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Some Juvenile Hormone Analogs
A Critical Appraisal

PHILIP A. CRUICKSHANK

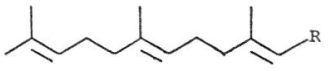
As a major producer and formulator of pesticides in the United States, the FMC Corporation became interested in the insect juvenile hormone early in 1960. The work being carried out at various academic institutions was followed fairly closely with some support being given to efforts toward isolating the natural hormone from various species of moths. By 1963, when I joined the company, the interest was sufficient to undertake an in-house program on the concept of insect population control through the juvenile hormone. By this time the discovery of Schmialek (1) that farnesol and farnesol derivates possessed significant juvenile hormone activity had been well documented and synthesis programs on structure activity relationships were possible. Our work involved two different aspects : first, an attempt to isolate the natural hormone from *Cynthia* moths and second, syntheses revolving around the known active farnesol derivatives.

Our efforts to isolate the *Cynthia* hormone were terminated upon the elegant work of Röller and his group (2) and of Schneidermann and Meyer (3) and their coworkers leading to the isolation and structure elucidation of the two *Cecropia* hormones.

Our synthesis program, however, has led to some highly active substances about which I will speak today. Our initial screening work was done with the yellow mealworm, *Tenebrio molitor*, a species utilized by many workers in this field (4). Figure 1 shows our results with the simple farnesol derivatives. This data serves as a baseline for comparison with other laboratories which have reported on the same compounds. In our assay we indicate the percentage of test insects which show a positive response at least at the level of pupal-adult intermediates. Thus, the white cuticular patch utilized as a positive response by many workers would not be included in evaluating our results. The responses are also indicated in these figures as the test dose in micrograms per gram of insect weight rather than in micrograms per insect. This allows a better comparison between different insect species, as well as comparison with the activity of more classical pesticidal substances which will be made later. For *Tenebrio* the test dose in microgram per insect is roughly $^1/_{10}$ of the value indicated in the figures.

Figure 1

TENEBRIO MOLITOR SCREENING OF FARNESYL DERIVATIVES



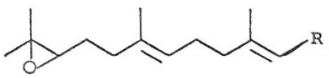
R	% RESPONSE AT TEST DOSE (μg/g) 1000	100	10
CH_2OH	80	-	-
CH_2OCH_3	100	100	75
$CH_2N(C_2H_5)_2$	100	95	-
CO_2CH_3	-	79	45
$CO_2C_2H_5$	-	100	20

As can be seen, the simple farnesol derivatives are relatively inactive when compared to the best compounds available today. Farnesyl methyl ether, farnesyldiethylamine, and ethyl farnesate were the best compounds in our hands but were fully effective only at test doses of 100 μg/gram, or 10 μg/test insect.

As part of the program directed toward analog synthesis and screening, we carried out a literature search of farnesol derivatives and began synthesizing compounds of interest. Among these were the 10,11-epoxides of farnesol derivatives. These compounds were first reported by Van Tamelen in 1963 (5). We began examining these compounds at about the same time Bowers undertook his work at the United

Figure 2

TENEBRIO MOLITOR SCREENING OF FARNESYL DERIVATIVES



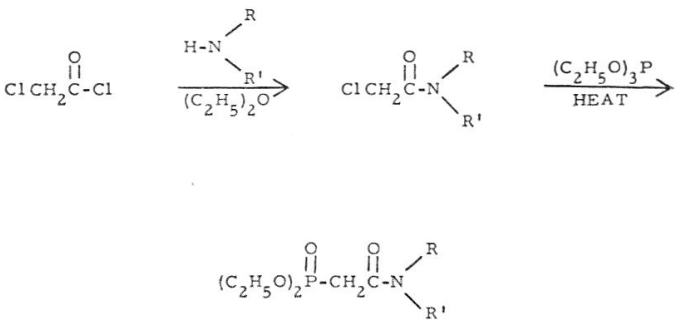
R	% RESPONSE AT TEST DOSE (μg/g) 100	10	1	0.1
CH_2OCH_3	100	80	36	-
$CH_2N(C_2H_5)_2$	100	100	100	20
CO_2CH_3	96	41	-	-
$CO_2C_2H_5$	100	94	88	-

States Department of Agriculture Laboratories in Beltsville (6). The epoxides were prepared by simple peracid oxidation of the farnesol derivatives; in the case of the diethylamino derivative, oxidation at the nitrogen was blocked through use of the trifluoroacetate salt. The increase in activity noted in the mealworm screen was dramatic. As shown in Figure 2, we now obtained high response levels at test doses of 1 μg/gram ($^1/_{10}$ μg/insect) with the epoxides of diethylfarnesylamine and ethyl farnesate. This gave encouragement to the hope that highly potent compounds could be discovered through a rational analog synthesis program. The activity of the esters and amines led us, quite naturally, into the synthesis of some farnesyl amides and it is this class of compounds which will take up the bulk of todays talk.

