corpora allata of the cecropia moth, *Hyalophora cecropia*. The second hormone (JH-II, *II*) was isolated from the same insect and identified by Meyer and co-workers[6] a year later. The third naturally occurring hormone (JH-III, *III*) was isolated and identified by American scientists[7] in 1973. Recently the fourth JH (JH-0, *IV*) was isolated[8] from developing embryos of the tobacco hornworm, *Manduca sexta*. A year later the same authors published[9] the isolation and identification of the fifth JH which is actually the isomer of JH-0 (iso-JH-0, *V*), from the same insect species.

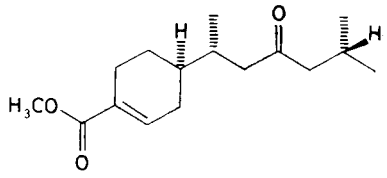



| Compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | absolute configuration |
|---|---|---|---|---|---|---|
| *I* | $CH_3$ | $C_2H_5$ | $C_2H_5$ | H | H | 10*R*,11*S* |
| *II* | $CH_3$ | $CH_3$ | $C_2H_5$ | H | H | 10*R*,11*S* |
| *III* | $CH_3$ | $CH_3$ | $CH_3$ | H | H | 10*R* |
| *IV* | $C_2H_5$ | $C_2H_5$ | $C_2H_5$ | H | H | unknown |
| *V* | $CH_3$ | $C_2H_5$ | $C_2H_5$ | $CH_3$ | H | 4*S*; (10,11 unknown) |

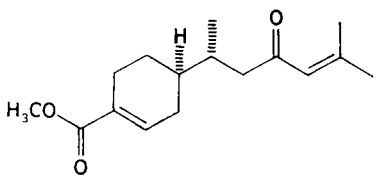
When identifying JH-I (*I*) Röller and co-workers[5] determined the (*E*)-configuration of both double bonds, but did not determine the absolute configuration on the oxirane cycle carbon atoms. Therefore Dahm and co-workers[10] synthetized all eight possible stereoisomers and found, by comparing the samples, that the substituents on the oxirane cycle have the *cis*-configuration in the natural JH. Later the absolute configuration of JH was found to be 10*R*, 11*S* on the basis of the synthesis of an intermediate of known absolute configuration and optical rotation data, circular dichroism and mass spectral data.[11–15] In 1987 a paper was published[16] the authors of which determined the absolute configuration of iso-JH-0 (*V*) on the carbon atom in position 4 as *S* on the basis of a biogenetic approach and using a combination of enzymatic synthesis and biotransformation.

### 3. JUVABIONE AND ITS NATURALLY OCCURRING ANALOGUES

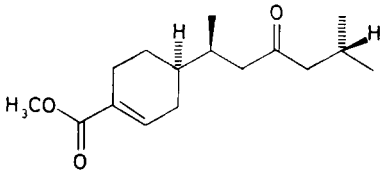
One of the first naturally occurring compounds isolated from plants and displaying an activity of the same type as JH was juvabione. The effect of this substance, called the "paper factor" was described by Sláma[17] during his stay in the U.S.A. The culture of bugs, which had been in contact with a paper produced from the wood of the Canadian balsam fir (*Abies balsamea* (L.) MILL.) for a certain time, displayed developmental disturbances. The active compound of the paper factor was isolated and identified by Bowers and co-workers[18] who gave it the name (+)-juvabione. Later on Czechoslovak scientists[19,20] also isolated from the wood of the balsam fir of Slovakian origin dehydrojuvabione (in addition to juvabione) which also had juvenilizing activity. The first synthesis of juvabione has been published by Mori and Matsui[21] and the first synthesis of its aromatic analogues was carried out in Czechoslovakia.[22,23] The originally published[19,20] absolute configuration of juvabione and dehydrojuvabione was soon revised.[24,25] Manville[26] announced the isolation of (*R*, *R*)-juvabione and (*R*, *R*)-dehydrojuvabione. He also expressed the assumption that the substances isolated by Černý and co-workers[19,20] possessed the (*R*, *S*)-configuration and that therefore they had (+)-epijuvabione and (+)-epidehydrojuvabione. However, it was no longer possible to confirm the identity of the samples. It remains a fact that 4 compounds were isolated, i.e. (+)-juvabione (*VI*) and (+)-dehydrojuvabione (*VII*) – both with an (*R*, *R*) absolute configuration – and (+)-epijuvabione (*VIII*) and (+)-epidehydrojuvabione (*IX*) – both with an (*R*, *S*) configuration. Gradually new synthetic ways have been discovered which were applied in the preparation of (±)-juvabione and (±)-epijuvabione. Among the most important are the studied by Ficini and coworkers[27], Trost and Tamaru[28]



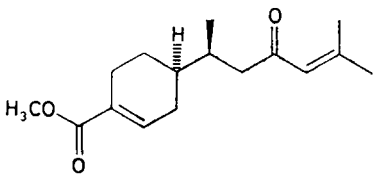

*VI*




*VII*

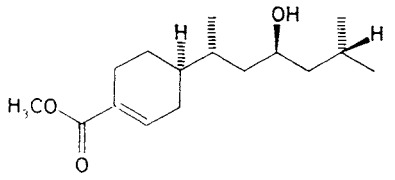



*VIII*

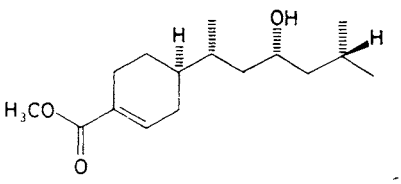



*IX*

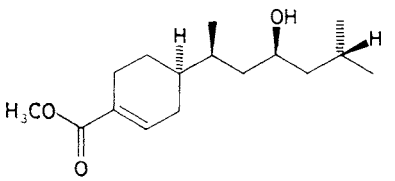
and Evans and Nelson.[29] Further research dealing with substances present in the wood of balsam fir was not unfertile either. The result was the discovery[30] of (+)-juvabiol (*X*) and (+)-isojuvabiol (*XI*). The same authors[31] obtained then from the wood of the Norway spruce in addition to (+)-juvabiol (*X*) also (+)-epijuvabiol (*XII*). All these compounds had JH activity. The last remaining product, (+)-isoepijuvabiol (*XIII*) was identified as a reduction product of (+)-epijuvabione (*VIII*). Williams and Phillips[32] described the first synthesis of all juvabiols.



