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Some juvenile hormone analogues

F. ŠORM

How did we, workers of the Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Science, Prague, get acquainted with juvenile hormones? It was thanks to the Czech entomologist, Dr. Karel Sláma. During his stay in the institute of Professor Williams in the USA, Dr. Sláma participated significantly in the discovery of the so-called paper factor, the extractive component of Canadian fir, exhibiting a high juvenile hormone activity. Dr. Sláma also performed numerous experiments with the so-called Williams' solution, obtained by the action of hydrogen chloride on the methanolic solution of farnesoic acid. This solution also showed a high activity on some insect species. After the return of Dr. Sláma to Czechoslovakia, we started some experiments with derivatives of farnesoic acid and in this connection prepared methyl farnesoate dihydrochloride which showed an extraordinary activity on the hemipterans of the family Pyrrhocoridae. We have also investigated the active component of the previously mentioned paper factor with the use of extracts prepared from firs of Slovak origin. Independently of Bowers and co-workers, we have isolated juvabione and an additional highly active substance, dehydrojuvabione.

The earlier tests of Dr. Sláma were performed on the hemipterans *Pyrrhocoris* and *Dysdercus* with the use of our first juvenile hormone analogue which were considerably active on this insect species. Since then, however, it has been found that *Pyrrhocoris* and *Dysdercus* are particularly less sensitive to structural changes in several fundamental analogue types. This finding is very interesting from the theoretical point of view, but rather less so in connection with practice since the hemipterans mentioned do not belong to important pests.

Formulae in Figure 1, though familiar to my readers, are shown to illustrate the structures which served as starting points for the synthesis of most juvenile hormone analogues hitherto prepared in our Institute. After the

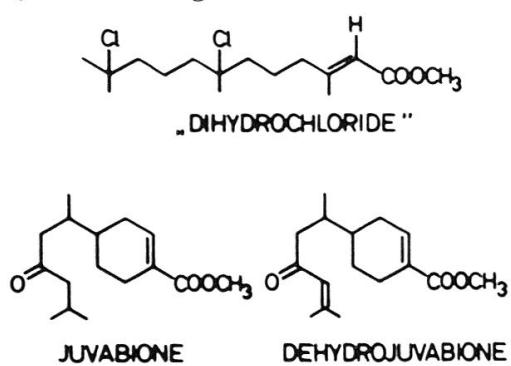


Fig. 1

discovery of the naturally occurring juvenile hormone and determination of its structure, we have also prepared some related compounds. The main purpose of our work was to prepare technically accessible substances which would be satisfactorily active and which could be used in practice in the control of insect pests. At the same time we were interested in relations between the chemical structure of our substances and their biological activity on some typical insect species, particularly the insect pests. For this reason, my lecture does not report on multistep complex syntheses but on simple and readily accessible compounds.

The substances prepared in this direction, may be divided into two groups, namely, into substances of the aromatic nature and of the aliphatic nature.

Preparations of substances of the first type are connected with the synthesis of the aromatic juvabione analogue, particularly a compound containing two tertiary chloro atoms. The latter compound exhibited — in contrast to juvabione — considerably high activity especially on the hemipteran *Dysdercus cingulatus* (Fig. 2). The activity is expressed in unit values which indicate that amount of the test substance in micrograms per specimen which causes formation of adultoids, that is half-larval, half-adult intermediates.

