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The Juvenile Hormone of Insects and Its Analogues

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The review deals with the chemistry of the juvenile hormone of insects and its analogues. The literature data on the isolation, determination of the structure, and synthesis of the juvenile hormone and natural compounds imitating its activity are quoted. Synthetic substances exhibiting the activity of the hormone are described and the problem of the relation between their structure and physiological activity is discussed.
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I. INTRODUCTION

In recent years there has been a considerable increase of interest in insect hormones. While the chemical nature of the hormones of vertebrates has been successfully investigated for more than 50 years, the information about the structure of the most important insect hormones was obtained only as late as the 1960's. Nevertheless, apart from their great theoretical importance, studied on the endocrinology of insects may lead to the creation of fundamentally new means for combating pests.

A distinctive feature of insects is a clear-cut development in discontinuous stages during the growth process according to the scheme egg → larva (several stages) → pupa → adult insect (imago). The development and growth of the larva is accompanied by moulting. In some families the chrysalis stage is absent. The larval development and metamorphosis (the transformation into the adult insect) are under hormonal control.

The endocrine system of insects consists of the following components: groups of neurosecretory cells of the brain and the abdominal nerve chain, corpora cardiaca, corpora allata, and prothoracic glands or their analogues. The polypeptide hormone of the neurosecretory cells has been called the activating hormone, since one of its main functions is to stimulate the activity of the prothoracic glands, which produce the moulting hormone (acdysone), and the corpora allata, which secrete the juvenile hormone (JH). The development of insects is controlled by the activating hormone, ecdysone, and the juvenile hormone[1-3]. Moulting takes place in the presence of an enhanced secretion of ecdysone, and the juvenile hormone prevents metamorphosis, preserving the larval nature of the moulting; it is non-specific even within different insect orders. The amount of juvenile hormone varies in different stages of insect development: it is absent in the embryonic period, appears in the moulting stage, and in pupal moulting its concentration falls. Moulting of the imago is possible only in the absence of the juvenile hormone. The removal of the corpora allata from larvae leads to the formation of dwarf imagos[4]. The introduction into the insect organism of the juvenile hormone in the pre-imago period, when the hormone should be absent, leads to additional moulting and the appearance of giant forms. It is noteworthy that the giant individuals are non-viable and as a rule soon die[5,6]. In adult insects the juvenile hormone again begins to be produced and fulfils a number of functions the principal of which is gonadotropic. It has been shown that the juvenile hormone is identical with the gonadotropic hormone[7-10] and that the necessary condition for the regulation of ovogenic processes by the juvenile hormone is the absence of ecdysone[6]. Finally, the juvenile hormone has a prothoracotropic activity, stimulating the function of the prothoracic glands, which produce ecdysone[11,12].

Even before the determination of the structure of the juvenile hormone, a number of natural and synthetic compounds with juvenile-hormonal activity were found. Such activity is shown by extracts of plant, bacterial, and animal origin[13,14]. The juvenile hormone and its analogues influence insects both following injection and local application. In this connection it has often been suggested that the juvenile hormone and substances imitating its activity might be applied to combat harmful insects[15-19]. Hormonal insecticides should have a number of advantages over "traditional" insecticides. It is believed that they ought to be non-toxic to warm-blooded animals, should be effective in trace amounts, and that insects would be unable to develop resistance to them.

Since a large number of compounds with juvenile-hormonal activity are now known, it has become necessary to estimate quantitatively their effectiveness. The most suitable object for this purpose proved to be the pupae of the flour beetle *Tenebrio molitor* and the wax moth *Galleria mellonell*. The activity is expressed in "tenebrio" and "galleria" units. One "tenebrio" unit[20] and one "galleria" unit[21] are defined as the minimum amount of the substance in microgrammes which has a positive effect in 40 and 50% respectively of the test insects. Hence the specific activity of substances may be expressed as the number of "tenebrio" or "galleria" units per microgramme. Frequently the amount of test substance in microgrammes per insect is recorded and the effect is determined from the extent of preservation of the larval or pupal characteristics and is estimated on an n-point scale established arbitrarily for the insect species tested[22,23].

In order to unify the methods for the estimation of juvenile-hormonal activity, Wigglesworth[24] suggested that the minimal amounts of the test substance, expressed in microgrammes per gramme of insect weight, which give rise to a positive effect should be compared.

There are a number of reviews in the Soviet[3,25] and non-Soviet[1,2,26-29] literature on insect hormones. In most of them the biological aspects are considered. The latest review by Röller and Dahm deals mainly with the work of the authors themselves[28]. Nevertheless the problem of the synthesis of the juvenile hormone has attracted the attention of chemists in various countries: in the last two years nine versions of the synthesis of the juvenile hormone have been published. The problem of the relation between the structure and biological activity of juvenile hormone analogues is also extremely important. Therefore it is of interest to review the information on the chemistry of the juvenile hormone and substances imitating its activity.

II. ISOLATION AND DETERMINATION OF THE STRUCTURE OF THE JUVENILE HORMONE

Work on the isolation and determination of the structure of the juvenile hormone is associated with the name of the great American entomologist Williams. It is extremely difficult to isolate the juvenile hormone from the corpora allata because the glands contain a negligible amount of the hormone. Williams observed that the abdomens of the males of the large butterflies *Hyalophora cecropia* and *Samia cinthia* contain an unusually large amount of the juvenile hormone[30-33]. By extracting with ether the abdomens of the males of *Hyalophora cecropia*, he obtained a neutral oil with a considerable juvenile-hormonal activity. This extract, called "cecropia oil", served as a source for the isolation of the juvenile hormone. The preparation of purified extracts has been frequently reported[20,27,34]. Karlson[20] used for this purpose double chromatography on alumina and achieved purification by a factor of 8.

By 1965 three groups of American investigators carried out intensive research on the isolation of the juvenile hormone from "cecropia oil". It is interesting to compare their results. Williams and Law[35], who employed extraction with methanol, chromatography on silicic acid, and gas–liquid chromatography, obtained a fraction which was more active than the initial "cecropia oil" by a factor of 50 000. They showed by mass-spectrometry that the active component in an epoxy-derivative of the ethyl ether of a C_{16} aliphatic acid with a molecular weight of 284. However, tests on synthetic specimens of methyl (±)-9,10-*cis*- and (±)-9,10-*trans*-epoxyhexadecanoates showed that they are completely inactive although their mass spectra did not differ from that of the active fraction isolated from "cecropia oil". The isomeric synthetic epoxides and the natural juvenile hormone were not separated on the gas-liquid chromatograph employed by Williams and Law. The investigators were at the threshold of discovery and only the inadequate resolving power of their instruments prevented them from determining the exact structure of the juvenile hormone[28].

Meyer[36] reported a degree of purification by a factor of 3×10^5 using a five-stage process including gas-liquid chromatography. Two active fractions were obtained. Repeated chromatography did not lead to the isolation of the individual substances. According to Röller[28], the active fractions contained an admixture of the pyrolysis products of the juvenile hormone, which is unstable in chromatography above 210°C.