The key intermediates for the farnesol derivatives are geranyl acetone, a commercially available intermediate, and the diethyl carbamoylmethylphosphonates (7). Preparation of the latter is shown in Figure 3. Chloroacetyl chloride is treated with the appropriate primary

Figure 3

PREPARATION OF DIETHYL CARBAMOYLMETHYLPHOSPHONATES



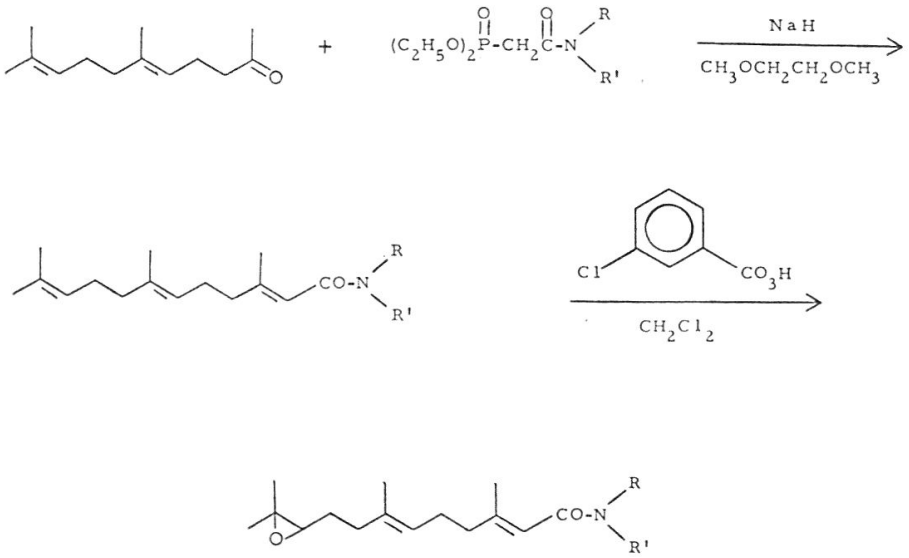
R AND R' = H OR LOWER ALKYL

or secondary amine in diethyl ether, affording the chloroacetamide derivatives in excellent yield. A Michaelis-Arbuzov reaction utilizing triethyl phosphite and chloroacetamide gives the desired carbamoylmethylphosphonate also in high yield. The Emmons (8) modification of the Wittig reaction is used to prepare the farnesamides (Fig. 4). These reactions proceed smoothly with both primary and secondary amides, i.e., where R and R′ are both alkyl or where R is hydrogen

and R′ is alkyl. These amides are smoothly converted to a mixture of epoxides by treatment with *meta*-chloroperbenzoic acid in methylene chloride. The desired 10,11-epoxides were isolated in pure form by column or preparative thin-layer chromatography on silica gel.

Figure 4

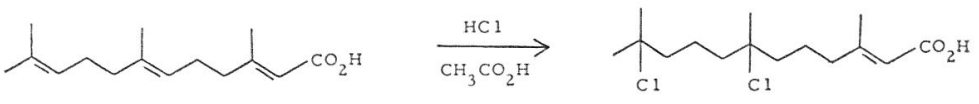
PREPARATION OF N-ALKYL AND
N, N-DIALKYLFARNESENAMIDE 10, 11-EPOXIDES



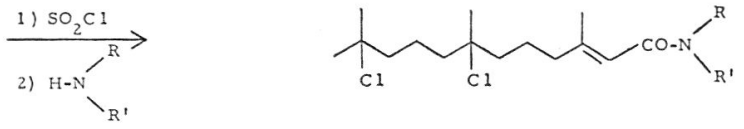
The products obtained by addition of hydrogen chloride to the 6,7- and 10,11-double bonds of the farnesol derivatives also were prepared for evaluation. These compounds followed from the observations by Williams and Law (9) that Fischer esterification of farnesoic

