protein degradation which involves a heterogeneity of degradation rates among different proteins, since some mechanism would be required for the recognition of whether a protein molecule is degraded, perhaps involving transport into a lysosome, acetylation, or formylation, etc.

Another possibility is that there are specific degrading enzymes for specific proteins. At the extreme, degradation of each protein would require a specific protein (enzyme). This, however, is logically impossible, since in liver there is continual replacement of essentially all proteins. Thus, if a protein were necessary to degrade each specific protein, then it would follow that a protein would be necessary to degrade a protein..... *ad infinitum.*

It might be most reasonable to consider that there are a number of mechanisms for degrading or otherwise inactivating enzymes. Lysosomes may be important when cell involution or gross changes in rates of total protein degradation occur, whereas the degradation that occurs in normal, steady-state conditions involves a system or systems that are not understood well or defined at present.

Clearly, the regulation of both synthesis and degradation of proteins in animal tissues is an area in which much work is needed.

The Juvenile Hormone of *Hyalophora cecropia*

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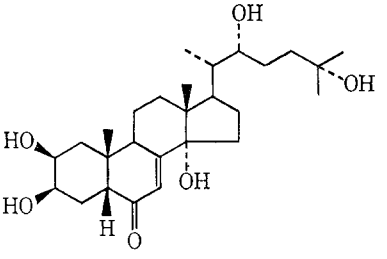
Received July 31, 1969

The molting process of insects involves the transformation of sexually immature individuals into reproducing adults of different form and structure. In some insects, this developmental sequence consists of a series of larval stages followed by pupal stage and finally the adult, whereas others do not have a pupal stage but molt directly from the larva to the adult. Control of these events of periodic molting rests with three different hormones (or hormonal systems).[1]

Neurosecretory cells secrete the brain hormone or prothoracotropic hormone whose action on the prothoracic gland initiates the synthesis and release of the prothoracic gland hormone also known as ecdysone. Ecdysone induces the events associated with each molt. Acting in contrast to ecdysone is a third hormone produced by a small gland known as the corpora allata. This hormone plays a regulatory role in the molting process. The type of molt that occurs appears to be a function of the concentration of this hormone which is called the juvenile hormone (henceforth abbreviated JH) since it induces the retention of juvenile characteristics.

Of the three hormones, prior to our work only ecdysone had been isolated and characterized. Karlson and his group[2] identified the hormone from silk worm pupae



ecdysone
2β,3β,14α,22β$_F$,25-pentahydroxy-5β,Δ7-cholesten-6-one

as a pentahydroxycholestenone derivative. The detailed structure was derived from X-ray data[3] and was confirmed by synthesis.[4] Molting hormones from other sources whose structures have been elucidated resemble ecdysone closely, differing mainly in the pattern and number of hydroxyl groups. It appears that all arthropods employ essentially the same compound as the molting hormone.

During the past few years, reports appeared describing attempts to isolate the juvenile hormone.[5] None of the active principles isolated and characterized possessed all the biological properties of the hormone itself. However, the finding that the active substances were farnesol or its derivatives led to a general testing of a wide range of acyclic terpenes in the hope of learn-

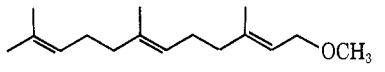
(1) (a) P. Karlson, *Angew. Chem., Intern. Ed. Engl.*, **2**, 175 (1963). (b) P. Karlson, *Pure Appl. Chem.*, **14**, 75 (1967). (c) N. A. Tamarina, *Usp. Sovrum. Biol.*, **62**, 415 (1966). (d) C. M. Williams, *Sci. Am.*, **217**, 13 (1967). (e) K. D. Highnam, *J. Endorcrinol.*, **39**, 115 (1967). (f) For simplicity in the subsequent discussion, reference is made to three hormones controlling insect development. At present, it is unknown whether the control of these processes involves three discrete chemical entities or whether each "hormone" is a mixture of compounds. The former case seems the more likely at present. It is unlikely that the same chemical entities serve as the various hormones in all species. C. E. Berkoff, *Quart. Rev.* (London), **23**, 372 (1969).

(2) P. Karlson, *Naturwissenschaften*, **53**, 445 (1966).

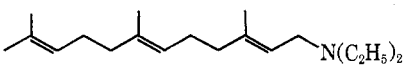
(3) (a) R. Huber and W. Hoppe, *Chem. Ber.*, **98**, 2403 (1965); (b) W. Hoppe, *Angew. Chem.*, **77**, 484 (1965).

(4) (a) V. Kerb, P. Hocks, R. Wiechert, A. Furlenmeier, A. Furst, A. Tangemann, and G. Waldvogel, *Tetrahedron Letters*, 1387 (1966); (b) J. B. Siddall, J. P. Marshall, A. Bomers, A. D. Cross, J. A. Edward, and J. H. Fried, *J. Am. Chem. Soc.*, **88**, 379 (1966); (c) J. B. Siddall, A. D. Cross, and J. H. Fried, *ibid.*, **88**, 862 (1966).

(5) (a) M. Gabe, P. Karlson, and J. Roche, *Comp. Biochem.*, **6**, 246 (1964); (b) P. Schmialek, *Z. Naturforsch.*, **16b**, 461 (1961); **18b**, 516 (1963); (c) H. Z. Levinson, *Rio. Parassitol.*, **27**, 47 (1966); (d) A. S. Meyer, H. A. Schneiderman, and L. J. Gilbert, *Nature*, **206**, 272 (1965).



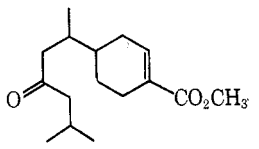
farnesyl methyl ether



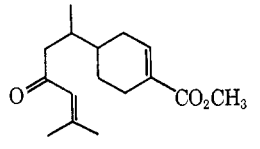
N,N-diethylfarnesylamine

ing something about the nature of juvenile hormone itself. From such studies, it was found that farnesyl methyl ether and N,N-diethylfarnesylamine possessed exceptionally high activity, the former being about one-fiftieth as active as the actual natural material.

More recently, Williams and Slama found that a compound of paper toweling made from balsam fir served as a juvenile hormone for the European bug *Pyrrhocoris apterus*.[6] Two active substances from this source, juvabione (**1**) and dehydrojuvabione (**2**), have been isolated[7] and characterized,[7] and the former was

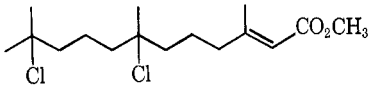


1



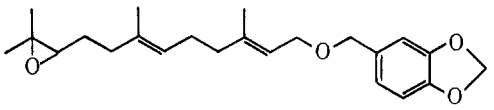
2

synthesized.[8] In the tenebrio test these compounds are about 10^5 less active than juvenile hormone itself. Law and coworkers[9] obtained a complex mixture of compounds from treatment of *trans,trans*-farnesoic acid with dry hydrogen chloride in absolute ethanol which possessed exceptionally high activity. Romanuk and coworkers[10] identified one of the active materials as the dihydrochloride **3** upon repetition of the reaction

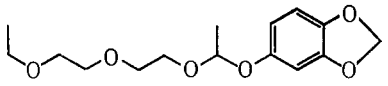


3

utilizing methyl *trans,trans*-farnesoate. However, this material has much lower activity than the crude extract. Indeed, one of the unknown principles of the Law mixture is the most potent substance prepared outside of the natural series; it has one-fifth the activity of the *cecropia* hormone. Bowers has reported high activity for several methylenedioxyphenyl derivatives.[11] Piperonyl 10,11-epoxyfarnesyl ether exhibited high activity, although sesoxane was generally more active. These compounds also serve as synergists.