Finally in the same year a group of investigators at Wisconsin University led by Röller[37,38] isolated the juvenile hormone from "cecropia oil" in a pure form having obtained a degree of purification by a factor of 1.05×10^5. At all stages biological control was based on *Tenebrio molitor* larvae. The initial unpurified "cecropia oil" had an activity of 25 "tenebrio" units, while the pure juvenile hormone had an activity of 2.6×10^6 "tenebrio" units per microlitre. Later Röller improved the method of isolation of the juvenile hormone by replacing one thin-layer chromatographic stage by molecular distillation (Scheme 1)[39].

Scheme 1

Isolation of the juvenile hormone from the butterflies *Hyalophora cecropia*

Process		Activity "tenebrio" units per μg	Overall activity, %
	875 abdomens (380 g)		
I. Extraction with ether	↓		
	180 g of crude oil	0.04	100
II. Precipitation at -80°C	↓		
	47 g of purified oil		
	↓	0.13	85
III. Molecular distillation (60–90°C, 2×10^{-5} mmHg)	5.4 g of distillate	1.1	83
	↓		
IV. Thin-layer chromatography, silica gel *G*, chloroform : ethyl acetate = 2 : 1, zone with R_f = 0.6–0.9	440 mg	13	80
	↓		
V. Thin-layer chromatography, silica gel *G*, chloroform : pentane = 2 : 1,	5.4 mg	100	75
	↓		
zone with R_f = 0.05–0.3	810 μg of JH		
VI. Gas–liquid chromatography		5000	56

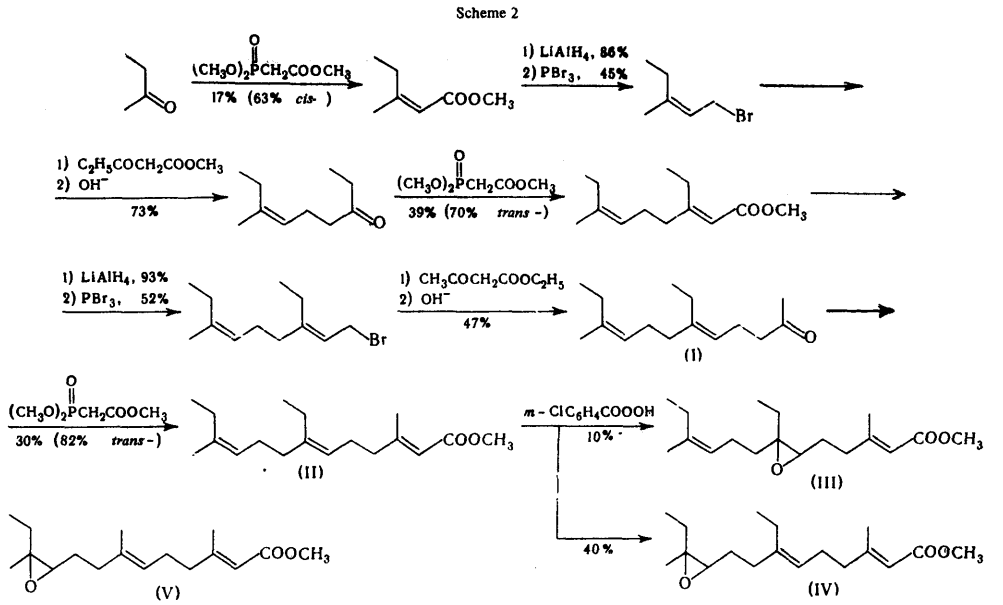
Although Röller and coworkers had at their disposal not more than 0.2–0.3 mg of the pure substance, the structure of the juvenile hormone was established in less than two years. The study of the juvenile hormone and the product of its reduction by hydrogen over palladium (20–30 μ g) on a combined gas chromatograph and mass-spectrometer[40] led to the determination of the overall formula ($C_{18}H_{30}O_3$), the molecular weight (294), the presence of a methoxycarbonyl group, branching, and three double bonds or rings[41]. The cleavage of 15 μg of the juvenile hormone with osmium tetroxide and periodate and investigation of the PMR spectrum (200 μg) in combination with mass-spectrometric data led to the identification of the juvenile hormone as methyl 10,11-epoxy-7-ethyl-3,11-dimethyltrideca-2,6-dienoate (IV) with the *trans*-configuration of the substituents at the 2,3-double bond.

The configuration of the substituents at the 6,7-double bond in the oxiran ring was not elucidated. A few months later Röller and coworkers[42] reported the first synthesis of racemic juvenile hormone. The synthesis was carried out by a gradual increase in chain length (Scheme 2).

The introduction of the double bonds by three applications of the phosphonate modification of the Wittig reaction was accompanied by the separation of the *cis*- and *trans*-isomers. In the first case the isomers were separated by fractionation on a 60 cm Teflon column and in the second and third cases by adsorption chromatography on silica gel. The last stage, the conversion of (II) into the epoxy-derivative with *m*-chloroperbenzoic acid, led to a mixture of epoxides (III) and (IV), which were separated by thin-layer chromatography on silica gel. Conversion of the triene ester (II) into the epoxy-derivative by the van Tamelen method[44] gives (IV) without an admixture of the isomer in a yield of 60%. At the same time Röller and Dahm[45] obtained by a similar mechanism a further four geometrical isomers of the juvenile hormone and later they synthesised all eight isomers of the hormone[28].

Comparison of the biological activities of the natural juvenile hormone and the synthetic specimens showed that

Scheme 2



synthetic methyl (±)-*trans*,trans,*cis*-10,11-epoxy-7-ethyl-3,11-dimethyltrideca-2,6-dienoate (IV) has the same activity as the natural hormone. The remaining isomers are less active (Table 1). All eight isomers of the juvenile hormone have also been obtained by the Hoffman La Roche Company, but their synthesis has not been published. The results of tests of these isomers on the bug *Rhodnius prolixus* are quoted by Wigglesworth[24] (Table 1).

Table 1. Physiological activity of the juvenile hormone and its isomers.

Compound		Configuration			Activity	
		C 2—3	C 6—7	C 10—11	"Tenebrio" units per μg (Ref.28)	g/g of insect wt. (Ref.24)
Natural hormone		—	—	—	5000	
Synthetic (±)-isomer	1	*trans*-	*trans*-	*cis*-	5000	0.18
Ditto	2	*trans*-	*trans*-	*trans*-	2000	0.6
»	3	*trans*-	*cis*-	*cis*-	200	1.8
»	4	*trans*-	*cis*-	*trans*-	150	13.5
»	5	*cis*-	*trans*-	*cis*-	10	9.0
»	6	*cis*-	*trans*-	*trans*-	10	16.0
»	7	*cis*-	*cis*-	*cis*-	10	63.0
»	8	*cis*-	*cis*-	*trans*-	10	45.0
Synthetic 6,7-epoxy-derivative of (±)- isomer		*trans*-	*trans*-	*trans*-	200	18.0
Synthetic ethyl ester of (±)-isomer	1	*trans*-	*trans*-	*cis*-	40000	0.18

It has still not been shown whether the juvenile hormone derived from "cecropia oil" is optically active. Biological tests of the (±)-*trans*,*trans*,*cis*-isomer on *Tenebrio molitor* showed that either the enantiomers have the same biological activity, or, what is more likely, the natural juvenile hormone is also a mixture of the (+)- and (−)-forms[28]. This problem will have to be solved in the future.

