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# Compounds related to insect juvenile hormones

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This paper is a review of the synthetic work done by our group in the Pesticide Chemicals Research Branch. Following the publication by Röller and coworkers [1] of the structure of the $C_{18}$-Cecropia JH, we carried out a convenient non-stereoselective synthesis of this compound [2]. We then decided to direct our efforts to preparing minor modifications of the JH structure to find out what structural features are necessary for activity.

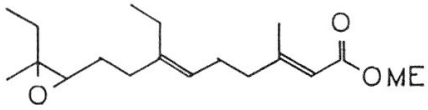
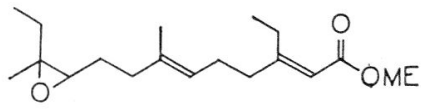
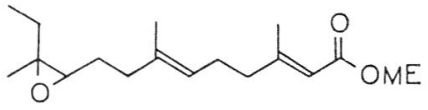
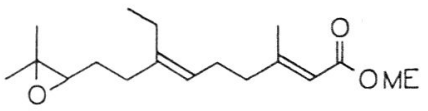
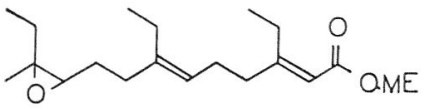
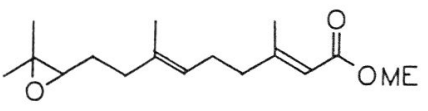
| | Activity (µg/Tenebrio) |
|---|---|
|  | 0.03 |
|  | 0.3 |
|  | 0.3 |
|  | 0.1 |
|  | 0.3 |
|  | 0.06 |

Table 1

The effect of ethyl branching on the methyl juvenate skeleton was first investigated. Table 1 shows the results of this study on the yellow mealworm, *Tenebrio molitor* (L) [3]. We concluded from this study that

the increased effect of ethyl branching on JH activity was of the order of ten [4]. We felt that this increase of activity did not warrant the additional work required for the preparation of ethyl-branched compounds for routine screening. Accordingly, the compounds reported in the remainder of this paper are normal isoprenoid derivatives.

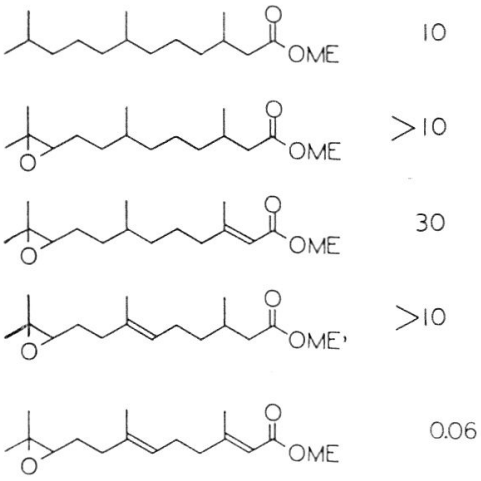
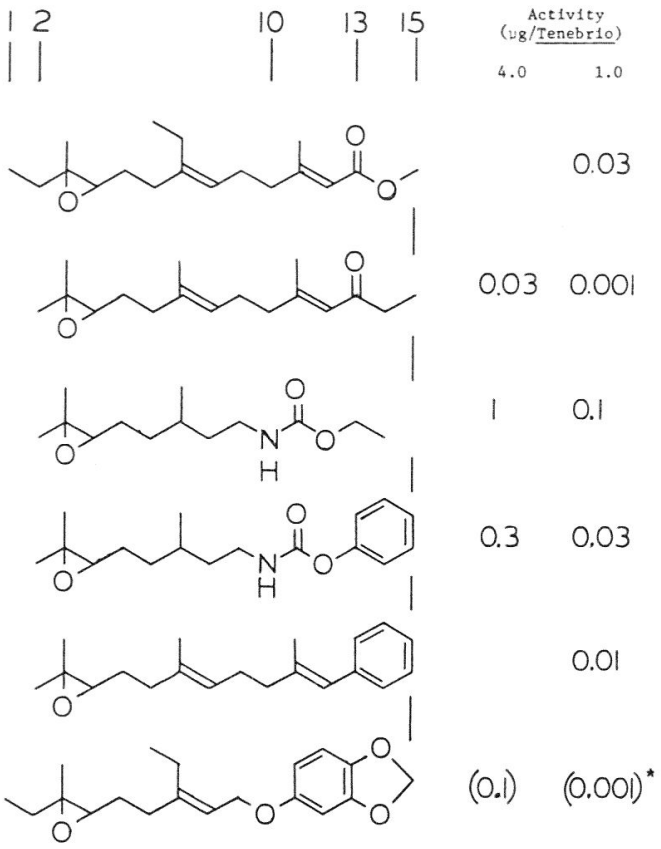