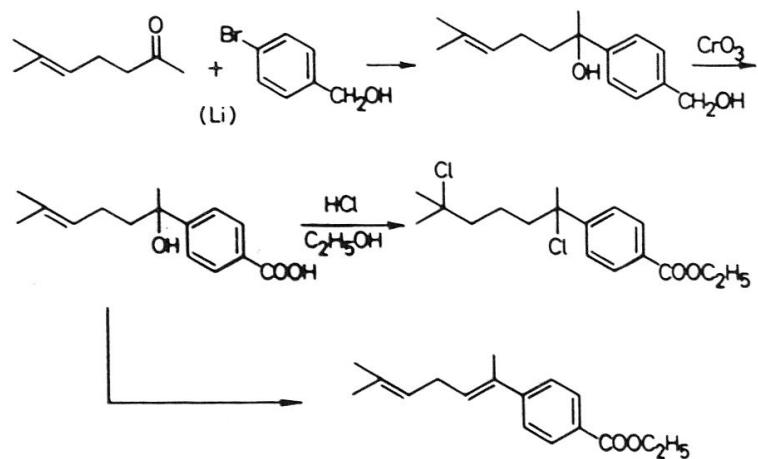


Fig. 2

The synthesis of the latter substance is not difficult and several other approaches are possible. Notwithstanding, we prepared some additional, more accessible analogues, in particular some benzoic acid derivatives substituted at the *para* position by a monoterpenoid residue. When our experiments were in progress, a paper of Bowers and co-workers appeared, reporting on an activity of the ethers of *p*-hydroxybenzoic acid and geraniol, especially the corresponding monoepoxide, on *Tenebrio* and the hemipteran *Oncopeltus* (Lygaeidae). In our own independent tests, the latter compound was found to exhibit a considerably high activity on some hemipterans, especially on the relatively

resistant pentatomid bug, *Graphosoma italicum*, which fact is of special interest. We have also prepared another compound with a side chain two carbon atoms shorter, which, in our opinion, was more similar to the aromatic juvabione type. The latter compound exhibited increased activity on Lygaeidae, while the activity on the other hemipterans, including *Graphosoma*, was considerably decreased (Fig. 3).

Substance	Pyr	Dys	Lygae	Gra	Ten
	0.05	0.05	0.05	0.01	100
	1	0.3	<u>0.01</u>	0.3	1000
	5	1	5	10	>1000
	0.8	0.3	-	-	-
	0.3	0.05	-	-	-

JH Activity in μg

Fig. 3

Interesting results were obtained with some p-aminobenzoic acid derivatives which were active on several, otherwise resistant insect species. The way of preparing these substances is shown in Figure 4. Special attention is merited by the high activity of monogeranyl and digeranyl derivatives of methyl p-aminobenzoate on the great hemipteran *Triatoma infestans* which transfers the pandemic Chagas disease, known in South America. The high biological activity of the methyl ester is

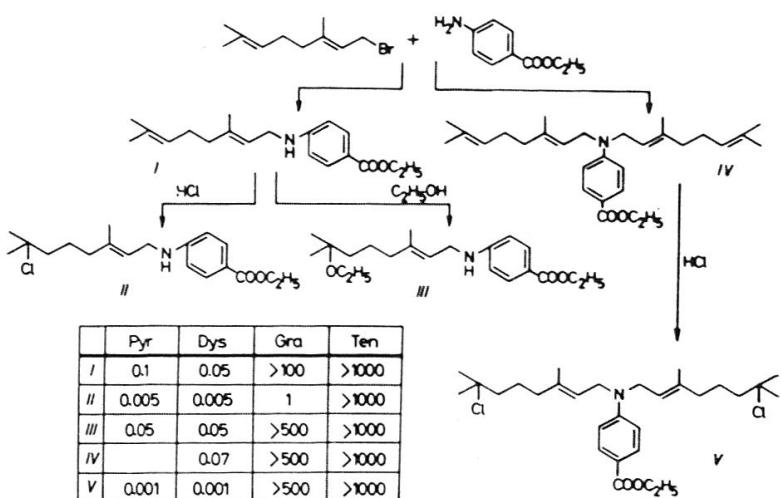
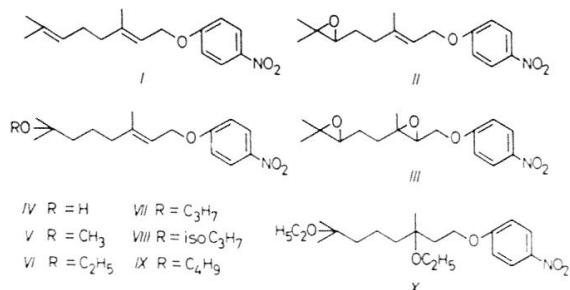


Fig. 4

remarkable while the ethyl ester is almost inactive. This finding might be explained by the presence of specific esterases in insects which attack the ester bond of the ethyl ester. The free amino acid is known to be quite inactive.