In 1968 Meyer isolated from "cecropia oil" a second juvenile hormone (V), which is produced by the corpora allata in smaller amounts. It differs from (IV) by the presence of a methyl instead of an ethyl group at C_7. The isolation was based on the application of gas–liquid chromatography in the last stage. It was shown[46] that the ratio of the hormones varies, depending on the stage of development of the insect, between 4 : 1 and 7 : 1. It is suggested[18] that the second hormone is a precursor in the biosynthesis of (IV) and is responsible for 13–20% of the endocrine activity. Röller[28] did not detect the second active substance in "cecropia oil".

The biosynthetic pathways for the juvenile hormone are unknown. It has been established that insects synthesise the acyclic sesquiterpenes farnesal and farnesol from mevalonate[47,48]. However, so far it has not been shown whether the isoprene units are methylated at some stage in the biosynthesis or whether insects employ other precursors.

The mechanism of the action of the juvenile hormone is also unknown. The latest electrophysiological studies[49] appear to confirm the earlier hypothesis that the juvenile hormone affects the permeability of cell membranes[50].

All the hormones known until recent years belong to two classes of natural substances. They are either peptides and aminoacids or steroids. Ecdysone is not an exception in this sense, since it contains the hydrocarbon skeleton of cholesterol. The determination of the structure of the juvenile hormone of insects, which is a terpenoid, significantly extends out concepts concerning hormones. In this connection it should be noted that recently substances with a powerful hormonal activity—prostaglandins—were discovered in the secretions of vertebrates; like the juvenile hormone, they do not belong to any of the classes indicated above[51].

III. SYNTHESIS OF THE JUVENILE HORMONE

Less than two years have elapsed since the first synthesis of the juvenile hormone achieved by Röller and Dahm. During this period, eight versions of the synthesis of this biologically active compound have been reported. Synthetic studies are being carried on in the

laboratories of the largest universities and commercial companies in the USA and Western Europe. Few natural substances are being investigated so intensively, which is evidence of a considerable interest in the juvenile hormone. In the synthesis of the juvenile hormone molecule the greatest difficulties are encountered in the formation of three centres which can give rise to geometrical isomers. Two approaches to the problem of the synthesis of the juvenile hormone can be clearly distinguished. The first is based on the use of highly stereospecific reactions which lead to the formation of the required isomers and the second involves reactions which yield a mixture of the *cis*- and *trans*-isomers with their subsequent separation by means of effective fractionating columns, and column, thin-layer, or gas-liquid chromatography.

It is at present difficult to assess fully the advantages and disadvantages of all the known syntheses of the juvenile hormone. Many of these have been described very schematically. So far as is known, no attempt has been made so far to separate the synthetic juvenile hormone into enantiomers.

The stereospecific syntheses consist of a large number of stages and use certain new reactions, methods, and reagents. Below they are described in greater detail.

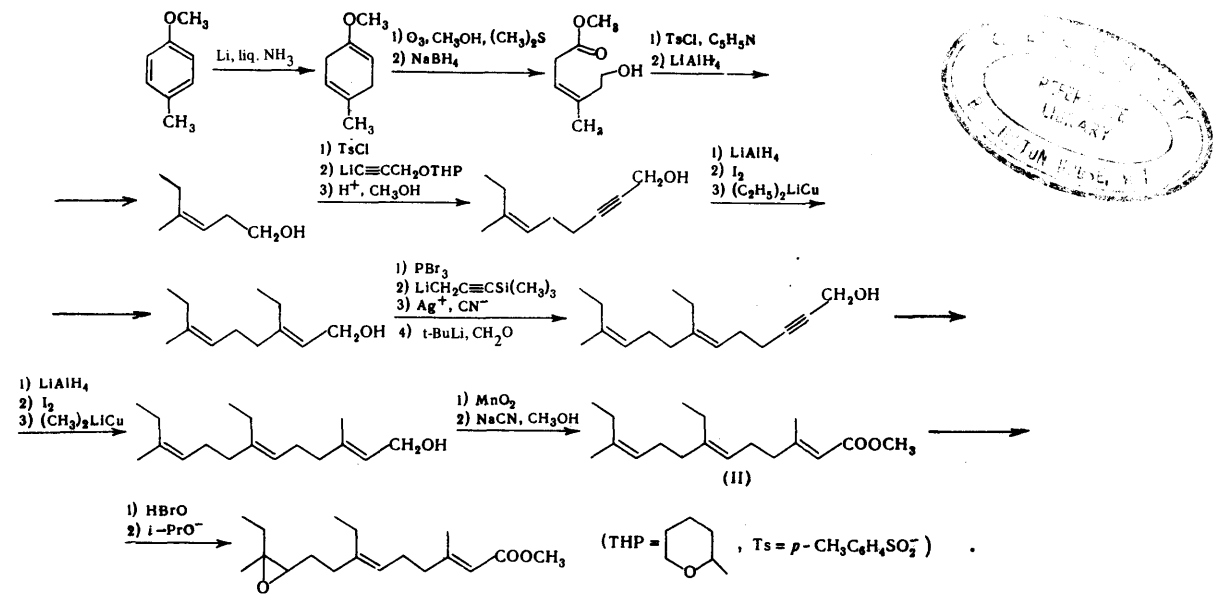
The stereospecific synthesis of the juvenile hormone was achieved in 1968 by Corey and coworkers[52] at Harvard University. Corey's scheme is based on a starting material which ensures the formation of the *cis*-configuration in the oxiran ring and certain new methods developed by the author were employed (Scheme 3).

The product of the Birch reduction of *p*-methoxytoluene was ozonised, converted into an aldehyde-ester, and reduced with sodium borohydride. The reduction of the *p*-toluenesulphonate of the resulting hydroxyester with lithium aluminium hydride led to the formation of the *cis*-isomer of a C_7 unsaturated alcohol. The reaction of the *p*-toluenesulphonate of the unsaturated C_7 alcohol with the lithium derivative of propargyl tetrahydropyranyl ether in hexamethylphosphoramide and subsequent treatment with acid methanol gave an acetylenic C_{10} alcohol. To convert the latter into *trans*, cis-3-ethyl-7-methylnona-2,6-dienol, Corey employed the stereoselective *C*-alkylation with alkylcopper reagents which he discovered recently[53-55]. Next the diene alcohol was converted into the bromide, which was alkylated with the lithium derivative of 1-trimethylsilylpropyne[56]. After the removal of the trimethylsilyl protecting group, an unsaturated hydrocarbon was obtained, which was converted by the action of t-butyllithium and paraformaldehyde into a C_{16} acetylenic alcohol. The repeated application of the stereoselective alkylation reaction in the synthesis led to the preparation of a C_{17} *trans,trans,cis*-triene alcohol. Treatment of the C_{17} alcohol with an excess of manganese dioxide in hexane at 0°C and subsequently with sodium cyanide and methanol gave the methyl ester of a trienoic acid (II). This new method for the conversion of aldehydes into carboxylic acid esters was also developed by Corey[57] and is of general value (yields in excess of 95%). The ester (II) was converted into the epoxy-derivative by treatment with hypobromite and subsequent elimination of hydrogen bromide.