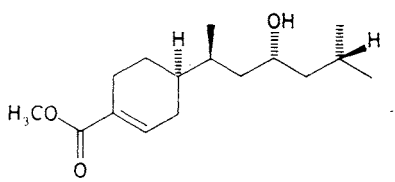

*X*




*XI*

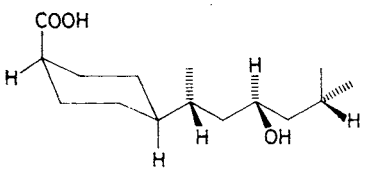



*XII*

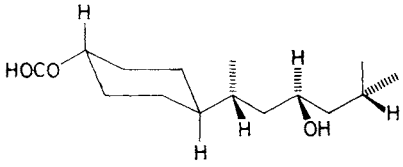



*XIII*

Japanese authors[33] published in 1983 the isolation of further juvabione analogues with a JH activity, this time from the wood of *Abies sachalinensis* MAST. growing on Hakkaido island. In addition to the already known (+)-juvabione (*VI*) they also isolated compounds *XIV* and *XV*.



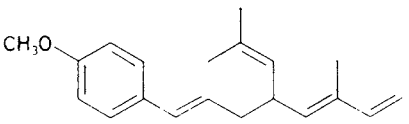

*XIV*



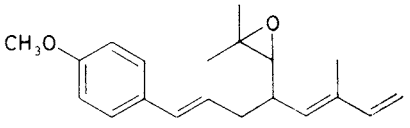

*XV*

Nishida and co-workers[34,35] obtained from *Ocimum basilicum* L. (from which some biologically active compounds had been isolated before[36]) two highly active aromatic derivatives, juvocimene I (*XVI*) and juvocimene II (*XVII*). Both compounds were synthetized[35] at the same time together with several analogues. Synthetic juvocimenes were tested for their JH activity. In tests with bugs the activity of juvo-

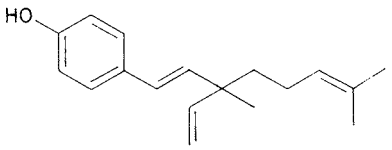
cimene II (*XVII*) was about 3 000 times higher than the activity of JH-I (*I*). Juvocimene I (*XVI*) is about 10 times less active than juvocimene II (*XVII*).




*XVI*




*XVII*



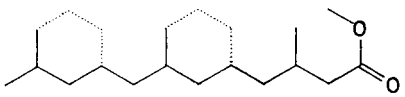

*XVIII*

In 1984 the isolation of a further aromatic analogue of juvocimene from the seeds of *Psoralea cordifolia* L. was published[37]. The compound was given the name bakuchiol (*XVIII*) and it displayed JH activity in tests with the bug *Dysdercus koenigii*. Together with bakuchiol (*XVIII*) several analogues of this compound were synthetized.[37] The values of their biological activities were comparable with that of bakuchiol *XVIII*.

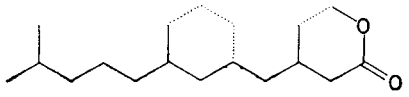
## 4. JUVENOIDS AND THEIR BIOLOGICAL PROPERTIES

The compounds of the juvabione and juvocimene type were neither the first nor the only plant substances with JH activity. The priority belongs undoubtedly to the sesquiterpenic alcohol farnesol[38], known for many years as occurring in many plant species. Its JH activity and the activity of its derivatives, including the farnesilic acid esters and its dichloro derivative, has already been described in the middle sixties.[39–42] These results, together with the determination of the structure of JH on one hand and juvabione, juvocimene and their further analogues on the other suggest the ways of the starting research of the structures of suitable synthetic JH analogues: *a*) The synthesis of aliphatic analogues derived from the structure of JH and intended to find optimal modifications of the JH structure, leading to a higher stability, under simultaneous preservation of biological activity. The influence of various structural factors on activity was studied. *b*) The synthesis of analogues of juvabione or juvocimenes, characterized by the incorporation of a *p*-substituted aromatic nucleus into the molecule. *c*) Later a group of substances appeared, bearing two and more cycles in its molecule. Their origin may be regarded as both derived from a suitable

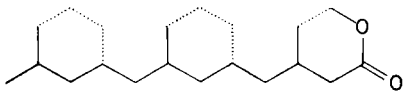
modification of the basic skeleton of JH structure (formulae A to C), and the modification of the structure of juvocimenes (*XVI*, *XVII*).



A



B



C

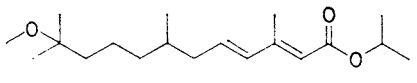
There are a number of publications dealing with this problem. The review by Henrick[43] from 1982 may be regarded as one of the latest. This paper presents not only a survey of the development of the research in the field of structure–activity relationships, but also a complete survey of structures and activities of juvenoids known up to that time.

### 4.1 *Aliphatic Juvenoids*

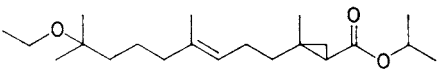
The investigation of structure-activity relationships in the syntheses of juvenoids of this group may be divided into several partial goals in which the effects of the presence of double bonds and their geometry, the length and the branching of the chain, the functional groups and hetero atoms and their position in the basic chain on activity were studied.

The structure–activity relationships demonstrated clearly the effect of the position of the double bond in the molecule on activity. The most active compounds usually belong to the group of 2,4- or also suitably substituted 2,6-dienoates in which the substituents on the double bonds have (*E*)-configuration.[1,43] According to present observations, the length of the basic chain should correspond approximately to the length of the natural JH chain, i.e. 1·9–2·1 nm (refs[1,43–45]). The absence of chain branching on C(3) has a strong effect on the loss of activity.[43] The substitution of the 10,11-epoxy group by a 10,11-imino group leads to a loss of activity (cf. Anderson and co-workers[46] or Mori and co-workers[47]). In contrast to this finding the substitution of the 10,11-epoxy group by a 11-methoxy group usually improves the properties of juvenoids. The most successful substance was isopropyl (2*E*, 4*E*)-11-methoxy--3,7,11-trimethyl-2,4-dodecadienoate (methoprene, *XIX*), synthetized and studied by Henrick and co-workers.[48–50] It is active especially against mosquitoes, aphids, stored product pests, further against the very unpopular pharaoh ants (*Monomorium*

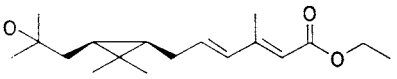
*pharaonis*) and others. It was the first juvenoid to be produced commercially with the widest spectrum of registered application forms.