Figure 5

PREPARATION OF 7, 11-DICHLORO-3, 7, 11, TRIMETHYLDODECENAMIDES



SLAMA, ROMANUK AND SORM 1969



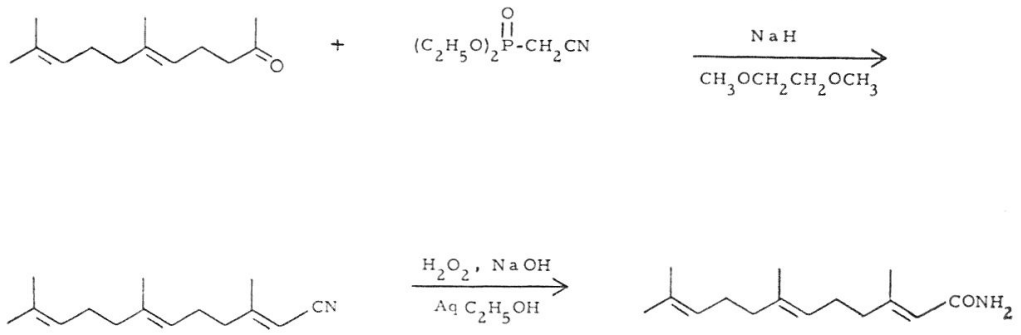
acid with hydrogen chloride and ethanol gave a highly potent juvenile hormone mimic. The work by Romaňuk, Sláma and Šorm (10) later showed that ethyl 7,11-dichloro-3,7,11-trimethyldodecenoate was an active component of the esterification mixture.

Our attempts to add hydrogen chloride directly to the amides were unsuccessful. Syntheses of the dichloro amides are shown in Figure 5. The dichloro acid was prepared by addition of hydrogen chloride to farnesoic acid in acetic acid — a method developed by Sláma, Romaňuk, and Šorm (11). This acid could then be smoothly converted to the dichloro amides by treatment with thionyl chloride followed by the appropriate primary or secondary amine.

Preparation of the nitrile and the unsubstituted amide are shown in Figure 6. The Emmons condensation of geranyl-acetone with diethyl

Figure 6

PREPARATION OF FARNESENAMIDE



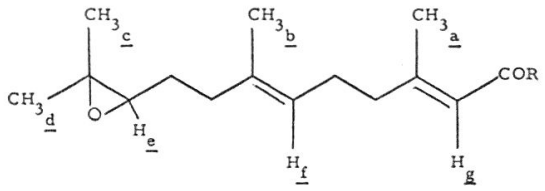
cyanomethylphosphonate gave the farnesonitrile. Hydrolysis of this in aqueous ethanol gave the desired unsubstituted farnesamide which could be converted to the 10,11-epoxy derivative by peracid.

For the most part, our compounds were characterized by nmr spectrometry. The *trans* and *cis* isomers can be clearly differentiated and the position of the epoxide ring clearly established. Figure 7 summarizes the nmr results. The proton signals are given in parts per million from tetramethylsilane standard. Figure 8 summarizes the nmr data for the dichloroamide derivatives. Again, the *cis* and *trans* isomers are clearly differentiated and the location of the chloro groups established.

We also have prepared the amide analogs of the *Cecropia* hormone. Synthesis of the *N*-ethyl derivative from the appropriate ketone intermediate and diethyl *N*-ethylcarbamoylmethylphosphonate gave a mixture of *trans, trans, cis* and *cis, trans, cis* isomers in an 85 : 15 ratio

Figure 7

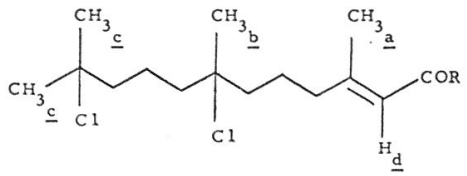
NMR SPECTRA OF FARNESYL DERIVATIVES (PPM)



R	a cis	a trans	b cis	b trans	c and d	e	f	g
OC_2H_5	1.88	2.13	1.70	1.62	1.22 and 1.25	2.53	5.12	5.60
NHC_2H_5	1.83	2.17	1.69	1.62	1.26 and 1.30	2.74	5.17	5.67
$N(C_2H_5)_2$	1.85	1.93	1.70	1.63	1.27 and 1.32	2.73	5.17	5.85

Figure 8

NMR SPECTRA OF DICHLOROAMIDES (PPM)



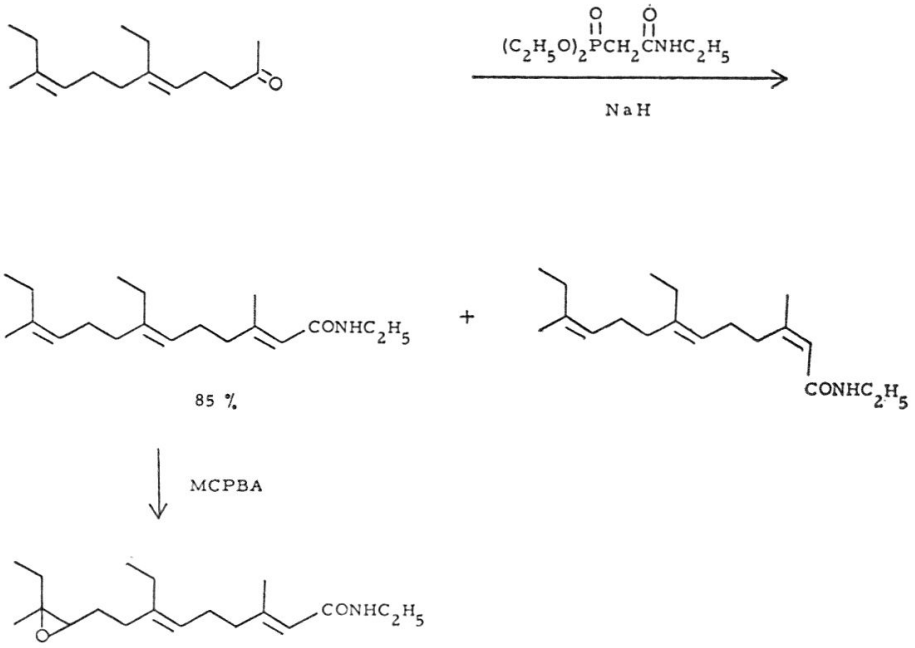
R	a cis	a trans	b	c	d
OC_2H_5	1.91	2.19	1.60	1.55	5.71
NHC_2H_5	1.84	2.17	1.60	1.55	5.59
$N(C_2H_5)_2$	1.85	1.93	1.59	1.54	5.83