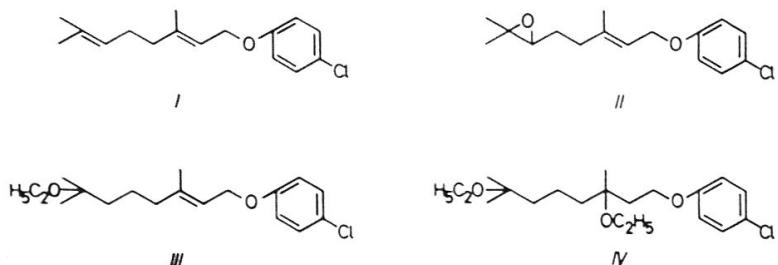
Since our preparations of p-aminobenzoic acid derivatives are relatively stable, we have entered into contact with the World Health Organization regarding the potential use of these derivatives on *Triatoma*.



	Pyr	Dys	Gra	Ten
I	3	5	0.8	30
II	1	1	0.07	5
III	1	0.1	300	>500
IV	0.5	0.5	1	5
V	0.07	0.1	0.5	3
VI	0.1	0.08	0.5	0.005
VII	5	4	5	0.005
VIII	3	0.5	30	100
IX	7	3	10	100-500
X	>100	>100	>500	>500

Fig. 5

however, in view of the remarkable juvenile hormone activity of p-halophenyl ethers on some insect species. Structures and activities of this type of compounds are shown in Figures 5 and 6.



	Pyr	Dys	Gra	Ten
I	50	10	5	7
II	5	4	0.07	0.5
III	0.5	0.5	0.5	0.001
IV	500	500	>500	(~5)

Fig. 6

Numerous p-nitroaniline and sulfanilic acid derivatives were also prepared but none of them showed any remarkable biological activity.

An interesting and completely new group of substances possessing juvenile hormone activity is represented by p-aminobenzoic acid derivatives containing the peptidic bond. The detailed investigations within this group were initiated by the relatively high activity of L-isoleucyl-L-alanyl-p-aminobenzoate (prepared for the first time in our Institute) on the hemipterans *Pyrrhocoris apterus* and *Dysdercus cingulatus*. We have prepared, and protected by patent applications, numerous analogues of the parent compound. The method of preparation is shown in Figure 7.

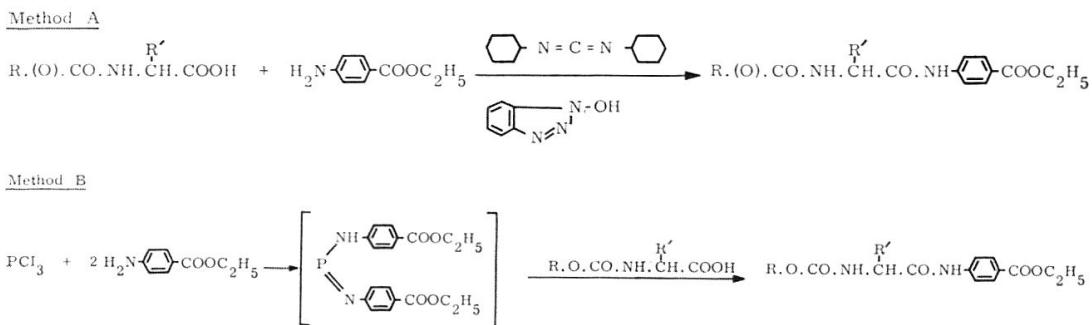


Fig. 7

In particular, the derivatives with a protected terminal amino group exhibit a surprisingly high activity, though exclusively on the hemipterans mentioned. Furthermore, the activity of peptide derivatives strongly depends on the optical configuration of the amino acid moiety. Derivatives containing glycine or D-alanine are almost inactive in contrast to those containing the amino acids of the L-configuration (Fig. 8). On the other hand, the optical isomers of juvabione prepared in the laboratories of Hoffmann-La Roche did not show any remarkable difference in their biological activities, as observed in the tests of Dr. Sláma (Fig. 9). These findings require some explanation. Experiments in this direction are in progress.