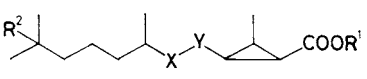
*XIX*



*XX*

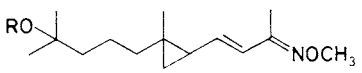


*XXI*

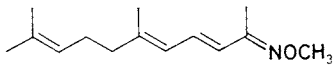


*XXII*

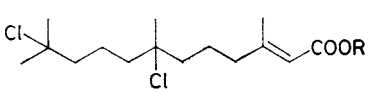
The biological activity of this skeleton remains partly preserved even after substitution of the double bond in position C(2) by a cyclopropane unit[51-53] (cycloprene, *XX*). Polish authors[53] investigated the effect of the location of a three- to six-membered cycle in the molecule. In addition to cycloprene (*XX*), the derivative *XXI* (Sobotka and co-workers[53,54]) also has an interesting spectrum of activity. Recently, compounds with a three-membered cycle in the molecule were synthetized by Baán and co-workers.[55] They compared compounds of formula *XXII* in which they changed the ester alkyl (ethyl or isopropyl) and the substituent in position C(11), i.e. they investigated the presence or absence of the alkoxy group in the presence or absence of a multiple bond in position X–Y (*XXII*). The biological activity of these compounds has not been published yet. A further variation of this skeleton consisted in the synthesis of O-methyloximes in the presence[56] or absence[57] of a three-membered cycle in the molecule; their structure is illustrated by the formulae *XXIII* and *XXIV*. The results of structure–activity studies have not so far been published in the case of these compounds either. The synthesis of compounds with a four-membered[53,58], five-membered[53,59,60] or six-membered[53,61] cycle in the molecule results in compounds with a low activity. Several 2,4-dienoates[60], however, represent so far the only known exception.



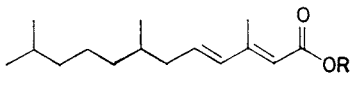
*XXIII*



*XXIV*



*XXV*

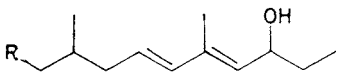


*XXVI*, R = $CH_2CH_3$
*XXVII*, R = $CH_2C{\equiv}CH$

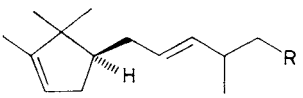
In some instances the substitution of certain functional groups in the basic chain by chlorine (*XXV*) also had a positive effect on the activity and species specificity of the compounds obtained[42,62] in comparison with that of native JH.

Further alkyl (2*E*, 4*E*)-3,7,11-trimethyl-2,4-dodecadienoates *XXVI* and *XXVII*, prepared by Henrick and co-workers[48,49], which are structurally very simple compounds, were found to be highly active juvenoids. Hydroprene (*XXVI*) is very active against insects of the Lepidoptera, Coleoptera and Homoptera orders (for example Benskin and Perron[63], Hrdý and Zelený[64] or Radwan and Sehnal[65]). Some time ago kinoprene (*XXVII*) displayed promising activities against Homoptera, as described by Henrick and co-workers[50], Hrdý[3] or Staal and co-workers.[66]

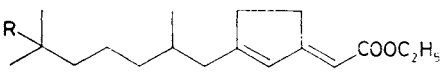
The synthesis of 2,4-unsaturated secondary alcohols[67] *XXVIIIa*–*XXVIIIc* also proved promising results, where just the derivatives containing a cyclohexane cycle (*XXVIIIc*) in the molecule displayed a high activity in tests with the yellow mealworm (*Tenebrio molitor*). The compounds containing a five-membered cycle in the molecule were synthetized by Wawrzenczyk and co-workers[60,68]. In their synthesis they started from the optically active (1*R*)-(+)-2,2,3-trimethyl-3-cyclopenten-1-ylacetonitrile and obtained several juvenoid derivatives among which compounds *XXIX*–*XXXI* displayed a high JH activity against the Indian cotton stainer, *Dysdercus*




*XXVIII a*, R = 
*XXVIII b*, R = 
*XXVIII c*, R = 



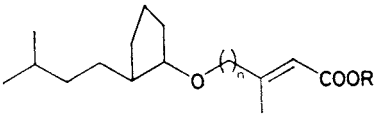

*XXIX*, R = $COOC_2H_5$
*XXX*, R = $CH_2CH_2C(CH_3)=CHCOOCH(CH_3)_2$
*XXXI*, R = $CH=CHC(CH_3)=CHCOOCH(CH_3)_2$



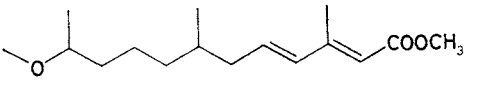

*XXXII*, R = H
*XXXIII*, R = $OCH_3$

*cingulatus*. Novák and co-workers[69] have published the preparation of other cyclopentenyl derivatives. They carried out activity tests on two different insect species (*Pieris brassicae* and *Sarcophaga bullata*) and compared their activity with that of methoprene (*XIX*) and hydroprene (*XXVI*) on the same insect species. The two most active derivatives of their series have the formulae *XXXII* and *XXXIII*. The (2*Z*)-isomers of compounds *XXXII* and *XXXIII* were about a hundred times less active.

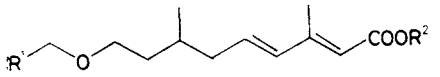
Jarolím[70] has published a review article on the structure–activity relationships of aliphatic JH oxa-analogues. The activity of the derivatives depends considerably on the position of the oxygen atom in the basic chain. While 5-oxa- and 10-oxa-analogues display high activities, the 4-oxa-, 6-oxa-, 8-oxa- and 9-oxa-analogues have a very low activity or are inactive. It is, however, interesting that 2,4-unsaturated derivatives of 9-oxa- and 10-oxa-analogues display high activities on some species of social insects. 5,10-Dioxa-analogues exert a high activity against the cyclorrhaphous fly species *Ceratitis capitata*, while their effect on other Diptera is only average. The 5,8-dioxa-, 5,9-dioxa-, 6,9-dioxa- and 6,10-dioxa-analogues with a five-membered cycle in the molecule (*XXXIV*) display good activity against the Indian cotton stainer, *Dysdercus cingulatus*, but they are poorly active against other bugs or beetles.[71] Biernacki and Gdula[72] prepared 11-oxa-analogue *XXXV* which also belonged among averagely active juvenoids. Borowiecki and co-workers[73] synthetized 10-oxa-



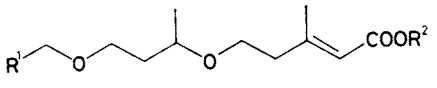

*XXXIV a*, n = 1
*XXXIV b*, n = 2



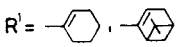

*XXXV*

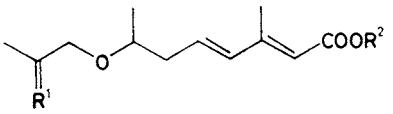



*XXXVI*




*XXXVII*



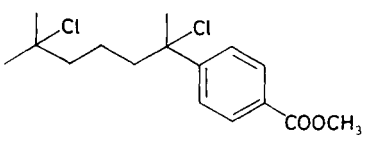

*XXXVIII*, $R^1$ = O, $(OCH_3)_2$, $OCH_2CH_2O$

and 6,10-dioxa-analogues with a terminal 1-cyclohexenyl or 2-pinen-10-yl-substituent (*XXXVI–XXXVII*). These compounds displayed a certain biological activity, but the authors[73] did not mention further details in comparison with some juvenoids described earlier. While 8-oxa-analogues of JH were only weakly active[70], the introduction of the 10-oxa-group into the molecule caused an increase in biological activity[74] (*XXXVIII*).