piperonyl 10,11-epoxyfarnesyl ether



sesoxane

Isolation from *Hyalopora cecropia*

The key to chemical investigations arose in the work of Williams and his group who found that ethereal extracts of the abdomina of adult male *Hyalophora cecropia* possessed the precious hormone.[12] Attempts by them to isolate the pure juvenile hormone led to the obtention of a chromatographically homogeneous compound which they identified as methyl 9,10-epoxyhexadecanoate.[13] However, none of the synthetic isomers of this compound showed any detectable amount of juvenile hormonal activity. This epoxy ester must have been an artifact of their isolation procedure. A comparison of the gas chromatographic properties of the isolated ester to that of natural juvenile hormone reveals that a small amount of juvenile hormone could have cochromatographed with their material under their column conditions. Meyer and coworkers reported the material decomposed as the extracts were concentrated.[5d]

In 1965, a team of workers in the Zoology Department of the University of Wisconsin, headed by Roeller,[14] isolated juvenile hormone utilizing a five-step purification scheme. A low-temperature precipitation of the *cecropia* extract concentrated the hormone in the filtrate. Molecular distillation at 60–90° (2×10^{-5} mm) removed most higher and lower molecular weight compounds. Two thin-layer chromatographies on silica gel followed by gas chromatography on a silicone column produced the pure material. Each abdomen yielded about 0.5–1.0 μg. At any one time, approximately 200 μg of juvenile hormone was available. With this material, Roeller's group and myself began the chemical investigations leading to the structure elucidation and synthesis of the *cecropia* hormone.

Chemical and Spectral Properties

With sufficient quantity of the hormone available the stage was set for the structural work.[15] Mass spectral analysis indicated a molecular weight of 294 and a formula of $C_{18}H_{30}O_3$ for the hormone. Catalytic hydrogenation over palladium on carbon in ethanol led to the uptake of 3 mol of hydrogen and the loss of one oxygen.

(6) K. Slama and G. M. Williams, *Biol. Bull.*, **130**, 235, 247 (1966).
(7) (a) W. S. Bowers, H. M. Thompson, and E. C. Uebel, *Science*, **154**, 1020 (1966); (b) V. Cerny, L. Dolejs, L. Labler, F. Sorm, and K. Slama, *Collection Czech. Chem. Commun.*, **32**, 3926 (1967); (c) J. F. Blount, B. A. Pawson, and G. Saucy, *Chem. Commun.*, 715 (1969).
(8) (a) K. Mori and M. Matsui, *Tetrahedron*, **24**, 3127 (1968); (b) K. S. Ayyar and G. S. K. Rao, *Tetrahedron Letters*, 4677 (1967); (c) B. A. Pawson, H. C. Cheung, S. Gurbaxani, and G. Saucy, *Chem. Commun.*, 1057 (1968)
(9) J. H. Law, C. Yuan, and C. M. Williams, *Proc. Natl. Acad. Sci. U. S.*, **55**, 576 (1966).
(10) M. Romanuk, S. Slama, and F. Sorm, *ibid.*, **57**, 349 (196)7.
(11) W. S. Bowers, *Science*, **156**, 895 (1968).
(12) C. M. Williams, *Nature*, **178**, 212 (1956).
(13) C. M. Williams and J. H. Law, *J. Insect Physiol.*, **11**, 569 (1965).
(14) (a) H. Roeller and J. S. Bjerke, *Life Sci.*, **4**, 1617 (1965); (b) H. Roeller, J. S. Bjerke, D. W. Norgard, and W. H. McShan, "Proceedings of the International Symposium on Insect Endocrinology, Brno, Czechoslovakia, 1966," Academic Press, New York, N. Y., 1967.
(15) H. Roeller, K. H. Dahm, C. C. Sweeley, and B. M. Trost, *Angew. Chem., Intern. Ed. Engl.*, **6**, 179 (1967).

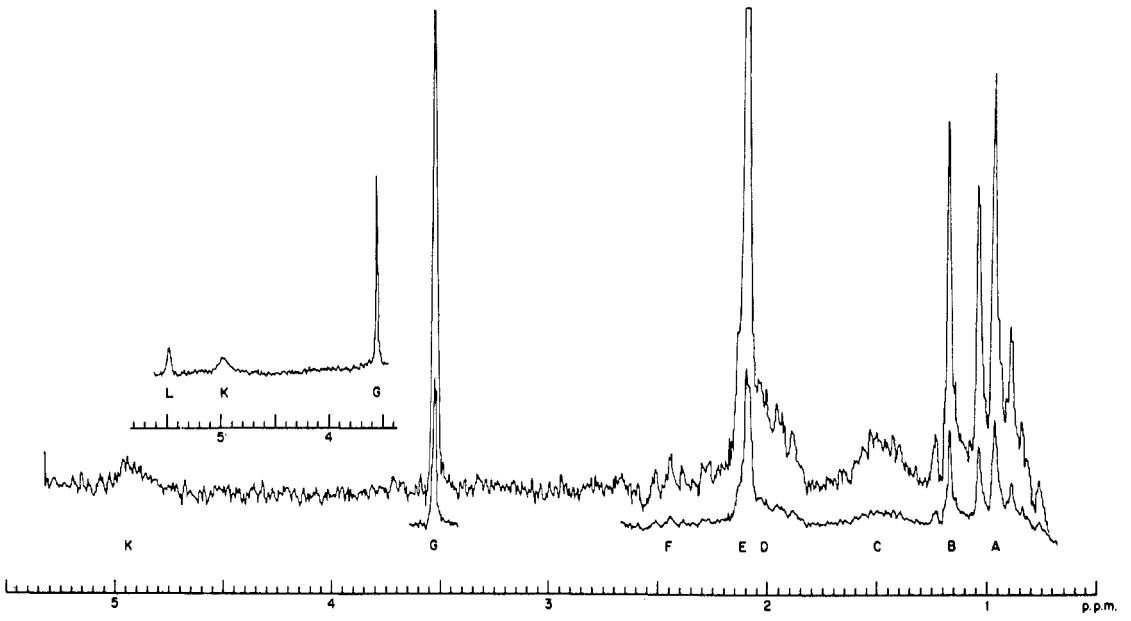


Figure 1. Nuclear magnetic resonance spectrum of juvenile hormone.

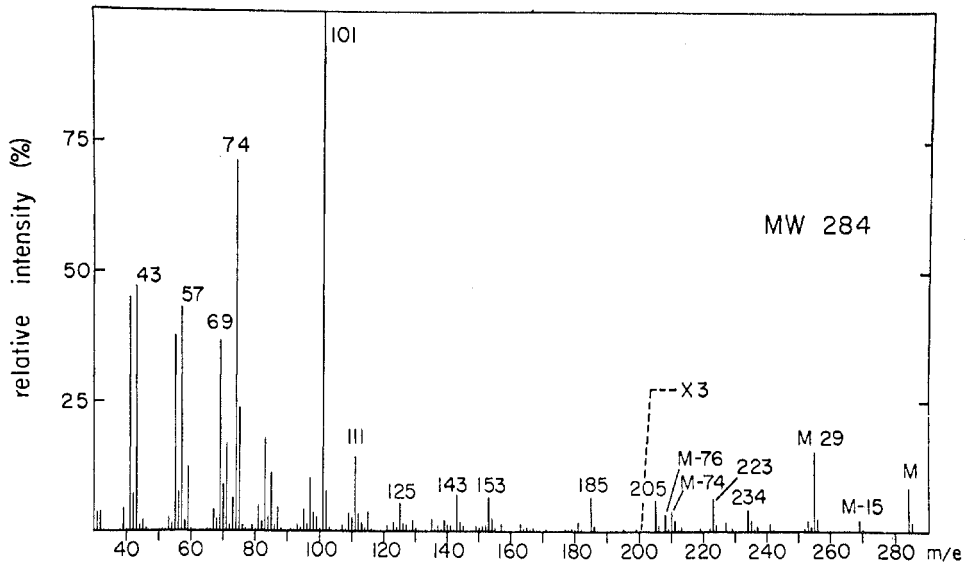


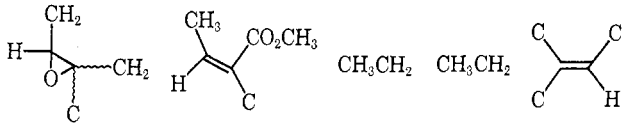
Figure 2. Mass spectrum of deoxohexahydro juvenile hormone.