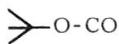
At this point, we may finish our survey of aromatic juvenile hormone analogues. Next, compounds of the aliphatic type will be discussed.

The model substance of this group is represented by the previously mentioned methyl farnesoate dihydrochloride. It is found that this compound is much more active in the form of the transisomer as regards the geometry of the double bond in conjugation with the carboxylic group. Like other laboratories, we have prepared numerous compounds of this type and observed that the activity on different insect species is dependent on the structural changes. These facts have been generally known. It is interesting, however, that the presence of two chlorine atoms in the molecule causes high activity for the hemipterans, whereas the activity on *Tenebrio* beetle is substantially lower than that of the

Compound	Method	Biological activity	
		Pyrrhocoris apterus	Dysdercus cingulatus
Boc-L-Ala-NH  COOC ₂ H ₅	A	0.1	0.5
Boc-L-Pro-NH  COOC ₂ H ₅	A	0.1	0.08
Boc-L-Ile-NH  COOC ₂ H ₅	A	0.05	0.01
L-Ile-L-Ala-NH  COOC ₂ H ₅		0.1	0.5
Boc-Gly-NH  COOC ₂ H ₅	A	500	500
Boc-Sar-NH  COOC ₂ H ₅	B	300	in
Boc-D-Ala-NH  COOC ₂ H ₅	A	300	500
Boc-D-Pro-NH  COOC ₂ H ₅	B	500	500

The values indicate a unit of juvenile hormone activity, expressed in μg of the compound per specimen which causes, by topical application in acetone, formation of half-larval, half-adult intermediates.

Fig. 8

Boc = 

Optical isomers of synthetic juvabione

	Pyr	Dys
(+)-juvabione	3	0.5
(\pm)-juvabione	1	0.4
(-)-juvabione	3	0.6
(+)-epijuabione	1	0.08
(-)-epijuabione	8	1

Fig. 9

monochloro derivatives containing only the conjugated double bond (Fig. 10). On the other hand, replacement of the ester function by the diethylamide group results in an opposite effect, i.e. an increase of the activity for *Tenebrio* and *Dermestes* and its loss for the hemipterans. The halogen or epoxide containing amides exhibits the highest activity on beetles of all compounds we have tested so far.

The quaternary carbon substituted chloro atom is known to be considerably unstable. For this reason, it was replaced in our analogues by the sterically similar methyl group. The choice of analogues and methods has been made in cooperation with Zoecon (Dr. Siddall). In our Institute, we used for the preparation of the analogues mentioned a combination of Kolbe syntheses. This route (Fig. 11) has

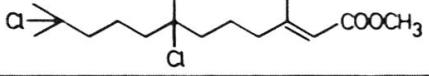
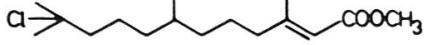
	Ten	Pyr
	~500	0.001
	1	0.05
	0.0005	5