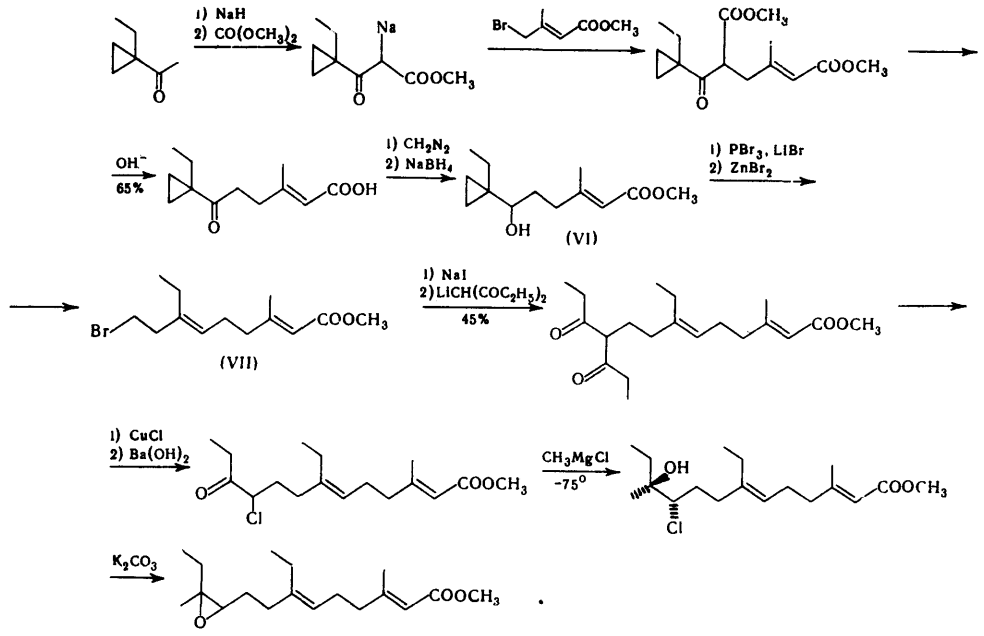
Johnson's twelve stage synthesis yields the racemic juvenile hormone containing admixtures of less than 8% of the *trans,trans,trans*-isomer and 0–5% of the *trans,cis, cis*-isomer. It is based on the application of Julia's method[59,60] for the synthesis of trisubstituted olefinic bonds, which includes the rearrangement of cyclopropylmethanols into homoallylic bromides. In all stages except two the products were obtained in yields greater than 90% (Scheme 4).

The sodio-derivative of the product of the Claisen condensation of 1-acetyl-1-ethylcyclopropane with carbonic ester was converted by reaction with methyl *trans*-γ-bromo-$\beta\beta$-dimethylacrylate[61] into a ketodiester. The latter was converted in three stages into the hydroxyester (VI) and then into the homoallylic bromide (VII) by a modification of Julia's method developed by the author[62]; (VII) contained less than 5% of the *trans,cis*-isomer. The bromide (VII) was converted into the corresponding iodide and condensed with the lithio-derivative of hepta-3,5-dione. After substitution with chlorine of the mobile hydrogen atom in the β-diketone formed and alkaline

Scheme 3



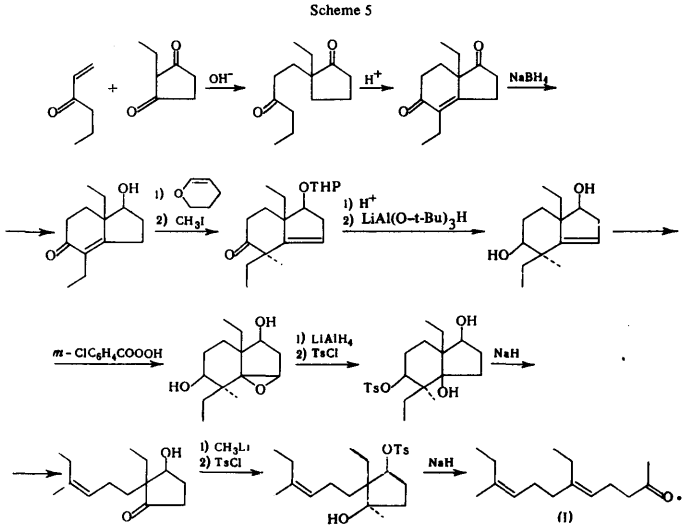
Scheme 4



hydrolysis, the reaction product was purified by preparative gas–liquid chromatography and then treated at −75°C with an excess of methylmagnesium chloride, hydrogen chloride being eliminated with potassium carbonate in methanol, which ensures the *cis*-configuration of the substituents in the oxiran ring (< 8% of the *trans*-isomer). The stereospecific synthesis of an important intermediate for the preparation of the juvenile hormone, *trans,cis*-6-ethyl-10-methyldodeca-5,9-dien-2-one, was achieved at the Institute of Steroid Chemistry of the Syntex Corporation in California [compound (I) in Scheme 5][63].

Brown et al.[64] developed two methods for the synthesis of a mixture of isomers of the juvenile hormone (Scheme 6).