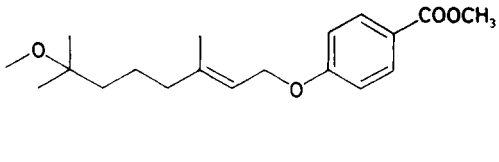
### 4.2 *Juvenoids with One Aromatic Ring in the Molecule*

As stressed earlier it is juvabione which may be considered the model substance of this group of compounds. The synthetic modifications of this natural model were concentrated mainly on: *a*) the method of substitution of the aromatic nucleus; *b*) the type of substitution of the aromatic nucleus; *c*) the length, branching, geometry and substitution of the aliphatic chain.

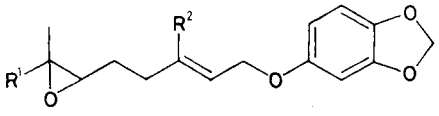
The effect of the type of substitution of the aromatic ring on the biological activity was already set in earlier studies (cf. Jacobson and co-workers[75] or Pallos and Menn[76]). The most active juvenoids of this group were always substituted in *para*-position. A substitution in *meta*- or *ortho*-position always meant a substantial decrease in JH activity.



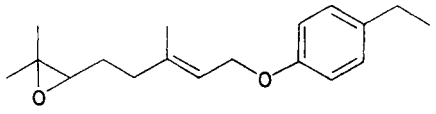

*XXXIX*




*XL*




*XLI*

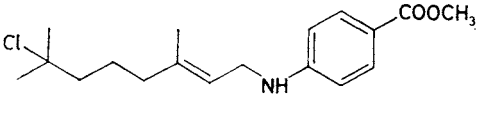



*XLII*

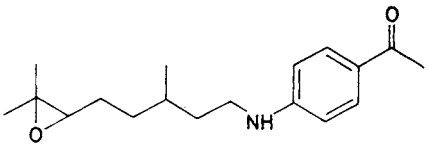
Among the synthetized derivatives with one aromatic ring in the molecule several structures (*XXXIX*, ref.[22]; *XL*, ref.[1]; *XLI*, ref.[77] and *XLII*, ref.[78]) appeared at the beginning of the seventies the biological activity of which departed from the average of this group of substances. 1-(4-Ethylphenoxy)-6,7-epoxy-3,7-dimethyl-2-octene (*XLII*) deserved more detailed field experiments[50,79] as well. Pallos and co-workers[78] also investigated the effect of the alkyl group in the series of 4-alkyl phenyl ethers on biological activity. The mentioned 1-(4-ethylphenoxy)-6,7-epoxy-3,7-dimethyl-

-2-octene (*XLII*) is the most active compound of this series, because the activity decreases in the order ethyl > isopropyl > methyl > propyl > tert. butyl for aliphatic part in the series of 4-alkyl phenyl ethers. 1-(3,4-Methylenedioxyphenoxy)--6.7-epoxy-3,7-dimethyl-2-octene (*XLI*, $R^1 = R^2 = CH_3$) was also characterized by a broad spectrum of activity and deserves thus a closer attention. It was very active against stored product pests *Trogoderma granarium* and *Caryedon gonagra*[80] and displayed a good activity against Colorado potato beetle (*Leptinotarsa decemlineata*).[44,81]

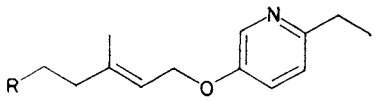
A replacement of the aromatic-aliphatic ether by an aromatic-aliphatic amine in derivatives of 4-aminobenzoic acid[1] (*XLIII*) or 4-aminoacetophenone[82] (*XLIV*) does not decrease the biological activity either. A replacement of the benzene ring by a pyridine one resulted in the synthesis of two further active juvenoids[83] (*XLV* and *XLVI*). Carbonanalogues[84] of the aforementioned ethers and amines are characterized by a considerable chemical stability and simultaneously good biological activity.




*XLIII*

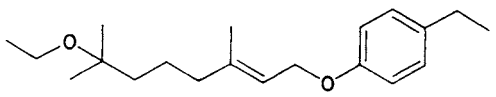



*XLIV*




*XLV*, R = CH(O)C(CH3)2

*XLVI*, R = $CH_2C(OC_2H_5)(CH_3)_2$



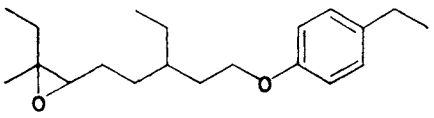

*XLVII*

The effort to exchange the terminal epoxy group for an alkoxy group resulted in the synthesis of 1-(4-ethylphenoxy)-7-ethoxy-3,7-dimethyl-2-octene (*XLVII*), also called JH-25, which was the most active one in the series of derivatives with different alkoxy groups[85,86], tested against the yellow mealworm. In the series of C(7)-substituted derivatives the activity decreased in the following order: ethoxy > propoxy > > isobutoxy > butoxy ⩾ isopropoxy > hydroxy > methoxy group as the ω-substituent.

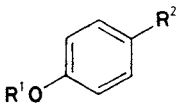
In 1976 Hangartner and co-workers[87] synthetized several further compounds in the laboratories of the Socar research group (a branch of the Swiss firm Hoffmann--La Roche), among which 1-(4-ethylphenoxy)-6,7-epoxy-3-ethyl-7-methylnonane (*XLVIII*), registered as epophenonane, had a satisfactory stability in contact with biotic or abiotic factors[79,87], which was higher, for example, than that of methoprene

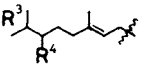
(*XIX*), and which also had a good juvenilizing effect against a number of species of insect pests.[79] Scheurer[88] mentions a successful use of epophenonane in field experiments carried out with leaf rollers making damage in orchards. Some time ago it had a chance to be one of the commercially exploited juvenoids. However, it was later substituted by a juvenoid which lacked the relatively instable and risky (from the toxicological point of view) oxirane cycle (see Chapter 4.3).