This fact indicated the presence of three double bonds and/or rings that are easily hydrogenated and the presence of a labile oxygen. Hydrogenation with palladium on carbon poisoned with triethylamine produces dihydro and tetrahydro compounds retaining all oxygens.

Figure 1 illustrates the nmr spectrum obtained and Chart I summarizes the structural features deduced from this spectrum. Two vinyl protons appear at δ 5.46 and 4.96, respectively. The multiplicities of these signals demonstrate that they are situated on different double bonds. Thus, two of the four unsaturations in JH are trisubstituted double bonds. A three-proton singlet at δ 3.59 suggests a methyl group of a methyl ester, thus accounting for an additional unsaturation and two oxygens. The remaining unsaturation must be either a hydrogenolyzable ring or a tetrasubstituted double bond. A sharp doublet at δ 2.12 is indicative of a vinyl methyl group *cis* and β to a carbonyl group. Its coupling suggests long-range transoid coupling to a single vinyl proton. The remaining hash under this methyl absorption accounts for eight allylic hydrogens. The broad absorption stretching from δ 1.3 to 1.7 indicates four hydrogens on simple saturated carbon. A singlet for three hydrogens at δ 1.16 suggests a somewhat deshielded methyl group such as a methyl β to an

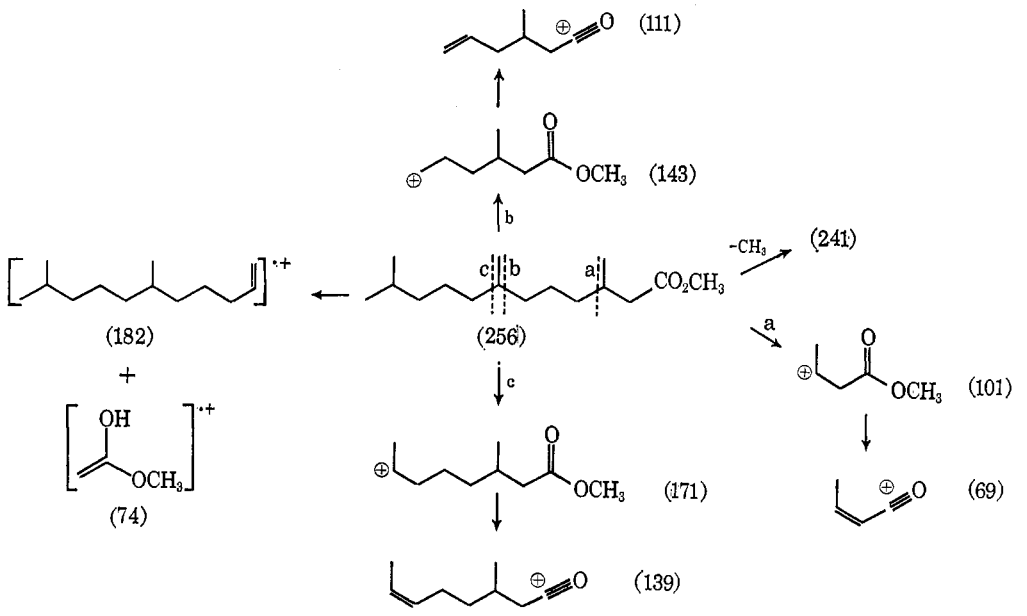
Chart I

Structural Components



Scheme I

Important Mass Spectral Cleavages of Methyl 3,7,11-Trimethyldodecanoate[a]



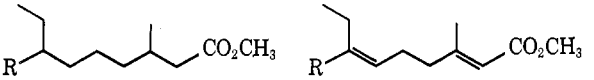
[a] *m/e* values in parentheses.

ethereal oxygen. The triplet for six hydrogens at δ 0.96 represents the methyls of two ethyl groups.

The remaining absorption is a one-proton triplet at δ 2.50. A search of the literature revealed that epoxide methines have this rather unusual chemical shift, for example, the epoxide methine hydrogen in methyl 10,11-epoxy-*trans,trans*-farnesoate (**4**).[16] Such a suggestion agrees with our previous data since it accounts for the last remaining unsaturation and for the presence of an easily hydrogenolyzable oxygen. The latter was further verified by hydrogenation of **4** which also absorbed 3 mol of hydrogen and lost one oxygen to produce methyl 3,7,11-trimethyldodecanoate (**5**).

Investigation into the nature of the basic carbon skeleton began with an examination of the mass spectrum of deoxohexahydro-JH (**6**) which is reproduced in Figure 2. To understand the nature of the fragmentation, we analyzed the spectrum of the model compound **5**. This analysis revealed the basic fragmentations summarized in Scheme I. In particular, important cleavages result at branch points in the chain. Furthermore, each of these fragments is characterized by loss of methanol. With this information in hand, we analyzed the spectrum of deoxohexahydro juvenile hormone (see Scheme II). Peaks at *m/e* 253 and 74 demonstrate the presence of a methyl ester with no branching α to the carbonyl. The base peak at *m/e* 101 further characterized by loss of 32 to give *m/e* 69 indicates the first branch occurs at C-3 and is a methyl branch identical with that of the model compound. These data confirm conclusions regarding the structure of deoxohexahydro juvenile hormone that can be extrapolated from the nmr spectrum of JH. Further, the presence of the *m/e* 143 and 111 peaks suggests identity of the chains in deoxohexahydro JH and **5** through C-6. The shift of peaks at *m/e* 171 and 139 in **5** (cleavage at c) to *m/e* 185 and 153 in **6** indicates the presence of an extra methylene group at C-7. Extrapolation from the nmr spectrum of JH suggests the extra methylene appears as an ethyl branch at C-7.

The combined information allows partial structure **7** to be written for **6**. In JH, the above evidence established the location of one double bond between C-2 and



7 **8**

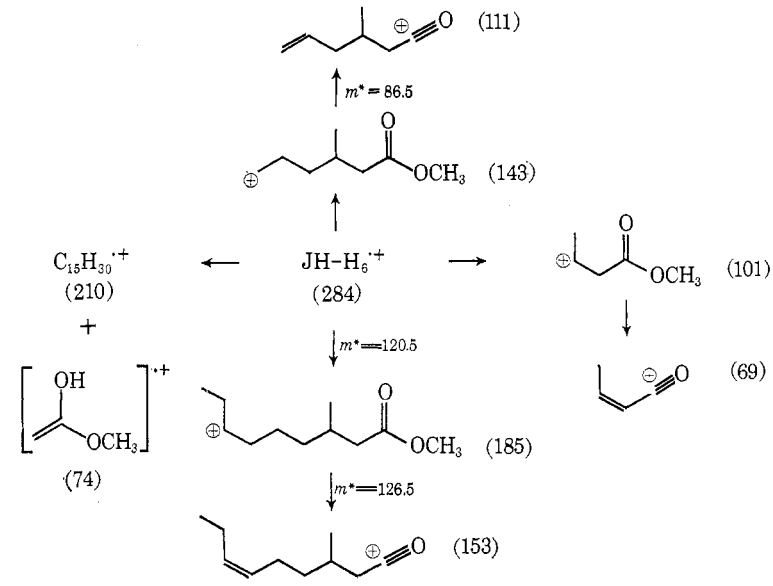
C-3. The establishment of the second double bond with respect to the conjugated one was determined by oxidative cleavage. Treatment of JH with osmium tetroxide and sodium metaperiodate produced levulinaldehyde which permits partial structure **8** to be written for JH.