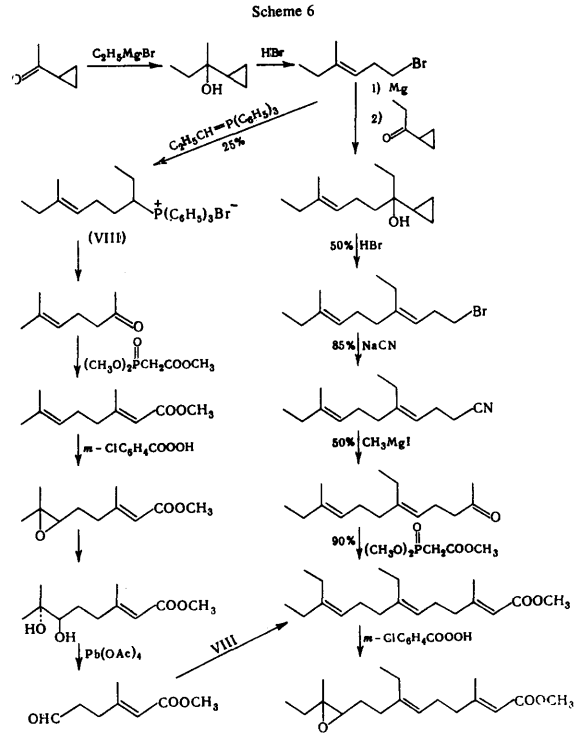
Scheme 5



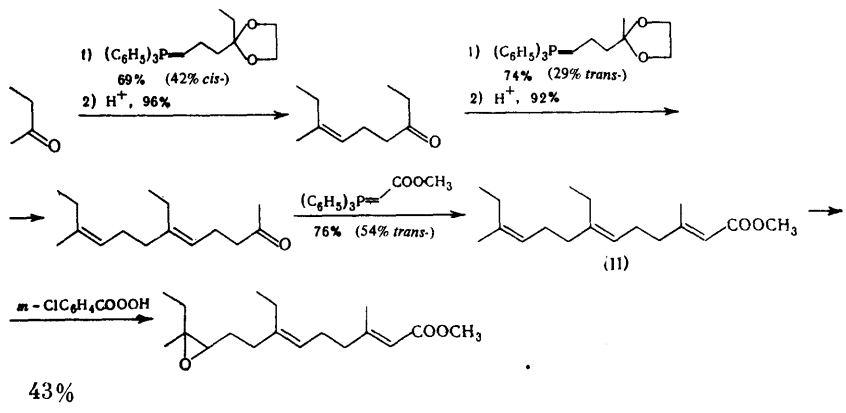
The authors state that the preparation exhibits 0.3 of the activity of the natural hormone and is used for entomological studies. Double bonds are formed both by the Julia method and by the Wittig reaction.

At the beginning of 1969 a further two papers on the synthesis of the juvenile hormone were published almost simultaneously. The synthesis achieved by Schulz[65]

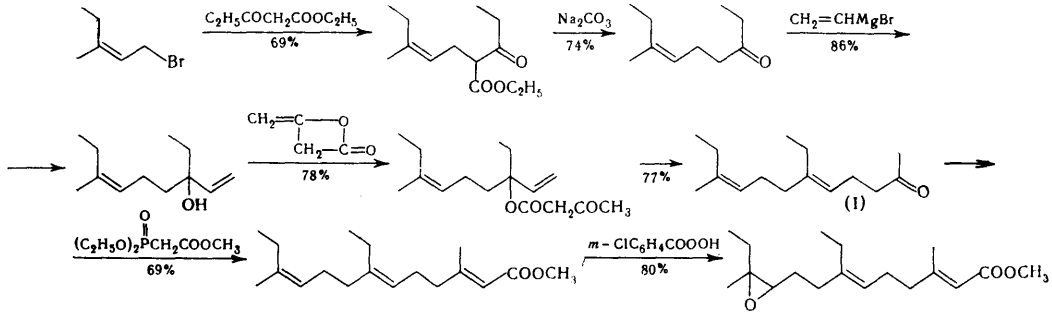
Scheme 6



Scheme 7



Scheme 8

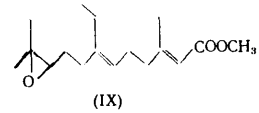


includes only three stages for the formation of the C_{17} skeleton: $C_4 + C_6 + C_5 + C_2$. The synthesis consists in a gradual increase in chain length using the Wittig reaction (Scheme 7).

The isomers of the C_{10} and C_{15} ketals and of the triene ester (II) were separated by fractionation on a Teflon column (l = 100 cm). The ketones obtained after hydrolysis were additionally purified by chromatography on silica gel. The authors state that they can obtain by this method all the geometrical isomers of the juvenile hormone and its homologues with different substituents at C_3, C_7, and C_{11}. However, it should be noted that the syntheses of the phosphoranes derived from the initial ketals and the separation of the isomers are fairly laborious processes.

Mori et al.[66] achieved a non-stereospecific synthesis of the juvenile hormone [compounds (IV) and (V)] and yet another homologue, which differs from the juvenile hormone by the presence of a methyl instead of an ethyl group at C_{11} [compound(IX)]. The final product consisted of a mixture of isomers. The synthesis is based on the application of the Normant[67] and the Carrol–Caymel[68] reactions and the phosphonate modification of the Wittig reaction[43]. The ratio of the *cis*- and *trans*-isomers in the intermediate and final product was determined by gas–liquid chromatography (Scheme 8).

The intermediate C_{10} and C_{15} ketones were obtained as individual isomers by the fractionation of the dioxolan derived from the C_{10} ketone[69] and repeated recrystallisation of the semicarbazone of the C_{15} ketone.



(IX)

IV. NATURAL AND SYNTHETIC ANALOGUES OF THE JUVENILE HORMONE

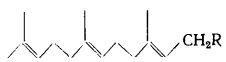
1. Farnesol Derivatives

At the beginning of the 1960's natural and synthetic compounds exhibiting the juvenile-hormonal activity in insects were discovered[20,27,70–75]. It was already clear that the structure of the juvenile hormone resembles that of terpenes. Farnesal and farnesol, acyclic sesquiterpenes widely distributed in nature, attracted particular attention. They were detected in the organisms of beetles[70], butterflies[47,76], bumble bees[77], and other insects. The hypothesis that farnesol functions as the juvenile hormone[70,72] was not confirmed[27,37,75]. Biological tests on a number of natural and synthetic terpenoids showed that none of them has a sufficiently high activity to be identified with the juvenile hormone[20,27,76,78].

Nevertheless these studies helped elucidate the structural elements responsible for the physiological activity, elucidate the relation between the shape and dimensions of the molecules and their juvenile-hormonal activity, and solve the problem of the mechanism of the action of the juvenile hormone at a molecular level. To obtain compounds more readily available than the juvenile hormone in order to combat harmful insects, the search for substances imitating its activity has been begun.

It is noteworthy that experiments designed to determine the juvenile-hormonal activity have been performed on different objects and by different methods (injection and surface application) and therefore it is frequently impossible to compare the results obtained by different investigators. Insects of different species show different sensitivity in relation to the juvenile hormone and its analogues. Hence there is a potential possibility of creating selective hormonal insecticides. The most active substances are described below and data on the relation between their structure and biological activity are given.

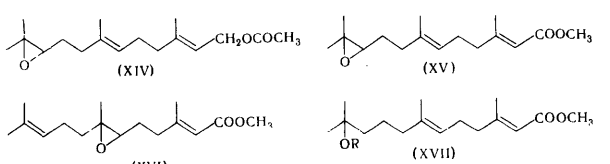
Tests of farnesol isomers on the pupae of the flour beetle *Tenebrio molitor* showed that *trans,trans*-farnesol (X) has the maximum activity[79]. This finding holds also for other sesquiterpenes: the *trans*-isomers are the most active[24,28]:



(X) R=OH, (XI) R=OCH_3, (XII) R=$N(C_2H_5)_2$, (XIII) R=$OCOCH_3$

Farnesyl methyl ether (XI) and farnesyldiethylamine (XII) are more effective by a factor of 10 and 17 respectively than farnesol (X) in tests on the pupae of the wax moth *Galleria mellonella*[80,81]. The length of the terpene alcohol molecule and the position of the hydroxy-group are important for juvenile-hormonal activity. Thus geraniol, linalo-ol and bisabolol are inactive. The effect of the length of the molecule on juvenile-hormonal activity is clearly shown by alkyl methyl ethers. Dodecyl methyl ether is the most active[80,82]. A change in chain length by three carbon atoms leads to total loss of activity. The presence of groups with a definite polarity is also essential for activity. Farnesene and dihydrofarnesene on the one hand and the highly polar farnesylic acid, dodecyl alcohol, and dodecylamine on the other are completely inactive or show a weak activity. Moreover, Schneiderman[80] noted the importance of molecular properties such as the capacity to form complexes with proteins and lipoproteins and to penetrate cell membranes.