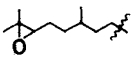
Kahovcová and Romaňuk[89–91] have published a series of papers on substances belonging to the group of variously substituted terpenyl aryl ethers *ILa* of which some had a good juvenilizing activity in tests with yellow mealworm and some other species of beetles.



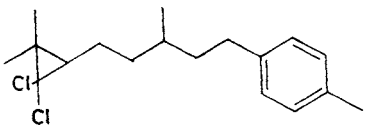
*XLVIII*



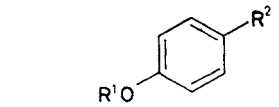
*IL a*, $R^1$=  ; $R^2$= alkyl or alkoxyl

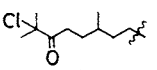
*IL b*, $R^1$=  ; $R^2$= isopropyl

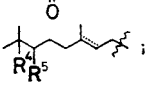
Indian authors[92–94] have published several papers concerning the synthesis of potential juvenoids with an aromatic ring in the molecule and their effect on the bug *Dysdercus koenigii*. Compounds *ILb* and *L* belonged among the most active ones. Derdzinski and Zabza[95] proceeded in a similar way when preparing a series of compounds of general formula *LIa*. These compounds displayed, however, a relatively low activity in tests with the puppae of *Tenebrio molitor* and larvae



*L*

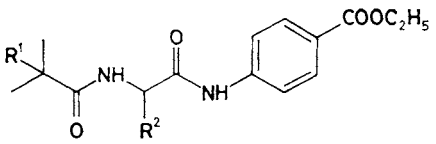


*LI a*, $R^1$= 

*LI b*, $R^1$=  ; $R^2$= $COOR^3$

of *Dysdercus cingulatus*. Borowiecki and co-workers[96] obtained a series of 4-substituted benzoates of general formula *LIb* with different substituents modifying the geranyl chain. However, the biological activities of these compounds were lower than the activities of similar juvenoids prepared by Kahovcová and Romaňuk.[89–91]

Derivatives of 4-aminobenzoic acid of general formula *LII*, with an α-amino acid residue in the side chain constitute an interesting group of juvenoids.[97–101] This series of compounds displays a distinct species specificity and a high juvenilizing activity against the bugs of the *Pyrrhocoridae* family. Ethyl-2-chloroisobutyryl-L--valyl-4-aminobenzoate[100] (*LII*; $R^1$ = Cl, $R^2$ = isopropyl) is the most active known

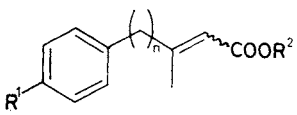



*LII*, $R^1$ = Cl, $R^2$ = isopropyl

juvenoid which displays a biological activity against the Indian cotton stainer, *Dysdercus cingulatus*, even in a concentration of 2 picogram per individual. Only L-amino acid derivatives are active.[1]

### 4.3 *Juvenoids with Two or More Cycles in the Molecule*

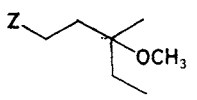
The strategy of the synthesis of JH analogues in this group of compounds started from the three possible cyclic modifications of the basic JH skeleton (structures A – C, see Chapter 4.). The aim of the structure–activity study was the determination of the effect of the location of the two cycles in the chain on the activity (cf. structures A and B), and also to try a synthesis of an analogue with three cycles and study the effect of the third cycle in the molecule on the biological activity of the preparation.



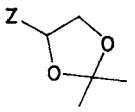

*LIII*, n = 0
*LIV*, n = 1
*LV*, n = 2
*LVI*, n = 3

In 1974 in his lecture at the Wartburg symposium Romaňuk introduced methyl 4-(2*H*-tetrahydropyran-2-yloxy)benzoate and its derivatives as the first example of

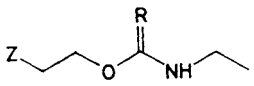
this new type of juvenoids with two cycles (published[45] in 1976). Later it became evident that a number of laboratories prepared juvenoids with two cycles with promising properties. Franke and co-workers prepared a large number of *p*-substituted derivatives of 3-phenyl-2-butenoic acid[102] (*LIII*), 4-phenyl-3-methyl-2-butenoic acid[103](*LIV*), 5-phenyl-3-alkyl-2-pentenoic acid[104] (*LV*) and 6-phenyl-3--methyl-2-hexenoic acid[105] (*LVI*). Very similar compounds were also prepared by other Swiss authors.[106] For the synthesis of the majority of them they started from the common intermediate, 4-phenoxyphenol, from which they obtained the required juvenoids by one- to two-step synthesis. The junction inserted between the two aromatic rings serves primarily for the preservation of the required length of the



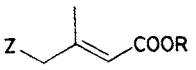

*LVII*



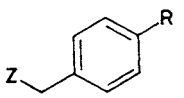

*LVIII*



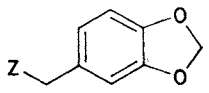

*LIX*, R = O
*LX*, R = S



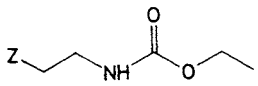

*LXI*



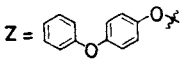

*LXII*, R = H
*LXIII*, R = $OCH_3$
*LXIV*, R = $C_2H_5$
*LXVI*, R = $COOCH_3$




*LXV*




*LXVII*



molecule (i.e. 1·9 – 2·1 nm), and it is most frequently formed by the $CH_2$, $CH_2O$ or CO group or by a hetero atom, most commonly oxygen or sulphur, or the NH group.

Karrer and co-workers[106,107] investigated the structure–activity relationships in groups of compounds with two or more cycles, prepared by them, in tests with the larvae of some beetles and butterflies. The following belonged among the most active ones: 1-(4-phenoxyphenoxy)-3-methoxy-3-methylpentane (*LVII*), the acetal *LVIII*, the carbamate *LIX* and thiocarbamate derivative *LX* and alkyl (2*E*)-4-(4--phenoxyphenoxy)-3-methyl-2-butenoates (*LXI*). Among the compounds with three cycles the highest JH activity was displayed by compounds *LXII* – *LXV*. An up to 100 times lower activity of ester *LXVI*, in comparison with compounds *LXII* – *LXIV*, in tests with the aforementioned insects represents an interesting finding.