The problem now narrowed to the structure of the R group. We recall that it must contain an epoxide ring bearing methyl, a methine hydrogen split by methylene, and an ethyl group. For the required information we turned to the mass spectrum of JH (see Figure 3) and of our model compound methyl 10,11-epoxy-*trans,trans*-farnesoate (**4**). Scheme III outlines the fragmentations of interest in the model compound for the further elucidation of the chain. In particular, fragments at *m/e* 195, 163, and 81 locate the position of the epoxide with respect to the branch at C-7. Analysis of the spectrum of JH (see Scheme IV) revealed these peaks shifted fourteen mass units to *m/e* 209, 177, and 95. This fact demonstrated the epoxide ring was situated at the same position in the chain in JH as in the model

(16) W. S. Bowers, M. J. Thompson, and E. C. Uebel, *Life Sci.*, **4**, 2323 (1965); E. E. van Tamelen, A. Storni, E. J. Hessler, and M. Schwartz, *J. Am. Chem. Soc.*, **85**, 3295 (1963).

Scheme II

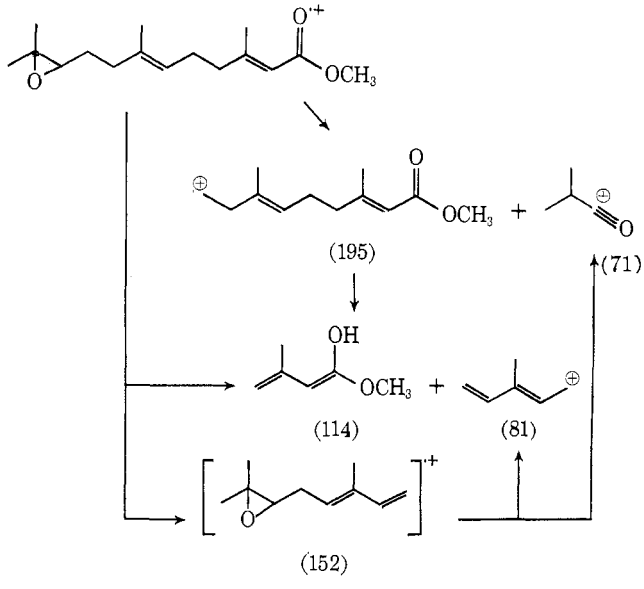
Important Mass Spectral Cleavages of Deoxohexahydro Juvenile Hormone[a]



[a] *m/e* values in parentheses.

Scheme III

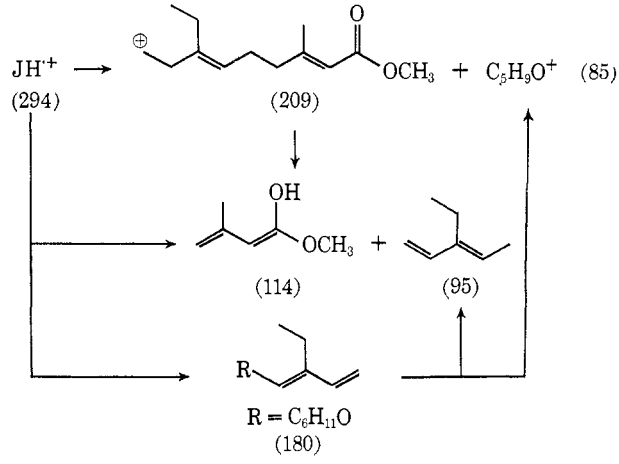
Important Mass Spectral Cleavages of Methyl 10,11-Epoxy-*trans,trans*-farnesoate[a]



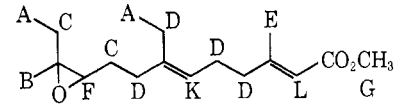
[a] *m/e* values in parentheses.

Scheme IV

Important Mass Spectral Cleavages of Juvenile Hormone[a]



[a] *m/e* values in parentheses.



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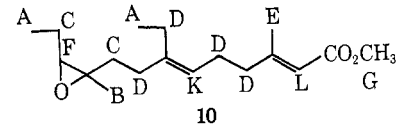


10

(letters refer to assignments in the nmr spectrum)

compound since the 14 mass unit difference reflects the change from a methyl branch at C-7 in **5** to an ethyl branch in JH.

We can now formulate two possibilities for JH, **9** and **10**. Differentiation was tentatively established by consideration of the mass spectrum of tetrahydrojuvenile hormone. This spectrum established the fact that the conjugated ester moiety remained intact, leaving two possible structures for this compound, **11** and **12**. In the spectrum of **11**, an intense peak should appear at *m/e* 73, whereas **12** should exhibit an intense peak at *m/e* 87 (cleavage at dotted lines). The absence of a *m/e* 87 peak indicated **11** as the correct structure for the tetrahydro derivative and consequently **9** for JH.

The last remaining point regards the stereochemistry of the double bonds and the epoxide ring. The first double bond is clearly *trans* based on the nmr arguments

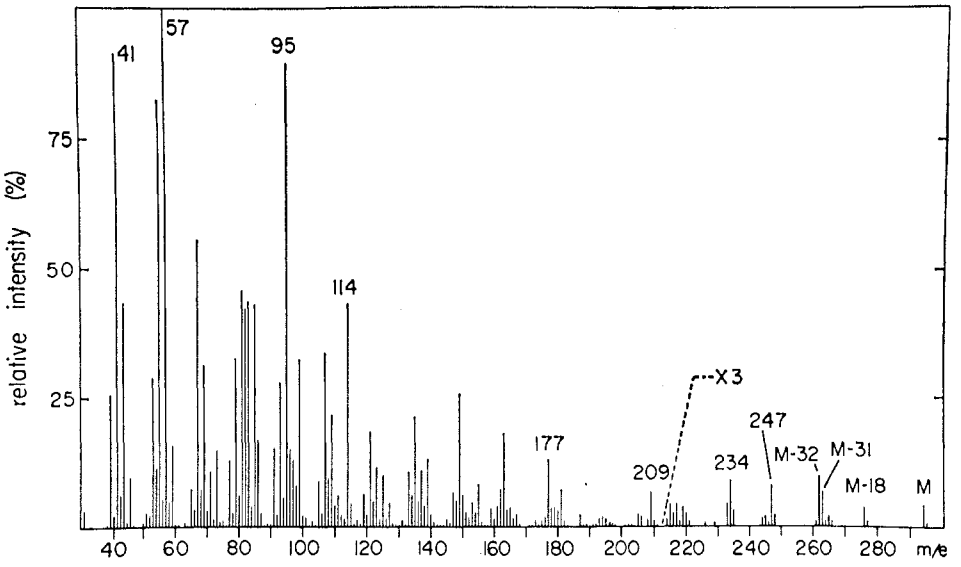
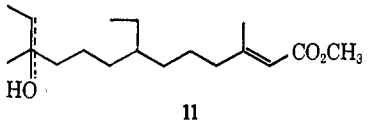


Figure 3. Mass spectrum of juvenile hormone.



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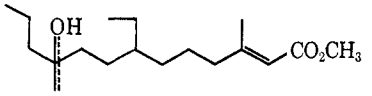

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presented above. The half-band width of the vinyl hydrogen of the central double bond suggests it is also *trans*. The evidence thus far allows no unambiguous assignment of the stereochemistry of the epoxide.