After the detection of the epoxy-group in the juvenile hormone, a number of sesquiterpene epoxides were obtained. 10,11-Epoxy-*trans,trans*-farnesyl acetate (XIV) shows a higher activity than farnesyl acetate (XIII).[44,83] The conversion of the methyl ester of *trans,trans*-farnesylic acid into an epoxy-derivative with *m*-chloroperbenzoic acid in dichloromethane gives a mixture of epoxides [80% of (XV) and 20% of (XVI)], which were separated by thin-layer chromatography:



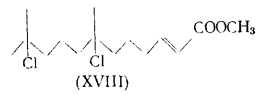
(XIV) (XV) (XVI) (XVII) (R=CH_3, C_2H_5)

Tests with surface application on *Tenebrio molitor* showed that (XV) is 1600 times more active than farnesol (X), while (XVI) is inactive[83]. It is interesting that (XV) is less active than farnesol when injected[28].

Compounds with *O*-alkyl substituents at C_{11} [compound (XVII)] also exhibit juvenile-hormonal activity[84].

Law and Williams[85] obtained the most active synthetic product by passing hydrogen chloride through an alcoholic solution of farnesylic acid. It consists of at least 22 components, five of which are active[39] and is known as "Law's mixture"[86] or "synthetic juvenile hormone"[87]. When "Law's mixture" is obtained in various alcohols, the juvenile-hormonal activity varies as follows: ethanol > methanol > propanol > pentanol. When the reaction is carried out in ethanol, a highly active product, effective in insects of various species, is obtained[24,85,88-90].

Sorm and coworkers[91] isolated the principal component of "Law's mixture" obtained in methanol. It is the dihydrochloride of the methyl ester of farnesylic acid (XVIII):



(XVIII)

Compound (XVIII) showed a high juvenile-hormonal activity in relation to the bugs *Pyrrhocoris apterus*[91-95], *Rhodnius prolixus*[24], and others.

Farnesol[96] and a number of similar compounds[97,98] have been patented as insecticides and agents preventing the metamorphosis of insects.

At the beginning of 1969 a very interesting paper was published by Wigglesworth[24] in which he quotes the results of tests of 42 compounds on *Rhodnius prolixus*. All eight isomers of the juvenile hormone (Table 1) and the most active synthetic and natural substances were tested for the first time under identical conditions. Most of the specimens tested by Wigglesworth were obtained from the Hoffman-La Roche Company. Many specimens have not been described in the literature. Table 2 lists the most interesting compounds. Using earlier data[79-81] and the results of his own investigations, Wigglesworth[24] formulated the following postulates.

1. A definite length and shape of the molecule is necessary for juvenile-hormonal activity. Substituents at the 2,3- and 6,7-double bonds must have the *trans*-configuration.

2. The balance between the lipophilic and hydrophilic groups in the molecule is significantly reflected in its juvenile-hormonal activity. Marked hydrophilic properties due to the presence of groups such as hydroxyls and carboxyls or, conversely, unduly lipophilic properties of the molecule lead to a decrease or disappearance of activity. The small differences in the structure of membranes in different insect species account for the significant difference in their sensitivity to juvenile hormone preparations.

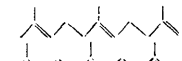
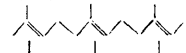
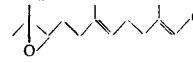
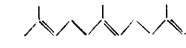
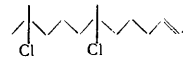
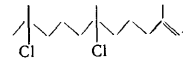
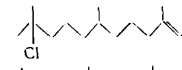
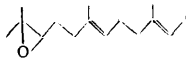
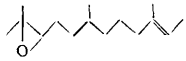
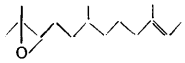
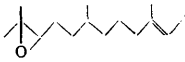
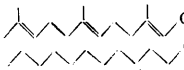
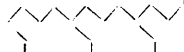
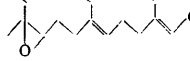
3. Substances which are most active on local application are also active when injected. There are, however, exceptions. The physical properties of the cuticle (the external skeleton of insects) and the amount of lipids in the haemolymph influence the penetration of the hormone and are responsible for the specific differences in sensitivity.

4. The differences in geometrical form and possibly in physical properties (for example, the proportions of the polar and non-polar groups in the molecule) appear to be more important for juvenile-hormonal activity than the presence of specific chemical groups.

5. In an early paper Schmialek[47] pointed out that an important factor influencing juvenile-hormonal activity is

the ease with which a given hormonal preparation breaks down in the insect organism. This, for example, explains the higher activity of farnesyl methyl ether compared with farnesol.

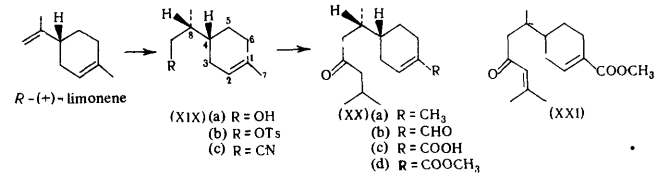
Table 2. Juvenile-hormonal activities of farnesol derivatives.

Compound	Structural formula	Activity, μg/g of insect wt.
Farnesol		45.0
Farnesyl methyl ether		0.6
10,11-Epoxyfarnesyl methyl ether		0.9
Farnesylic acid		90.0
Law's mixture		2.7
Dihydrochloride of methyl ester of farnesylic acid		2.2
Dihydrochloride of ethyl ester of farnesylic acid		0.5
Ethyl 11-chloro-3,7,11-trimethyldodeca-2-enoate		1.8
Ethyl ester of 10,11-epoxyfarnesylic acid		2.2
10,11-Epoxy-3,7,11-trimethyldodec-2-enoic amide		90.0
10,11-Epoxy-3,7,11-trimethyldodec-2-enoic *NN*-diethylamide		9.0
Ethyl 10,11-epoxy-3,7,11-trimethyldodec-2-enoate		0.5
Farnesyldiethylamine		1.8
Dodecyl methyl ether		250.0
Synthetic juvenile hormone		0.18

2. Juvabione and Its Analogues

In 1965 Sláma and Williams[99] accidently observed that the larvae of the bug *Pyrrhocoris apterus* undergo additional moulting on coming into contact with paper of American origin. Since such changes are caused only by the juvenile hormone[100], experiments were performed to isolate the active substance called the "paper factor"[99,101,102]. Bowers showed that the "paper factor" is present in the wood of the balsam fir *Abies balsamea*, which is used as the principal new material for the manufacture of paper pulp in Canada and the Northern USA. Further studies led to the determination in the structure of the "paper factor"[103]. It proved to be the methyl ester of the known todomatuic acid isolated by Japanese chemists from sulphite liquors, and was given the trivial name juvabione (XXd). Another active monocyclic sesquiterpene—dehydrojuvabione (XXI)—was isolated by Sorm and coworkers[104] from a fir native to Czechoslovakia.