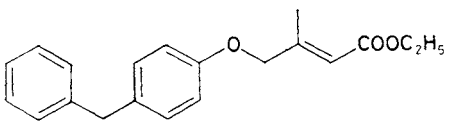
In 1979 a synthesis was described[108] of further carbamate derivatives of 4-phenoxyphenols of which the most active substance was ethyl N-(2-(4-phenoxyphenoxy)-ethyl)carbamate (*LXVII*). This compound was submitted to screening with many insect species (cf. Masner and co-workers[109,110], Dorn and co-workers[111], El-Ibrashy and Aref[112], Hammock[113], Varjas[114], Miura and Takahashi[115], Masner and co-workers[116], Charmillot and Bloesch[117] and others). Its very good activity and wide spectrum of activity against different species of insect pests were the reason for the introduction of this compound into production under the commercial name fenoxycarb, instead of the earlier registered epophenonane (Chapter 4.2). The synthesis of this compound starts again with 4-phenoxyphenol as the basic intermediate. The carbamate side chain was synthetized from ethyl N-methylcarbamate obtained by condensation of methylamine with ethyl chloroformate. After subsequent nitrosation of ethyl N-methylcarbamate to ethyl N-nitroso-N-methylcarbamate the reaction of the nitroso compound with ethyleneimine was carried out, affording ethyl N-aziridinecarboxylate which was converted to the required ethyl N-(2-chloroethyl)carbamate.

The derivatives of 4-benzylphenol also belong to the active compounds of the juvenoids with two cycles. Scheurer and co-workers[118,119] have published a synthesis and biological activity of ethyl (2*E*)-4-(4-benzylphenoxy)-3-methyl-2-butenoate (*LXVIII*) which showed in some instances[120] a higher activity than the corresponding oxa-derivative *LXI* did, for example against mosquitoes and which also had a more selective effect.

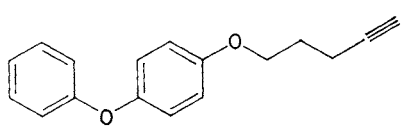
Karrer and Farooq[107] communicated a synthesis and activity of a further 4-phenoxyphenol derivative, i.e. 1-(4-phenoxyphenoxy)-4-pentyne (*LXIX*), the activity of which was somewhat lower in comparison with the other compounds synthetized together *LVII* – *LXV*.

A variant of juvenoid derivatives with a terminal triple or double bond in the side chain has been described later by Italian authors.[121–123] Among the most active compounds tested against stored product pests, the yellow mealworm, *Tenebrio*

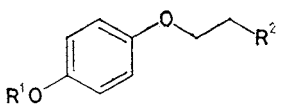
*molitor*, and the confused flour beetle, *Tribolium confusum*, and the butterfly *Ephestia kuehniella* belonged 1,4-bis(5-chloropent-4-ynyloxy)benzene (*LXX*; $R^1$ = = $ClC{\equiv}C(CH_2)_3$) as the representative of compounds with one aromatic ring, further 1-(4-phenoxyphenoxy)-5,5-dichloro-4-pentene (*LXXI*; $R^1$ = Ph) and 1-(4--phenoxyphenoxy)-5-chloro-4-pentyne (*LXX*; $R^1$ = Ph). Of the three derivatives the last mentioned compound displayed the best biological activity, and therefore it was submitted to field tests against flies and mosquitoes. However, this compound also displayed JH activity when applied to the ants *Solenopsis invicta*. Preliminary results of the toxicity tests on mice indicated a low oral toxicity ($LD_{90}$ is higher than 5 000 mg/kg). This compound also has the chance to become one of the commercially used modern pesticides. Its synthesis is relatively simple. The already mentioned 4-phenoxyphenol may again be used as the starting raw material. On reaction with 1,1,1,5-tetrachloropentane (commercially available) in non-aqueous alkaline medium it affords the required 1-(4-phenoxyphenoxy)-5-chloro-4-pentyne (*LXX*; $R^1$ = Ph).




*LXVIII*



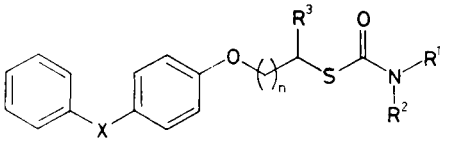

*LXIX*



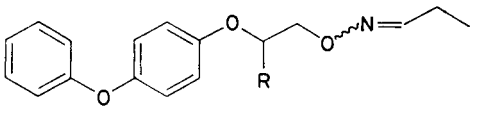

*LXX*, $R^2$= $CH_2C{\equiv}CCl$
*LXXI*, $R^2$= $CH_2CH{=}CCl_2$

Massardo and co-workers[123] also synthetized the corresponding *ortho*- and *meta*--substituted derivatives (the analogues of *LXX* and *LXXI*) and again confirmed their up to one thousand fold lower activity in comparison with corresponding *para*--substituted derivatives in tests with yellow mealworm.

4-Phenoxyphenol served as a starting intermediate for the preparation of juvenoids with two cycles for Hatakoshi and co-workers[124] as well. Among the compounds of the general formula *LXXII* two distincly most active preparations were found, i.e. N-methyl-2-(4-phenoxyphenoxy)ethylthiocarbamate (*LXXII*; X = O, $n$ = 1, $R^1$ = $R^3$ = H, $R^2$ = $CH_3$) and its N,N-dimethyl derivative. The first of the two displayed a higher activity in comparison with methoprene (*XIX*), when tested against the greater wax moth (*Galleria mellonella*) and the yellow-fever mosquito (*Aedes aegypti*).



*LXXII*

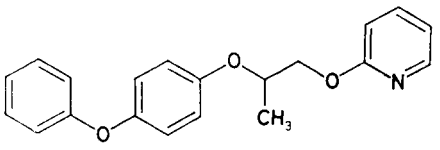


*LXXIII*

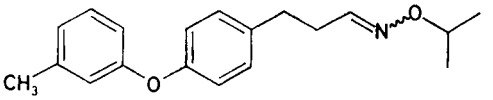
Some time later the synthesis of further juvenoid derivatives of 4-phenoxyphenol were published, with an oxime ether grouping in the side chain. Ohsumi and co-workers[125,126] used several procedures for the synthesis of these derivatives. The first way consisted in the condensation of 4-phenoxyphenol with α-chloroalkanoate and subsequent reduction of the ester group to a hydroxymethyl group. The product was converted to corresponding tosylate which was reacted with propanal oxime in dimethylformamide and in the presence of sodium hydride afforded the required juvenoid. The second way made use of the condensation of 4-phenoxyphenol with an equimolar amount of α,ω-dihalogenalkane. The product was either submitted to the same reaction with the aldehyde oxime, under formation of an oxime ether, or to the reaction with N-hydroxyphtalimide and subsequent reaction with hydroxylamine in acid medium, affording the corresponding 4-phenoxyphenoxyalkoxyamine which was converted to the required final product with the JH activity by reaction with an aldehyde or ketone. The most active compound of the whole series of derivatives was N-(2-(4-phenoxyphenoxy)-ethoxy)propanal oxime (*LXXIII*, R = H). This compound was 10 000 times more active in tests against the mosquito *Culex pipiens* and 10 times more active in tests with the house fly, in comparison with methoprene (*XIX*). A comparison of the activities of the separated *syn*- and *anti*-isomers of oxime *LXXIII* (R = H) showed that *syn*-oxime is about three times less active than the *anti*-isomer. According to the most recent information, derivative *LXXIV* (pyriproxyfen or Sumilarv) also shows a thousand times better activity than methoprene (*XIX*) against the third instar of the house fly larvae (*Musca domestica*). Its stability is also much higher.