Fig. 10

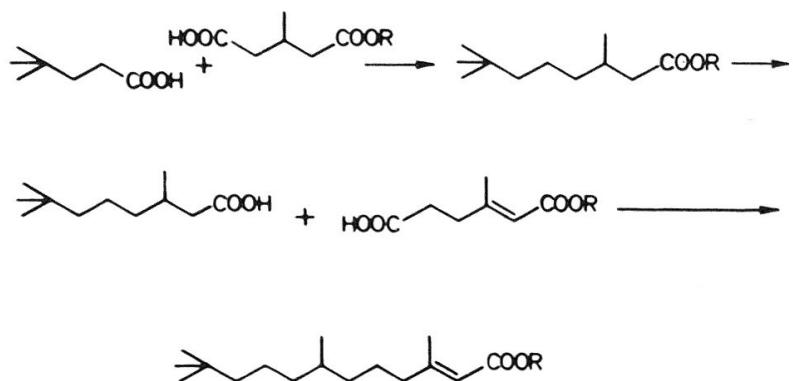


Fig. 11

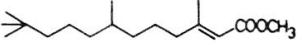
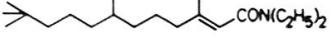
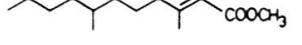
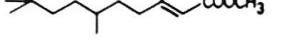
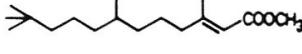
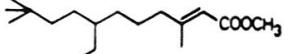
	Pyr	Ten	Gal
	1	1	20
	50	100	~1000
	1	5	<u>0.5</u>
	500	>1000	>10000
	0.1	8	10
	0.1	10	-

Fig. 12

been successfully used by us in the preparation of similar compounds where additional methyl has replaced the chlorine atom. Compounds obtained in this manner were slightly less active than the chlorine-containing substances. Nevertheless, their activity was remarkable and relatively less specific. Surprisingly, the above-mentioned replacement of the ester group by the diethylamide group in compounds of this type did not result in an enormous activity increase for *Tenebrio*, as obtained with halogen-containing analogues (Fig. 12). This finding indicates an existence of remarkable mutual interrelationships between different parts of the molecule and juvenile activity. We have also prepared compounds containing quaternary carbon atoms and shortened carbon chains. Thus, compounds containing in the chain one carbon atom less than the parent substances are almost equally active (even more active in *Galleria*) while the compounds containing two carbon atoms less (each in a different isoprene unit) are completely inactive, although the steric arrangement remains unchanged.

In connection with the replacement of chloro atoms by methyl groups we have also prepared some analogues of farnesoic acid bearing, vice versa, chlorine atoms instead of the methyl groups. Compounds of this type, however, are not very active. Moreover, the compound with the chloro atom at position 3 is, as expected, rather unstable (Fig. 13).

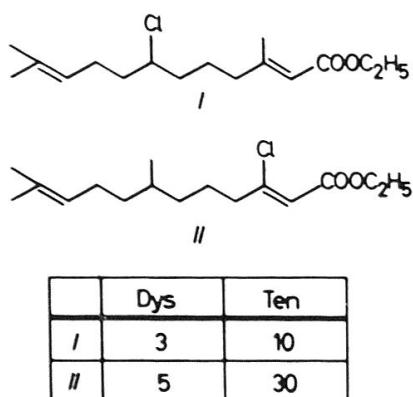


Fig. 13

With the aim of preparing synthetically readily accessible analogues, we are interested at the present time in compounds of the farnesoic acid or juvenile hormone type in which one or more carbon atoms of the aliphatic chain are replaced by heteroatoms, especially by oxygen. Various synthetic approaches may be used. I should like to mention the preparation of compounds carrying one oxygen atom in the central isoprene unit of the farnesoic acid molecule. The simplest route — namely, the reaction of bromosenecic acid and the corresponding alcohols — did not, as expected, produce satisfactory results. For this reason, we have used another route, shown in Figure 14. A list of