Table 2

Next, we systematically eliminated double bonds and/or the epoxide group from methyl juvenate [5]. We found that such manipulation of the molecule reduced JH activity by a factor of 100 in *Tenebrio*. Several such compounds are listed in Table 2. On *Rhodnius*, however, ethyl 6,7-dihydrojuvenate was reported by Wigglesworth [6] to be one of the two most active compounds tested. It was four times as active as ethyl juvenate, which can be explained only by species specificity. Not so easily explained are the data reported very recently by Zaoral and Slama [7], who found that methyl 6,7,10,11-tetrahydrofarnesate was ten times as active as methyl farnesate on *Tenebrio*. At present, we cannot account for this discrepancy.

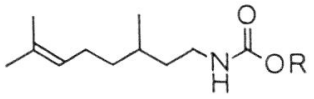
Our next efforts were directed at discovering new types of compounds with high JH activity. Of the many compounds tested, those with the highest activity on *Tenebrio* are listed in Table 3. The $C_{18}$-*Cecropia* JH and the methylenedioxyphenyl derivative are included for the purpose of comparison. The numbers across the top represent the "chain length" of the molecules. The importance of chain length in JH active compounds has been pointed out before [4, 6, 8, 9] and is again demonstrated here. When the epoxy groups are lined up, as in Table 3, every compound, except one, has a "chain length" of 15. The shape of the molecule was also considered to be important by Wigglesworth [6], and was one of the factors leading him to propose that JH may be interacting with membranes. Unfortunately, three of the compounds in Table 3 have bulky phenyl rings, seemingly contradicting that por-




* W. S. Bowers, Science 164, 323 (1969).

Table 3

tion of Wigglesworth's argument [10]. Among specific compounds, the higher activity of the ethyl ketone over the $C_{18}$-*Cecropia* JH is particularly interesting in view of the earlier disclosure at this Symposium by Dr. Siddall that the two metabolites of the $C_{18}$-*Cecropia* JH which had been identified were the corresponding acid and the acid diol (formed by epoxide ring opening). The ketone, of course, would not be expected to degrade this way. The two carbamates listed are derivatives of citronellylamine rather than geranylamine. In these cases, the absence of the central double bond does not make much difference in JH activity on *Tenebrio* [11, 12]. Propyl and propargyl citronellylcarbamates were also prepared to bring the "chain lengths" up to 15 but these compounds were less active than ethyl citronellylcarbamate. As an extension of our discovery of the high activity of phenyl citronellylcarbamate a number of substituted phenylcarbamates were prepared to study electronic effects on JH activity [13]. As shown in Table 4, any substitution, from the highly electronegative nitro group to the strongly electron-donating alkoxy groups, on the phenyl ring reduced activity.