A further paper by Japanese authors[127] is devoted to the conformational analysis of oxime ether derivatives which are compared with the very similar aforementioned carbamate juvenoids. A considerable similarity of the conformation of the molecules of oxime ether and carbamate juvenoids was found when comparing their interaction with receptor centres. The mechanism of interaction proper was simulated by means of the Advanced Computer Aided Chemistry System (ACACS) developed by the Japanese firm Sumitomo. The Japanese authors[128] investigated the oxime ether juvenoids intensively, especially with respect to their favourable biological properties. Several papers are also known dealing with the study of quantitative structure–activity relationships.[129,130] On the basis of the results obtained a development of novel structures is taking place. Niwa and co-workers[131] have published

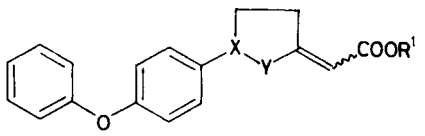
a paper where 4-phenoxyphenoxy- or 4-benzylphenoxy derivatives with juvenoid activity were extended by further structures. Among them compound *LXXV* was found best.



*LXXIV*



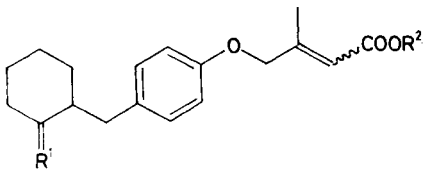
*LXXV*



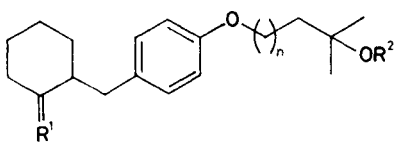
*LXXVI*, X—Y = C=C
*LXXVII*, X—Y = C—C

In addition to a series of aliphatic juvenoids, Novák and co-workers[69] also prepared several compounds with three cycles of formulae *LXXVI* and *LXXVII*. The compounds derived from structure *LXXVI* with a (2*E*)-configuration of the double bond displayed in tests with the large white (*Pieris brassicae*) an activity comparable to methoprene (*XIX*).

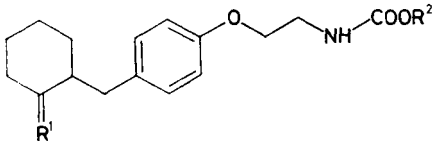
Wimmer and Romaňuk[132–135] synthetized a number of derivatives of 1-(4-hydro-



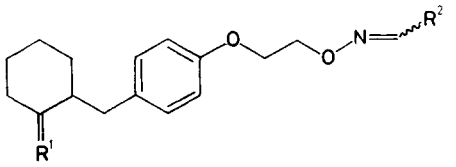
*LXXVIII*



*LXXIX*



*LXXX*



*LXXXI*

xybenzyl)-1-cyclohexanone. This intermediate was prepared by a multistep synthesis from 4-methoxybenzyl alcohol, which, when reacted with hydrochloric acid, gave 4-methoxybenzyl chloride. On Stork reaction of this chloride with the enamine of cyclohexanone 2-(4-methoxybenzyl)-1-cyclohexanone was obtained. The effect of azeotropic hydrobromic acid in acetic anhydride was used for the cleavage of the phenyl methyl ether bond. The authors synthetized compounds of the four main groups (*LXXVIII–LXXXI*). In all groups the activities of the ketones ($R^1 = O$), alcohols ($R^1 = H, OH$) and acetals ($R^1 = (OR^3)_2$) were compared.

The juvenoids with a secondary alcoholic group in the molecule, derived from the general structures *LXXVIII–LXXXI*, were also used successfully for the preparation of a novel type of hormonogen substances – juvenogens (see Chapter 5.).

### 4.4 *Optically Active Juvenoids*

Many of the juvenoids mentioned in Chapters 4.1 to 4.3 have at least one asymmetric centre in the molecule. Henrick and co-workers[136] investigated some of the highly biologically active juvenoids in their chiral – though not always quite optically pure – forms (see Table I). Similarly, Ohsumi and co-workers[126] compared the biological activity of both optical isomers of N-(2-(4-phenoxyphenoxy)propoxy)propanal oxime (*LXXIII*, $R = CH_3$). When comparing the values of the biological activities of (*S*)-(+)- or (*R*)-(−)-isomers of methoprene (*XIX*; of an optical purity at least 98%) on fly, Henrick and co-workers[136] found a hundred to thousand times better activity for the (*S*)-(+)-isomer. A similar result was also obtained in tests with yellow mealworm (*Tenebrio molitor*). The difference in activity with the yellow-fever mosquito, *Aedes aegypti*, and the greater wax moth, *Galleria mellonella*, as large as one to two orders of magnitude, was also found to be in favour of the (*S*)-(+)-isomer of hydroprene (*XXVI*), even though this isomer was prepared only in a 70% optical purity, as compared with the almost 98% optical purity of the (*R*)-(−)-isomer. On the other hand, when (*S*)- and (*R*)-isomers of the Japanese preparation *LXXIII* ($R = CH_3$) were compared in tests with some flies[126] a difference of about one order of magnitude was found for activity values in favour of the (*R*)-isomer, while the optical purity of both enantiomers was comparable, i.e. 85–90%. It may be conjectured that optical isomers of juvenoids may play a certain role in the interaction of juvenoids with the receptor sites and so decide in favour of one of the optical isomers, but only under the assumption that the optically active centre of the juvenoid molecule takes a direct part in, or is very close to the interacting part of the molecule with the receptor site. With the exception of several results obtained with methoprene *XIX*, in which a difference of several orders of magnitude was observed in the activities of optical isomers, the differences in the activities of optical isomers of further investigated juvenoids are too small to permit deducing a more general conclusion from these studies.