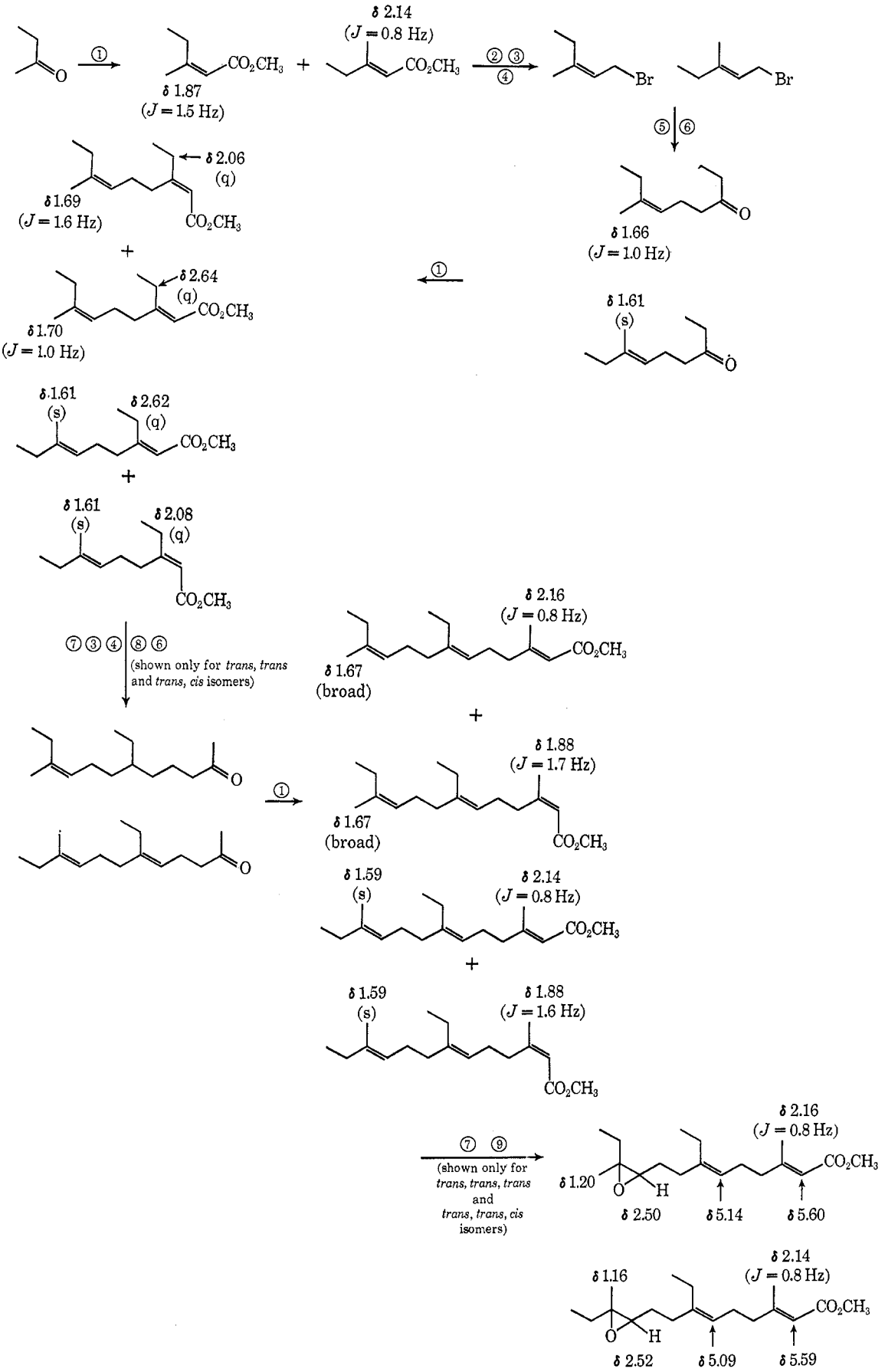
Synthetic Studies

With a tentative structure deduced almost exclusively from spectral data, conformation by synthesis became essential. The initial studies were designed to prove the correctness of the carbon skeleton and to establish unambiguously the stereochemistry of the sites of unsaturation.[17,18] To accomplish the latter feat, we deemed it necessary to have each isomer after introduction of each double bond and to be able to distinguish unambiguously between the geometric isomers. To facilitate isomer identification and separation, each unsaturation was introduced as part of an α,β-unsaturated ester. Scheme V outlines the synthesis. Reaction of 2-butanone with the sodium salt of methyl diethylphosphonoacetate produced a mixture of one part of *cis*- and two parts of *trans*-3-methyl-2-pentenoates. Spinning-band distillation easily separated the isomers. Assignment of stereochemistry rests on the chemical shifts and coupling constants of the vinyl methyl groups. The vinyl methyl group *cis* and β to the ester function is strongly deshielded by the proximate carbonyl group. Furthermore, the generality that *cisoid* allylic coupling is larger than *transoid* verifies the conclusions based on chemical shifts.[19] Conversion of each ester separately to the allylic bromide proceeded by lithium aluminum hydride reduction followed by phosphorus tribromide treatment. Alkylation of ethyl propionoacetate with the allylic bromide followed by hydrolysis and decarboxylation produced *trans*- and *cis*-7-methyl-6-nonen-3-one in which the vinyl methyl group absorptions confirmed the assigned geometries. In these instances, the methyl group *cis* to an alkyl chain experiences a small shielding effect because of the diamagnetic anisotropy associated with carbon–carbon single bonds. Repetition of the phosphonoacetate anion procedure generated from each isomer two additional geometric isomers whose stereochemistries are based upon the arguments presented above (see Scheme V for the spectral information). Preparation of the C-17 esters involved the standard chain extension utilized previously except that ethyl acetoacetate was employed as the active methylene component. Epoxidation of the triene esters produced as the major component the 10,11-epoxide. That epoxide derived from the *trans,trans,cis* triene was identical in nmr and mass spectral properties as well as in thin layer and gas chromatographic properties with the isolated natural material.

The key test in identity rests on the biological activity. Table I summarizes the activities of the synthetic juvenile hormone as well as the related isomers and derivatives. Within the experimental error, *dl*-juvenile hormone has activity identical with that of the naturally occurring material. This fact suggests that either the natural material is racemic or that the two enantiomers cannot differ in activity by more than a factor of two.

(17) K. H. Dahm, H. Roeller, and B. M. Trost, *Life Sci.*, Part III, 7, 129 (1968).
(18) K. H. Dahm, B. M. Trost, and H. Roeller, *J. Am. Chem. Soc.*, 89, 5292 (1967).
(19) (a) S. Sternhell, *Rev. Pure Appl. Chem.*, 14, 15 (1964); (b) G. P. Newsoroff and S. Sternhell, *Tetrahedron Letters*, 6117 (1968).

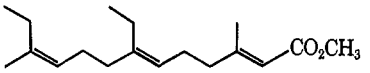
Scheme V: Synthetic Proof of Structure[a]



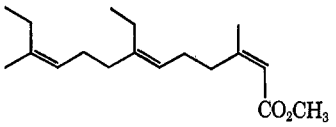
[a] ①, NaH, $(CH_3O)_2P(O)CH_2CO_2CH_3$, DME; ②, separate by spinning-band distillation; ③, $LiAlH_4$–ether; ④, PBr_3–ether—pyridine; ⑤, $NaOC_2H_5$–$CH_3CH_2C(O)CH_2CO_2C_2H_5$–$C_2H_5OH$; ⑥, KOH–$H_2O$; ⑦, separate by column chromatography; ⑧, $NaOC_2H_5$–$CH_3COCH_2CO_2C_2H_5$–C_2H_5OH; ⑨, *m*-chloroperbenzoic acid–ether.