| R | Activity 1.0 (µg/Tenebrio) | R | Activity 1.0 (µg/Tenebrio) |
|---|---|---|---|
| Phenyl | 0.03 | Phenyl, 4-chloro | 10 |
| Phenyl, 2-methyl | 1 | Phenyl, 2,4-dichloro | 10 |
| Phenyl, 3-methyl | 1 | Phenyl, 4-bromo | 1 |
| Phenyl, 4-methyl | 1 | Phenyl, 2-methoxy | 10 |
| Phenyl, 2,3-dimethyl | > 10 | Phenyl, 3-methoxy | 10 |
| Phenyl, 3,4-dimethyl | > 10 | Phenyl, 4-methoxy | 10 |
| Phenyl, 2,4-dimethyl | 1 | Phenyl, 4-benzyloxy | > 10 |
| Phenyl, 2,5-dimethyl | > 10 | Phenyl, 2,6-dimethoxy | 10 |
| Phenyl, 3-ethyl | 10 | Phenyl, 3,4-methylenedioxy | 1 |
| Phenyl, 4-ethyl | 1 | Phenyl, 3-acetyl | 10 |
| Phenyl, 4-isopropyl | > 10 | Phenyl, 4-acetyl | 10 |
| Phenyl, 2,6-diisopropyl | > 10 | Phenyl, 4-propionyl | 5 |
| Phenyl, 4-tert-butyl | > 10 | Phenyl, 4-nitro | 5 |
| Phenyl, 2-phenyl | > 10 | Benzyl | > 10 |
| Phenyl, 4-phenyl | > 10 | Benzyl, 9-chloro | > 10 |
| Phenyl, 2,3-benzo(1-naphthyl) | > 10 | Cyclopentyl | 1 |
| Phenyl, 3,4-benzo(2-naphthyl) | > 10 | Cyclohexyl, 4-acetyl | 10 |
| Phenyl, 2-chloro | 0.1 | | |
| Phenyl, 3-chloro | 5 | | |

Table 4

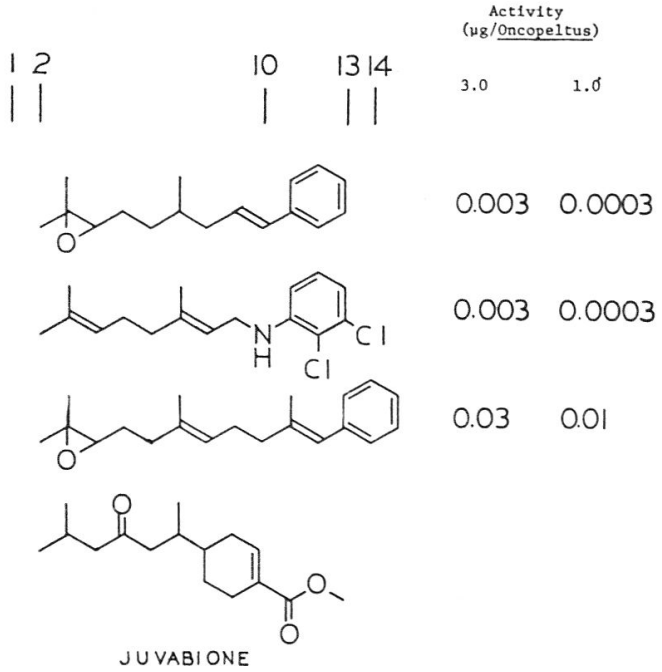
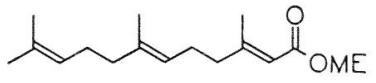
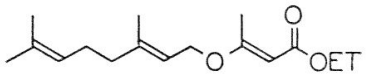
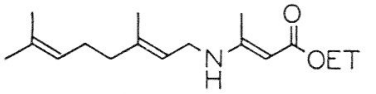
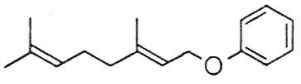
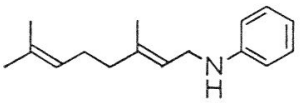
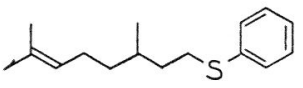



Table 5

Electronic effects, thus, are unimportant. What does seem to be important is that substitutions, at least at the *meta* or *para* positions, necessarily increase the chain length of the molecule beyond the optimum length of 15. In fact, methylenedioxy substitution, which increased the activity of phenyl geranyl ether so dramatically,[14] actually reduced activity in this case. On the other hand, the cyclopentyl ester, which is considered to be an isostere of, but otherwise quite dissimilar to, the phenyl ring, showed more activity than some simply substituted phenyl esters.

The compounds we prepared were also screened against the milkweed bug, *Oncopeltus fasciatus* (Dallas). Those compounds with the highest activity against this insect are listed in Table 5. Again, as in Table 3, the epoxy groups are lined up and occupy the 3,4-position. This time, juvabione is included for the purpose of comparison, since it was very active on another hemiptera, *Pyrrhocoris apterus*. When this is done, we find that these compounds, except for the less active third compound, have "chain lengths" of 13 or two carbons less than that of the ccmpounds found to be most active on *Tenebrio*. The

| | Activity (µg/Tenebrio) | |
|---|---|---|
| | 4.0 | 1.0 |
|  | 30 | 1 |
|  | 30 | 10 |
|  | 3 | 0.3 |
|  | Epoxide was inactive at 0.1* | |
|  | | 0.3 |
|  | | |

* W. S. Bowers, Science 164, 323 (1969).