TABLE I

Comparison of biological activities of chiral and racemic forms of methoprene (*XIX*), hydroprene (*XXVI*) and juvenoid *LXXIII* (R = $CH_3$)

| Compound | Configuration | Enantiomeric excess, % | *Aedes aegypti* ppm | *Galleria mellonella* μg/pupa | *Tenebrio molitor* μg/pupa | *Musca domestica* μg/prepupa |
|---|---|---|---|---|---|---|
| | *S* | 98·1 | 0·000075 | 2·5 | 0·0022 | 0·0015 |
| *XIX* | *RS* | 0·0 | 0·00017 | 5·7 | 0·004 | 0·0035 |
| | *R* | 99·5 | 0·025 | >100 | 0·7 | 0·15 |
| | *S* | 69·6 | 0·0045 | 0·041 | 0·18 | 4·7 |
| *XXVI* | *RS* | 0·0 | 0·0078 | 0·040 | 0·25 | 18 |
| | *R* | 97·8 | 0·19 | 0·49 | 1·7 | 32 |
| *LXXIII* | *S* | 86·0 | — | — | — | 1·1[a] |
| (R = $CH_3$) | *RS* | 0·0 | — | — | — | 0·24[a] |
| | *R* | 89·7 | — | — | — | 0·2[a] |

[a] $IC_{50}$ (μmol $l^{-1}$) value. The authors state by comparing the values of the biological activities (on the basis of the standard Galleria Wax Test) that the activity of the racemic derivative *LXXIII* (R = $CH_3$) is 5 900 times higher than the activity of methoprene *XIX* (cf. ref.[126]).

As mentioned in Chapter 4.2 the only exception are derivatives of 4-aminobenzoic acid of general formula *LII*, in which compounds with an L-amino acid residue have a picogram activity, while a D-amino acid makes the substances completely inactive.[1]

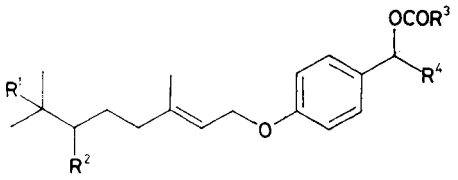
## 5. JUVENOGENS

In 1976 Sláma and Romaňuk[137] published the discovery of juvenogen. This term was used to describe a group of complex substances capable of liberating a biologically active juvenoid under the influence of biotic or abiotic factors. The search for such complex juvenogen compounds was encouraged by the attempt to change temporarily the physical properties of juvenoids and thus the way of their application. The ester function constitutes an important group in native JH, the cleavage of which takes place owing to the presence of carboxyl esterases. The juvenoid acid formed is quite inactive (Eq. (*A*)). Sláma and Romaňuk[137] assumed that it will be possible – analogously – to set free the biologically active alcohol (Eq. (*B*)) from esters in which the

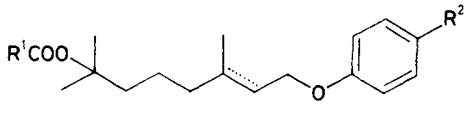
$$R^1COOCH_3 \longrightarrow R^1COOH + CH_3OH \qquad (A)$$

$$R^1COOR^2 \longrightarrow R^1COOH + R^2OH \qquad (B)$$

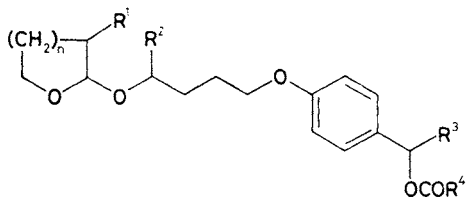
alcohol moiety is the active component, and they checked their hypothesis by preparing and studying the biological properties of an inactive juvenogen ester prepared from a biologically active secondary juvenoid alcohol (*XXVIIIb*) and stearic acid. The results of the study of the biological properties of this compound and a series of juvenogen esters of general formulae *LXXXII*–*LXXXVI* and β-D-glucosides *LXXXVII* prepared later (see refs[89,90,138–141]) confirmed that the activity of non-specific esterases in the insect haemolymph and the activity of the corresponding glucosidase in the intestinal tract of the insect are sufficiently high for the liberation of the alcohol from corresponding juvenogens, in amounts sufficient to elicit a proper juvenilizing effect, and indicated the possibility of using juvenogens for theoretical studies in the field of insect endocrinology and of using them in practice.



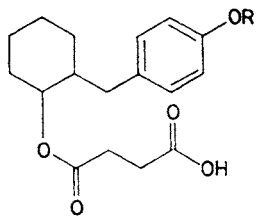

*LXXXII*



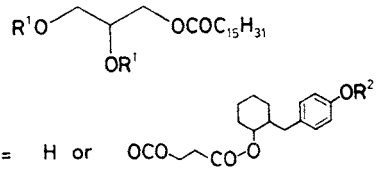

*LXXXIII*



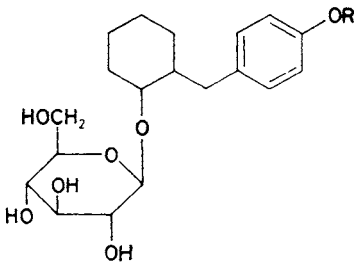
*LXXXIV*



*LXXXV*



*LXXXVI*, $R^1$= H or



*LXXXVII*

The study of the systemic effect of these compounds, their formation and cleavage in plants assumes new forms in connection with the study of their biotransformations by means of plant cell cultures.[142]

## 6. CONCLUSION

During the whole research of the substances displaying JH activity so far thousands of compounds were synthetized in the world. Together with them many studies on structure–activity relationships have also appeared, the validity of which was more or less limited, but which proved valuable for the intended syntheses of juvenoids. Today it is still impossible to formulate generally valid structure-activity rules. It should be kept in mind that the biological activity and the species specificity of the effect of juvenoids is affected by a number of factors, as for example their penetration through the cuticule, binding to transport proteins in the haemolymph, rate of enzymatic cleavage of the substance in the insect organism and the rate of their

elimination from the body, and finally (though not negligibly), the ability to interact with the receptor sites. The role of each of these factors warrants further intensive study in basic research and its elucidation would undoubtedly facilitate the difficult task of introducing juvenoids into practice.

The work of tens of years by many laboratories is already utilized today in the form of, so far, several commercially available juvenoids. Selected compounds, which are today in the centre of interest of applied research, should serve mainly for the protection of cultured plants and harvests of the basic staple production against economically important insect pests and for the protection of human society against social insect pests.

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Translated by Ž. Procházka.

*Note added in proof:*

*1*) Formula *XXI*: Oxygen on C(10) should be replaced by $OCH_3$.
*2*) Formula *ILa*: Insert a single bond between $R^3$ and the geminal carbon atom.
*3*) Formula *LXXIV*: The methyl group should be connected with the neighbouring carbon atom.