Table I

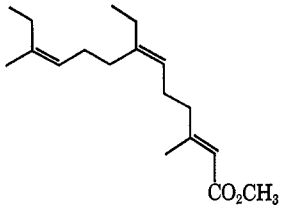
Biological Activity of Synthetic Compounds[a]



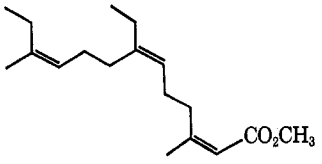
500
10,11-epoxide 5000
ethyl ester 10,11-epoxide 50,000
6,7-epoxide ≤200



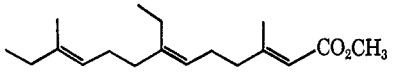
<10
10,11-epoxide <10



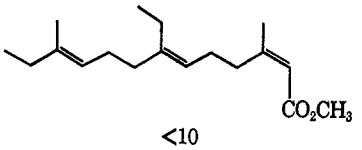
<10
10,11-epoxide <10



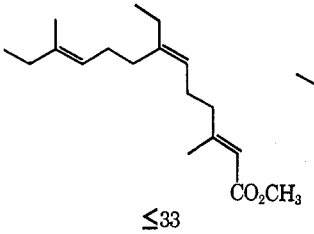
<10
10,11-epoxide <10



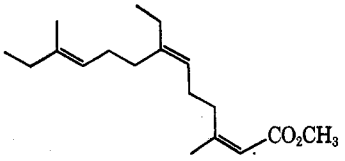
200
10,11-epoxide 2000
ethyl ester 10,11-epoxide 20,000



<10
10,11-epoxide <10



≤33
10,11-epoxide ≤20

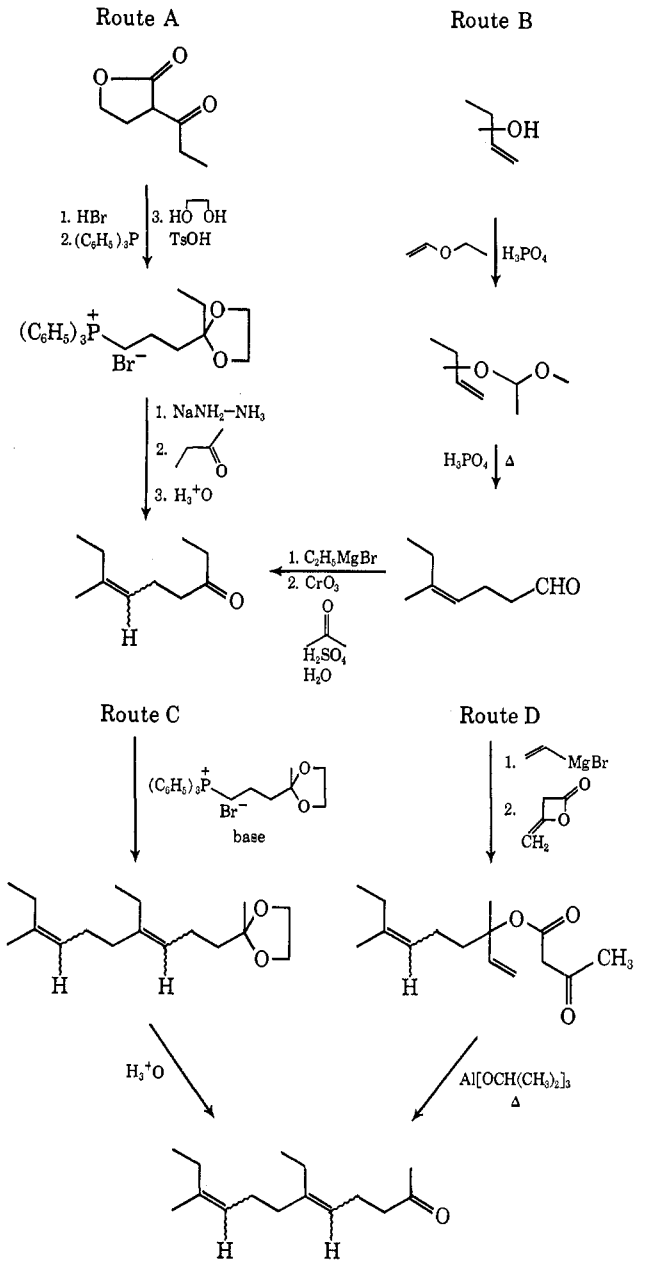


<10
10,11-epoxide <10

[a] Specific activities in tenebrio units per microgram.

Subsequent to the unambiguous establishment of the structure of the JH of *cecropia*, several additional nonstereospecific syntheses evolved. The first is modelled quite closely after the above and utilizes the Wittig reaction as shown in Scheme VI (routes A + C[20a] and route C[20b]) to extend the chain; however, only approximately equimolar mixtures are obtained after introduction of each double bond. A synthesis of the isomeric mixture was also produced by a sequence employing the rearrangement of the acetoacetic esters of allylic alcohols (Scheme VI, routes B + D[21]).

Scheme VI



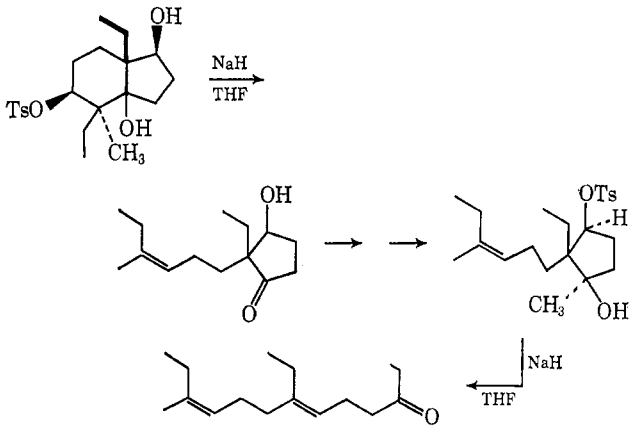
With the structure unambiguously established and several processes available for the nonspecific synthesis of the hormone, the background was established for the stereospecific synthesis of juvenile hormone. The basic problem involves the stereospecific (or stereoselective) construction of trisubstituted double bonds. One of the most elegant solutions to this problem utilizes the conversion of ring geometry into olefin geometry by fragmentation. This procedure reduces the problem to control of ring stereochemistry, a task that is well documented. Siddall and coworkers utilized this approach to synthesize *trans,cis*-6-ethyl-10-methyldodeca-5,9-dien-2-one (**13**).[22] The key fragmentation steps which establish the stereochemistry of the double

(20) (a) H. Schulz and I. Sprung, *Angew. Chem.*, **81**, 258 (1969); (b) J. A. Findlay and W. D. MacKay, *Chem. Commun.*, 733 (1969).

(21) K. Mori, B. Stalla-Bourdillon, M. Ohki, M. Matsui, and W. S. Bowers, *Tetrahedron*, **25**, 1667 (1969).