Table 6

chlorine in the second compound replaces a hydrogen, and is therefore not considered. We seem to have here a species specificity based on the length of the molecule in addition to those based on "rigidity" [15] and functional groups.

Effects of heteroatoms on otherwise similar compounds are tabulated in Tables 6 and 7. No clear pattern emerges from these tables.

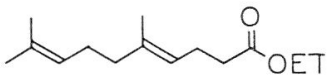
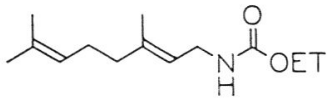
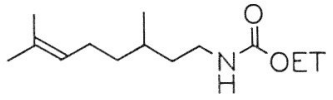
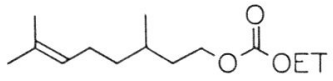
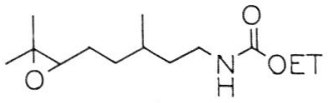
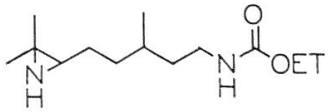
| | Activity (μg/Tenebrio) | |
|---|---|---|
| | 4.0 | 1.0 |
|  | | 300 |
|  | 10 | 3 |
|  | | 3 |
|  | | 300 |
|  | 1 | 0.1 |
|  | | 1 |

Table 7

In general, however, derivatives of citronellylamine or geranylamine were more active than derivatives of citronellol or geraniol, with the exception of methylenedioxyphenyl ethers.

The JH mimics presented thus far retained the geranyl or citronellyl (or their epoxides) moiety in their structures. We have seen that diverse functional groups on the other half of the molecule were capable of imparting high JH activity to the compounds. Listed in Table 8 are several compounds in which the epoxide end of methyl juvenate was modified. On *Tenebrio*, JH activity was greatly reduced [16].

Some compounds closely related to known JH mimics are listed in Table 9, along with two chemosterilant-type compounds. When one

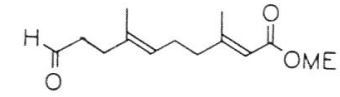
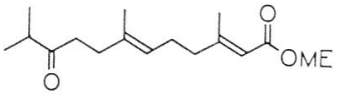
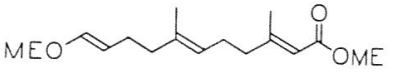
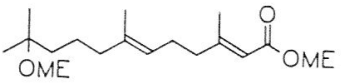
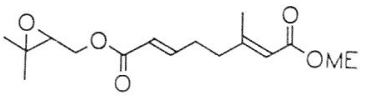
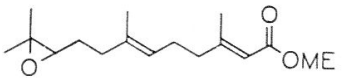
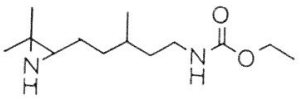
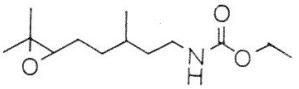
| | Activity 1.0 (µg/Tenebrio) |
|---|---|
|  | 10 |
|  | 25 |
|  | 10 |
|  | 15 |
|  | - |
|  | 0.06 |
|  | 1 |
|  | 0.1 |

Table 8

| | Activity 1.0 (µg/Tenebrio) |
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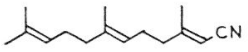
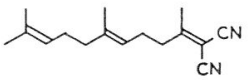
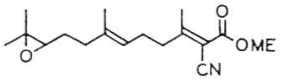
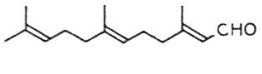
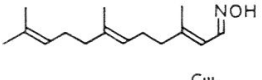
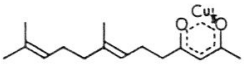
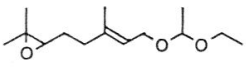
|  | 1 |
|  | 3 |
|  | 0.1 |
|  | 10 |
|  | 3 |
|  | 3 |
|  | 30 |