Juvabione and dehydrojuvabione act selectively on bugs of the family *Pyrrhocoridae* and are inactive in tests on other insects[24,99,101,104]. Recently the absolute configuration of juvabione was established. Earlier Japanese investigators believed that both asymmetric centres of the (+)-todomatuic acid have the *R*-configuration[105]. The conversion of *R*-(+)-limonene into (+)-todomatuic acid (XXc) and (+)-juvabione (XXd), identical with the natural compounds, was achieved in 1968.[106]

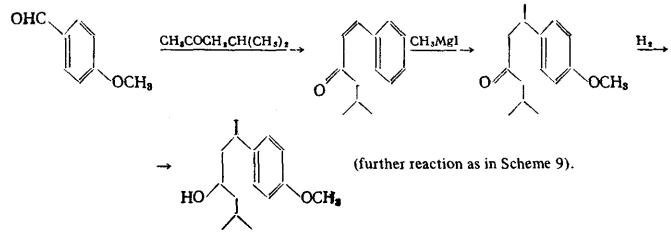


The unsaturated alcohol (XIXa) was obtained by the hydroboration and oxidation of natural limonene with subsequent separation of the 3,5-dinitrobenzoates of the epimeric alcohols. Initially the configuration of compound (XIXa) was established incorrectly. Subsequently X-ray diffraction analysis of the *p*-iodobenzoate of the alcohol (XIXa) showed that the (+)-todomatuic acid and (+)-juvabione obtained by the authors have the 4(*R*),8(*S*)-configuration of the asymmetric centres[107].

The first synthesis of (±)-juvabione was achieved by a 15-stage procedure starting with *p*-methoxyacetophenone (Scheme 9). All the stages take place with high yields; the overall yield of the mixture of the diastereoisomers of todomatuic acid was 6.8%. The diastereoisomers were separated by the crystallisation of the semicarbazones[108,109].

Tests of the biological activities of the compounds obtained on *Pyrrhocoris apterus* showed that the synthetic (±)-juvabione is less active by a factor of approximately 2 than the natural (±)-juvabione (XXd). The methyl ester of (±)-epitodomatuic acid is even less active.

A mixture of (±)-juvabione diastereoisomers was obtained by Indian investigators by a similar procedure, differing only in the first stages[110]:

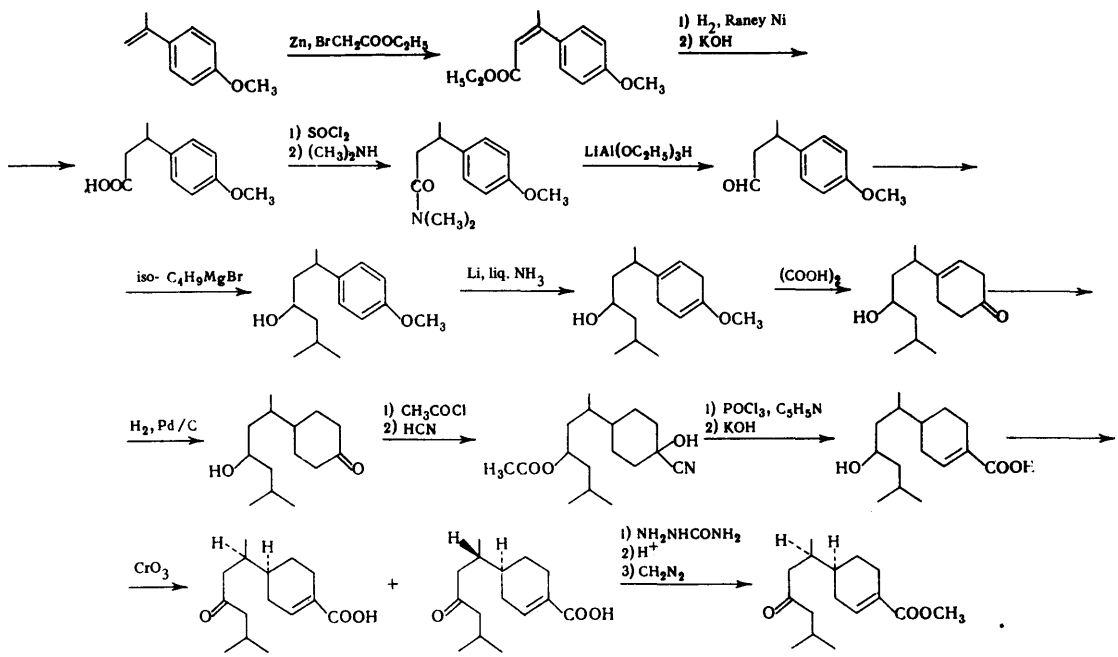


The diastereoisomers could not be separated by thin-layer or gas–liquid chromatography, as had been noted also by Japanese chemists[109].

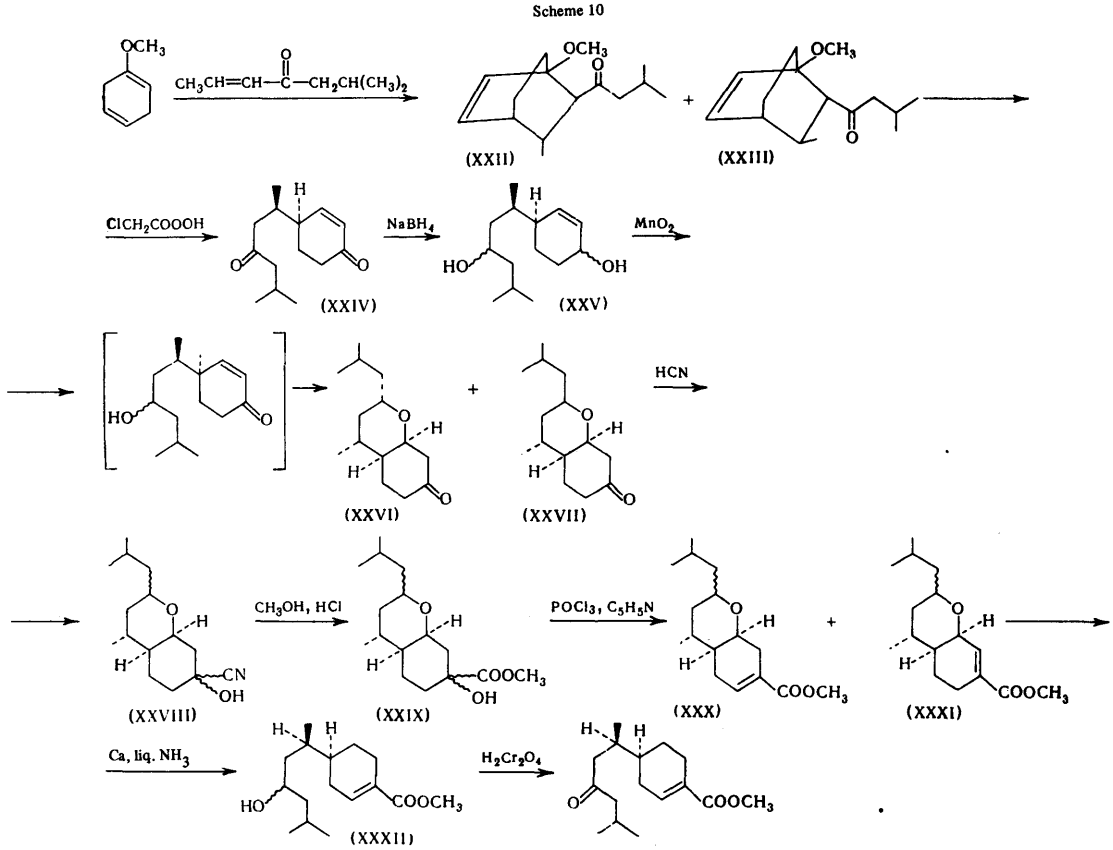
Birch et al.[111] developed a novel stereospecific synthesis (±)-juvabione (Scheme 10). Diels–Alder condensation of 1-methoxycyclohexa-1,4-diene with *trans*-6-methylhept-2-en-4-one gave a 75–80% yield of the adducts (XXII) and (XXIII) in proportions of 1 : 1. The rigid cyclic system and the different positions of the carbonyl group and the double bond ensure sufficient differences in the properties of the isomers to allow their separation on a fractionating column. Oxidation of the isomer (XXII) with chloroperacetic acid gave the diketone (XXIV), which was reduced with sodium borohydride to a mixture of stereoisomeric diols.