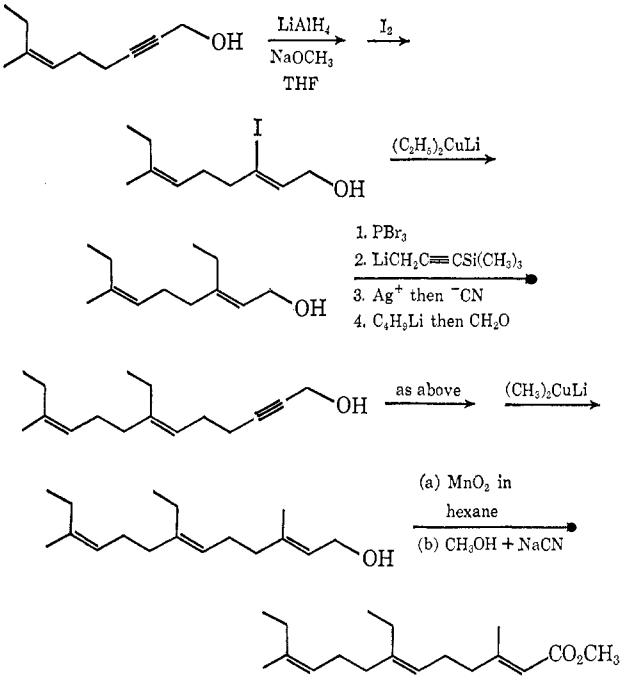
(22) R. Zurfluh, E. N. Wall, J. B. Siddall, and J. Edwards, *J. Am. Chem. Soc.*, **90**, 6224 (1968).

bonds involve the cleavage of a monotosylate of a 1,3-diol, a process known to possess strict stereochemical requirements.[23]



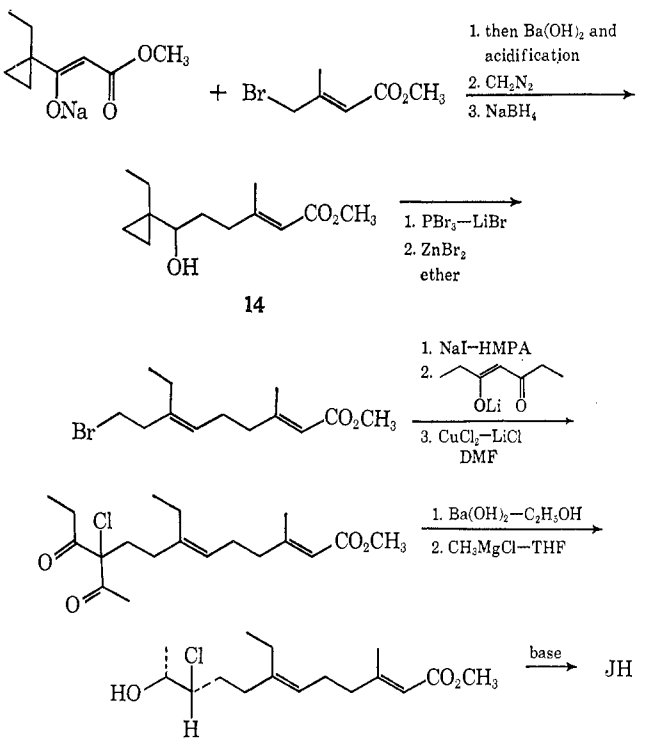
A second approach utilizes additions to acetylenes for control of trisubstituted olefin geometry.[24] The essential steps are illustrated in Scheme VII. Functionalization of the acetylene through the organoaluminum followed by coupling of the resultant vinyl iodide with an organocopper generated the trialkyl-substituted systems stereospecifically.

Scheme VII



All of the approaches discussed so far involve starting with the hydrocarbon end of the molecule and building toward the ester. The ultimate product was the triene esters which subsequently were selectively epoxidized in some manner. An alternate approach began at the conjugated ester portion and built the chain utilizing the stereoselective ring opening of

Scheme VIII

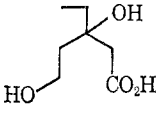


cyclopropylcarbinyl alcohols through the corresponding bromides with zinc bromide to generate the trisubstituted double bonds.[25] Thus, treatment of the cyclopropyl compound **14** under the conditions specified (Scheme VIII) produced virtually exclusively the desired *trans,trans* diene ester. A series of further reactions of the homoallylic bromide generated the chlorohydrin which upon base treatment produced the epoxide. The stereochemistry of the chlorohydrin is determined by the stereoselective approach of an organometallic to an α-chloro ketone. All the syntheses developed to date suffer from either lack of specificity or their undue length.

We are presently engaged in a stereoselective approach to juvenile hormone in order to obtain reasonable quantities for resolution and determination of absolute configuration, the last remaining structural problem.

Possible Biogenesis

Two conceivable modes of biogenesis must be considered. One route involves a homomevalonate unit (**15**) in biogenesis. Early work of Schmialek and



15

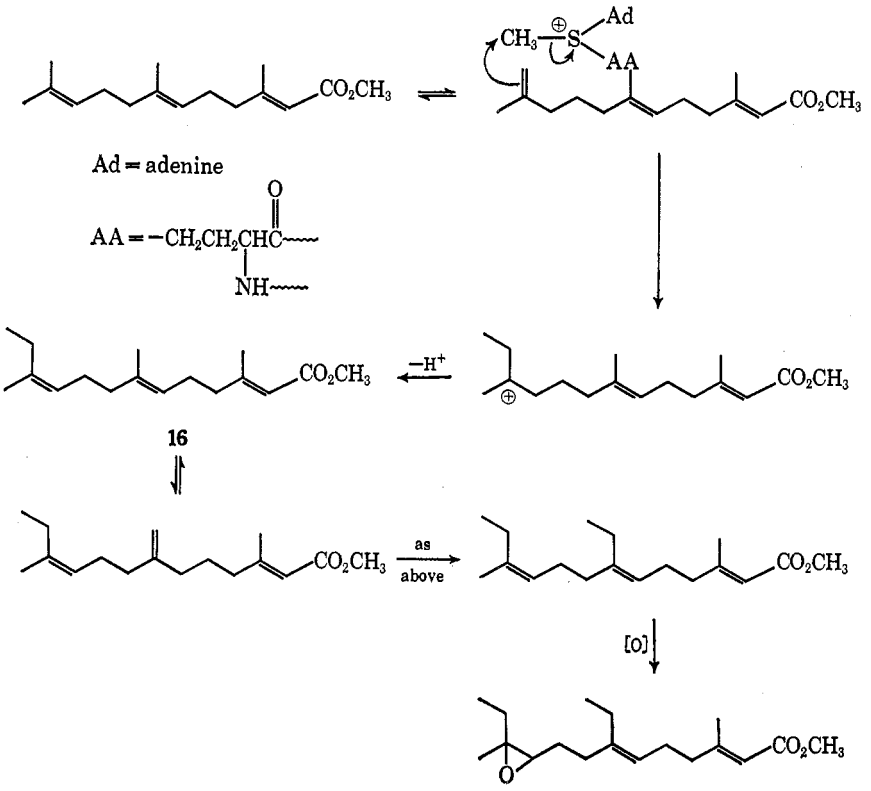
Popjak reported the failure to incorporate mevalonate or methionine in JH in *Cynthia* silk moth in support of this hypothesis. However, it is unclear that these

(23) P. S. Wharton, *J. Org. Chem.*, **26**, 4781 (1961), and references therein.

(24) E. J. Cory, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *J. Am. Chem. Soc.*, **90**, 5618 (1968).

(25) (a) W. S. Johnson, T. Ti, D. J. Faulkner, and S. F. Campbell, *ibid.*, **90**, 6225 (1968); (b) S. F. Brady, M. A. Ilton, and W. S. Johnson, *ibid.*, **90**, 2882 (1968); (c) M. Julia, S. Julia, and R. Guegan, *Bull. Soc. Chim. France*, 1072 (1960).

Scheme IX
Probable Biogenesis of Juvenile Hormone

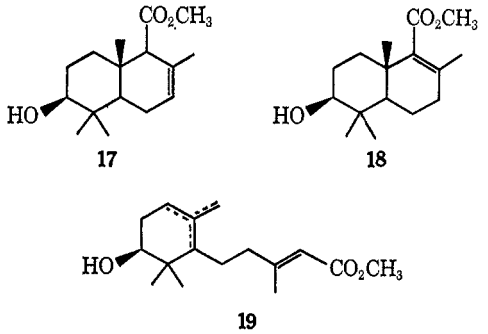


early workers indeed had the juvenile hormone in their extracts. More important, it is clear that the timing and manner of the introduction of the labeled material in the animal is very important. Thus, such negative results cannot be considered definitive. In fact, recent work suggests that methionine is indeed efficiently incorporated in *cecropia* moths.