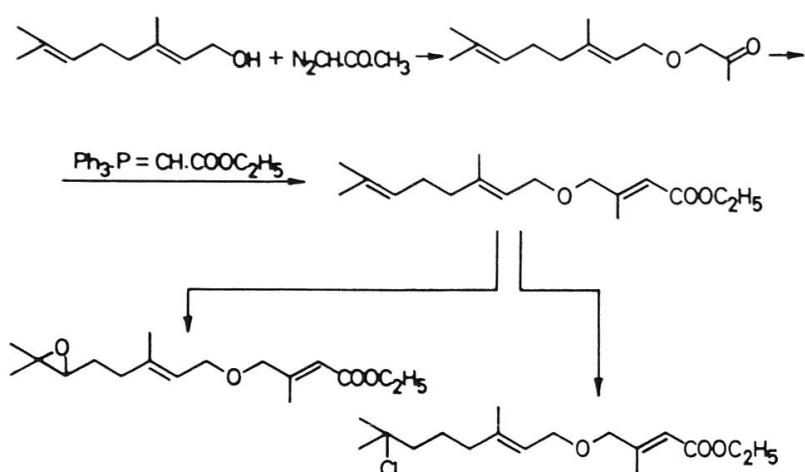
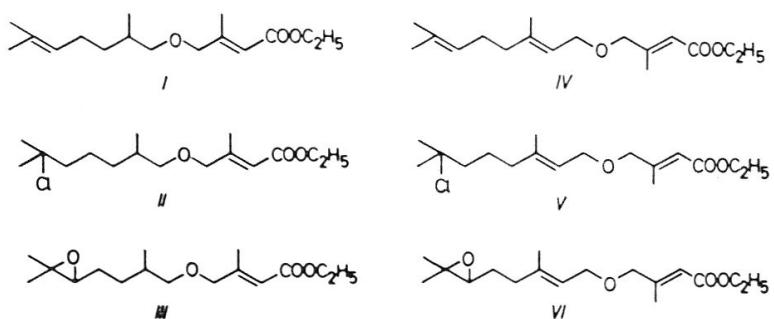


Fig. 14

these compounds and their activity on some insect species is shown in Figure 15. It may be seen that analogues structurally related to farnesoic acid, i.e. compounds possessing the same number of links in the basic carbon chain, are almost as active as the parent substances. Compounds containing one link more in the central isoprene unit, i.e. geraniol and citronellol ethers, are somewhat less active but their activity is still high enough. In contrast to farnesoic acid derivatives, their activity on beetles (*Tenebrio molitor*) does not increase when the ester function is replaced by the diethylamide group. This finding indicates again that the activity of juvenile hormone analogues depends on several structural features of the whole molecule and their mutual interference. Moreover, other variations of the aliphatic-ethereal type



	Pyr	Dys	Gra
I	0.8	0.1	8
II	0.005	0.008	5
III	0.01	0.005	0.1
IV	5	1	1
V	0.08	0.05	50
VI	1	0.3	0.8

Fig. 15

of juvenile analogues are possible. In this connection, numerous compounds have been prepared in our Institute with the use of methods suitable for large-scale production.

It may be seen from our syntheses of juvenile hormone analogues and the corresponding activity tests that a vast field of action is still open to the imagination of organic chemists. Numerous compounds structurally very remote from the juvenile hormone (let us mention our peptides derived from p-aminobenzoic acid) exhibit not only a high biological activity but in many cases are also strictly specific.

As to the practical use of juvenile hormone analogues in insect control, the organic chemists are expected to prepare highly active, specific, and sufficiently stable substances while the entomologists have to determine a suitable and economical application. In this connection, I should like to mention our experience in a field test carried out this summer in Bulgaria.

The field tests were performed on the serious grain pest, *Eurygaster intergriceps*, the hemipteran of the family Pentatomidae, with the use of one of our juvenile hormone analogues, nitrophenyl 6,7-epoxygeranyl ether, the activity of which was determined previously; in the laboratory, half adultoids were formed with the topical application of 0.05 microgram per specimen. Selected test areas of wheat fields were sprayed with oil solutions of the test substance in the concentration of 500 grams to 0.5 gram per hectare. The adult larvae were collected at various intervals after contamination, kept in isolators, and evaluated. It has been found during the molting that the test substance is highly active, causing the formation of deformed specimens even in low concentrations, but that the activity is limited to a very short period after application. As shown by this test, the practice will require substances stable under atmospherical conditions, that is against light, temperature, moisture, or the like.

In concluding this lecture on the research of juvenile hormone in our Institute and in the Entomological Institute, Czechoslovak Academy of Sciences, Prague, I should like to mention those who have contributed to the development of the subject, the chemists Dr. Romanuk, Dr. Jarolím, Dr. Hejno, Dr. Beran, Dr. Arnold, and Mrs. Kahovcová, and the entomologists Dr. Sláma and Dr. Sehnal. Thank you.

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