TEPA

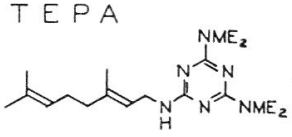
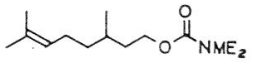
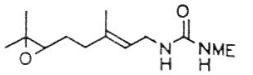
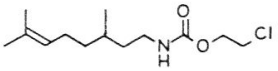
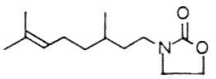
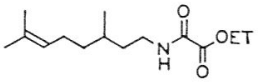
| | Activity 1.0 (µg/Tenebrio) |
|---|---|
|  | >300 |
|  | 300 |
|  | 0.3 |
|  | 3 |
|  | 10 |
|  | >300 |

Table 9

of these, TEPA (triethylenephosphoramide), was applied to a *Tenebrio* pupa, the insect molted into what appeared to be a second pupa. Closer examination, however, revealed the lack of gin traps or urogomphi. Since, the presence of these is the criterion for JH activity, TEPA is considered to be inactive. Adding geranyl side chains to TEPA or a chemosterilant of the triazine type removed this interesting effect and no JH activity was observed [17].

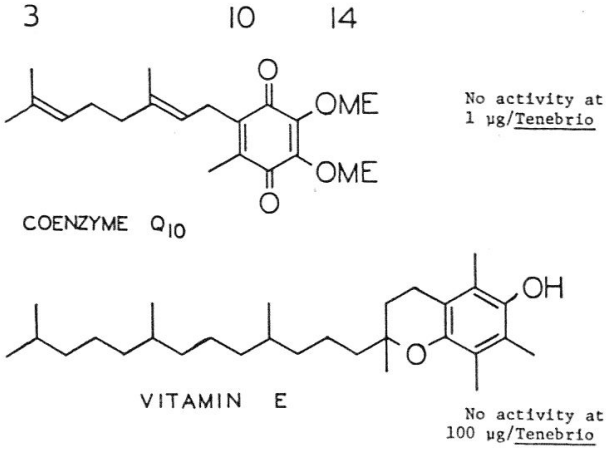



Table 10

We also tested for JH activity two biologically important natural products, as shown in Table 10. Coenzyme $Q_{10}$ [18], especially, bears a marked resemblance to the last compound in Table 3, but no JH activity was found.

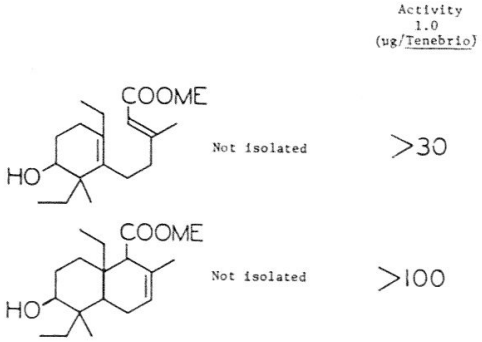



Fig. 11

The structure of the $C_{18}$-*Cecropia* JH brought to mind the squalene oxide-lanosterol-cholesterol transformation. We therefore treated our synthetic $C^{18}$ JH (mixed geometric isomers) with boron trifluoride etherate [19]. The products of this reaction had been determined previously by van Tamelen [20]. In a related study, Stork and Burgstahler [21] cyclized farnesic acid at two temperatures ; at 0° mainly monocyclic products and at 55° mainly bicyclic compounds were produced. The major monocyclic and bicyclic compounds are shown in Table 11.

Our cyclizations were carried out following the procedures of Stork and Burgstahler, and a examination of the conjugated ester absorptions of the crude products indicated that the high-temperature cyclization had indeed produced more bicyclic compound than the low temperature cyclization. The products were tested without isolation and were devoid of JH activity [22].

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[16] This statement probably does not hold true for other insects. However, Prof. COREY'S disclosure at this Symposium that the compound, in which the epoxide ring of methyl juvenate is replaced by an aziridine ring, synergizes methyl juvenate emphasizes the fact that this end of the molecule is not passive. L. M. Riddiford, A. M. Ajami, E. J. Corey, H. Yamamoto, and J. E. Anderson, *J. Am. Chem. Soc.*, **93**, 1815 (1971).

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