The more logical route involves simple homologation of a farnesol derivative utilizing methionine as outlined in Scheme IX. Such one-carbon transfer reactions are well documented in fatty acid and steroid biogenesis.[26] This route also provides an attractive rationale for the stereochemistry of JH. The enzyme (or enzyme system) responsible for homologation of C-7 methyl most likely is the same (or at least has the same stereochemical requirements) as the enzyme (or enzyme system) responsible for terminal methyl homologation. Thus, the terminal methyl group that bears a *cis* relationship to the aliphatic chain leading to the *trans,trans,-cis* isomer should be involved since it occupies an environment similar to the C-7 methyl. This stereochemistry does represent that of the natural product. Recent isolation of the 10,11-epoxide corresponding to **16** from *Hyalophora cecropia* suggests the correctness of this scheme.[27]

Mode of Action

The mode of action of juvenile hormone remains unknown. In anticipation that the epoxide served as an initiator for cyclization and that the true hormone was one of the cyclized materials, we investigated the relative biological behavior of methyl 10,11-epoxy-*trans,-trans*-farnesoate and some of its cyclized materials (**17, 18, 19**).[28] The fact that these materials are inert in comparison to the epoxy ester is a strong indication that cyclization is not involved in the biochemistry of action



17 **18**

19

of juvenile hormone. In fact, JH does cyclize under acid conditions. Although the exact structures of these cyclized materials remain unknown, mass spectral

(26) R. B. Clayton, *Quart. Rev.* (London), **19**, 201 (1965).
(27) A. S. Meyer, H. A. Schneiderman, E. Hanzmann, and J. H. Ko, *Proc. Natl. Acad. Sci. U. S.*, **60**, 853 (1968). Recently a synthesis of this compound has been reported; see W. S. Johnson, S. F. Campbell, A. Krishnakumaran, and A. S. Meyer, *ibid.*, **62**, 1005 (1969).
(28) E. E. van Tamelen, M. A. Schwartz, E. J. Hessler, and A. Storm, *Chem. Commun.*, 409 (1966), and references therein.

data suggest they are mono- and bicyclic substances. These compounds are relatively inactive.[29]

(29) NOTE ADDED IN PROOF. Two recent articles report testing a wide range of compounds for juvenile hormonal activity—many related to the *cecropia* hormone. See V. B. Wigglesworth, *J. Insect Physiol.*, **15**, 73 (1969); V. Jarolim, K. Hejno, F. Sehnal, and F. Sorm, *Life Sci.*, Part II, **8**, 831 (1969).

I wish to thank the National Institutes of Health for support of that porton of the described work performed in my laboratories. I especially express my gratitude to Drs. Roeller and Dahm for a fruitful, enjoyable, and exciting collaboration in our work on juvenile hormone.

Conjugated Cyclic Chlorocarbons

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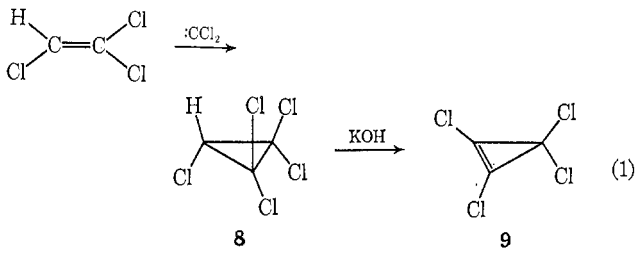
Received July 28, 1969

The chlorocarbons—highly or fully chlorinated organic compounds—have long been known and are manufactured on a large scale as solvents, insecticides, and flame retardants. The chemistry of the chlorocarbons has, however, been relatively underdeveloped in recent decades. Chlorocarbon chemistry now is undergoing a rebirth in which many of the most interesting findings are concerned with the family of cyclic conjugated polyenes, $(CCl)_n^{m\pm}$ (Figure 1). Of these compounds, only hexachlorobenzene (**5**) was known before 1964, but within the last 5 years the species $C_3Cl_3^+$, $C_7Cl_7^+$, and C_8Cl_8 have been isolated, and excellent evidence has been presented for the existence of C_4Cl_4, $C_5Cl_5^+$, and $C_5Cl_5^-$. Many of these species are highly reactive and give rise to derivatives with unusual electronic structures.

The family of species in Figure 1, like the cyclic polyenes from which they are derived, can be classified as aromatic if they contain $4n + 2$ and antiaromatic if they contain $4n$ π electrons.[1] Thus **1**, **4**, **5**, and **6** can be considered aromatic and so are expected to be stabilized, but **2**, **3**, and **7** are antiaromatic and should be destabilized, at least when planar. However, the chlorine substituents may perturb the carbocyclic π system by either withdrawing electronic charge inductively through the C–Cl σ bonds or by direct participation of the nonbonding pairs on the chlorine in π interaction with carbon. Fragmentary evidence suggests that both effects may be significant in certain delocalized chlorocarbons.

Trichlorocyclopropenium Ion. The smallest of the new species, and the first to be isolated, was the trichlorocyclopropenium ion, $C_3Cl_3^+$ (**1**).[2] The discovery of trichlorocyclopropenium followed closely upon the synthesis of tetrachlorocyclopropene (**9**).[3] A tetrahalocyclopropene was desired as a precursor to the still-unknown compound "deltic acid," or dihydroxycyclopropenone.[4] A logical route to **9** is dehydrochlorination of pentachlorocyclopropane (**8**), which in turn might be prepared by addition of dichlorocarbene to trichloroethylene (eq 1). The difficulty is that trichloroethylene



is a rather unreactive olefin toward carbene addition. However, when CCl_2 is obtained by thermolysis of sodium trichloroacetate in dimethoxyethane at 80°, it will add to trichloroethylene in 25% yield to produce **8**,[5] which is smoothly dehydrochlorinated by warm concentrated aqueous KOH to give **9**, a colorless liquid, bp 130–131°.[6] This method has recently found use in the commercial synthesis of tetrachlorocyclopropene, which is an effective fumigant as well as a useful intermediate.[7]

When **9** was mixed with aluminum chloride or other powerful chloride acceptor Lewis acids ($SbCl_5$, $GaCl_3$, or $FeCl_3$), stable, colorless crystalline salts of the trichlorocyclopropenium ion (**1**) were formed.[8] These compounds all have very simple infrared spectra, consistent with the symmetrical formulation for **1**. At the time it was discovered, **1** was the simplest aromatic species known[9] and seemed well suited for structural studies. Vibrational analysis was used to investigate the chemical bonding in **1**. The infrared and Raman frequen-

(1) R. Breslow, J. Brown, and J. Gajewski, *J. Am. Chem. Soc.*, **89**, 4383 (1967).
(2) S. W. Tobey and R. West, *ibid.*, **86**, 1459 (1964).
(3) S. W. Tobey and R. West, *Tetrahedron Letters*, 1179 (1963).
(4) Hydrolysis of **9** gives, however, none of the desired dihydroxycyclopropenone, but leads instead to the ring-opened product α,β-dichloroacrylic acid or its anhydride.
(5) S. W. Tobey and R. West, *J. Am. Chem. Soc.*, **88**, 2478 (1966).
(6) S. W. Tobey and R. West, *ibid.*, **88**, 2481 (1966).
(7) E. E. Gilbert, U. S. Patent 3,251,735 (May 17, 1966); *Chem. Abstr.*, **65**, 2944*h* (1966).
(8) R. West, A. Sadô, and S. W. Tobey, *J. Am. Chem. Soc.*, **88**, 2488 (1966).
(9) The cyclopropenium ion itself, $C_3H_3^+$, has recently been prepared. See R. Breslow, J. Groves, and G. Ryan, *ibid.*, **89**, 5048 (1967).