Oxidation of (XXV) with manganese dioxide gives a 5 : 1 mixture of the ketoesters (XXVI) and (XXVII), which were separated by chromatography on silica gel. The PMR spectra of both isomers indicate a *cis*-fusion of the rings,

Scheme 9

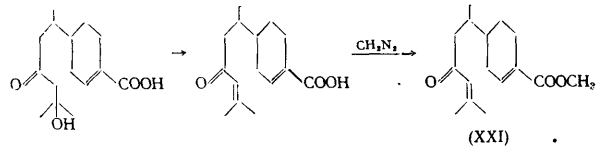


Scheme 10



i.e., they differ in the configuration of the side chain. Although both isomers can be converted into juvabione, only the isomer present in a larger amount was used in the preparation of the cyanohydrin (XXVIII). (XXVIII) was converted in the usual way into the hydroxyether (XXIX), the dehydration of which with phosphorus oxychloride in pyridine led to the formation of a 2 : 1 mixture of the unsaturated esters (XXX) and (XXXI), which were separated by chromatography on silica gel. Cleavage with calcium in liquid ammonia leads to the hydroxyester (XXXII), which is oxidised by chromic acid to (±)-juvabione.

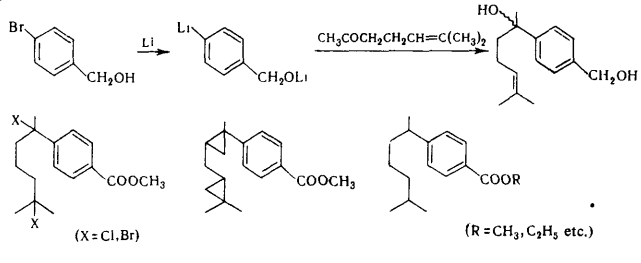
A non-stereospecific synthesis may be achieved by reduction of the double bond in (XXIV) followed by a selective reaction of the diketone with HCN and subsequent conversion of the cyanohydrin into an $\alpha\beta$-unsaturated ester. The authors of the first synthesis of (±)-juvabione obtained also dehydrojuvabione as a mixture of (±)-dihydrojuvabione and its stereoisomer. The method of synthesis resembles in many ways that of juvabione. The double bond conjugated with the carbonyl group was formed in the last stages by dehydration of the unsaturated hydroxyacid[112]:



(XXI)

Juvabione and dehydrojuvabione, which act selectively on different insect species, are active only when employed in microgramme amounts, while the juvenile hormone and some of its synthetic analogues suppress metamorphosis in amounts of 0.001–0.0001 μg. In search for more effective selective hormonal insecticides, Czechoslovak investigators[18] synthesised a series of aromatic analogues of juvabione. The specific effect of these compounds on bugs of the family *Pyrrhocoridae* is maintained[19,95].

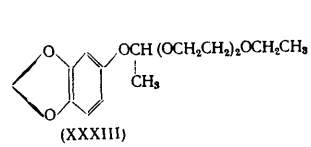
The compounds obtained were patented, since some of them are 100 times more active than juvabione[113]. Moreover, they are comparatively readily available. The key stage in the synthesis is the condensation of the lithium derivative of benzyl alcohol with 6-methylhept-5-en-2-one. The subsequent reactions yielded a number of analogues of juvabione which were tested on two species of the family *Pyrrhocoridae*:



The observed differences in sensitivity show that the preparations may be specific even within a single family.

3. Synergists

Synergists for insecticides such as pyrethrines or carbamates have found wide application in practice. In his attempt to employ the JH-active 10,11-epoxyfarnesyl methyl ether together with synergists, Bowers[114] observed that some of them exhibit a distinctive juvenile-hormonal activity. The experiments were performed on pupae of the flour beetle *Tenebrio amolitor* and larvae of the bug *Oncopeltus fasciatus*. The synthetic synergists sesoxane (XXXIII) (in doses up to 0.5 μg) and Niagara 16388 (XXXIV) show the highest activity. The remaining synthetic and natural synergistic agents (sesamin and sesamolin) are inactive or weakly active:



(XXXIII) (XXXIV)

Bowers showed that sesoxane acts similarly to other substances with juvenile-hormonal activity and not by activating the corpora allata.

At present the juvenile hormone and its analogues are being very intensively investigated. There is no doubt about the theoretical value of such studies. Certain important problems, in particular the determination of the mechanism of the action and of the biosynthesis of the juvenile hormone will probably be elucidated in the near future. Possibly a more rigorous correlation will be established between the structure and physiological activity of the compounds. The prospects for practical application of compounds with juvenile-hormonal activity as a "third generation" of chemical pesticides are very good and therefore further development of studies in this field is to be expected.

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During the preparation of the review for the press, a number of studies on the synthesis of the juvenile hormone[115–118] and substances with juvenile-hormonal activity were published[119–123]. The work of Czechoslovak investigators on tests of compounds of the farnesyl series on *Galleria mellonella* is noteworthy[124].

Studies on the mechanism of action[125,126] and the effect of JH-active substances on the metamorphosis[127,128], ovogenesis[129], and metabolism[130] of insects are being continued.

Bowers' report on the preparation of methylenedioxyphenyl ethers, some of which showed an activity higher than that of the juvenile hormone when tested on the beetle *Tenebrio molitor* and the bug *Oncopeltus fasciatus*, is extremely interesting[131]. The sterilising effect of JH-active substances on introduction into insect males is noteworthy[92,132].

The publication of two reviews on insect hormones[133,134] should be noted.

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