(Fig. 9). Separation of the isomers by preparative layer chromatography gave the pure *ttc* isomer, which was treated with *meta*-chloroperbenzoic acid to give the *N*-ethylamide analog of *Cecropia* hormone.

The preparation of the dichloro amide analogs of the *Cecropia* hormone was analogous to the preparation of the corresponding farnesamide derivatives, i.e., addition of hydrogen chloride to the carboxylic acid followed by treatment with thionyl chloride and ethylamine.

We turn now to a discussion of the biological screening results with these amide derivatives. In figure 10 is listed a series of *N,N*-diakylamide epoxide derivatives of farnesoic acid in which the alkyl groups vary from dimethyl through diisobutyl. You will recall that the minimum dose at which a significant response was observed with the epoxide derivative of ethyl farnesate was about 1 μg/gram. Here, two compounds give a significant response at doses one order of magnitude

Figure 9

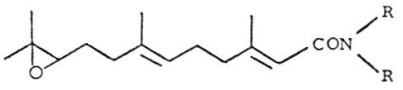


lower. These are the *N,N*-diethylamide and the *N,N*-di-n-butylamide. These doses correspond to 10 nanograms/*Tenebrio* pupa.

Our most startling results were obtained with the *N*-monoalkylamide epoxides as shown in Figure 11. Also included in this figure

Figure 10

TENEBRIO MOLITOR SCREENING OF N, N-DIALKYLAMIDE EPOXIDES

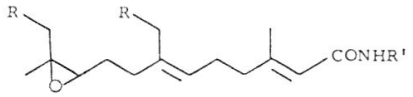


	% RESPONSE AT TEST DOSE (μg/g)				
R	100	10	1	0.1	0.01
CH_3	100	82	10	-	-
C_2H_5	100	100	100	68	0
n-C_3H_7	100	100	33	0	-
i-C_3H_7	100	100	27	20	-
n-C_4H_9	100	100	100	65	15
i-C_4H_9	-	95	85	5	0

are the unsubstituted farnesamide on the first line and the *N*-ethylamide of the *Cecropia* hormone on the last line. Ignoring for the moment the data on the last line, it is very apparent that a significant structure activity response is observed in this series of compounds. The unsubstituted amide does not show a significant response below 10 μg/gram test dose. This increases steadily to the *N*-ethylamide which gave a 100% response at 1 nanogram/gram and falling off rapidly as the length of the *N*-alkyl chain increases. The *Cecropia* amide analog is approximately one order of magnitude more potent in the *Tenebrio* screen with 70% response at a test dose of $^1/_{10}$ nanogram/gram.

Figure 11

TENEBRIO MOLITOR SCREENING OF N-ALKYLAMIDE EPOXIDES



		% RESPONSE AT TEST DOSE (μg/g)					
R	R'	100	10	1	0.1	0.01	0.001
H	H	100	70	10	5	-	-
H	CH_3	100	100	100	100	37	-
H	C_2H_5	100	100	100	100	100	100
H	n-C_3H_7	100	100	100	63	17	-
H	i-C_3H_7	100	100	100	7	-	-
H	n-C_4H_9	100	100	28	16	-	-
H	i-C_4H_9	100	100	0	-	-	-
CH_3	C_2H_5	100	100	100	100	100	100[a]

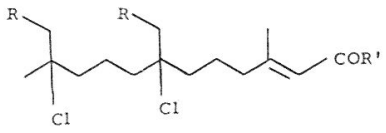
[a] 70% at 10^{-4} μg/g

Results of the *Tenebrio* screening with the dichloro amides are shown on Figure 12. We have included the results in our laboratory with the ethyl ester derivative obtained by treating the dichloro acid chloride with ethyl alcohol. As reported by Sláma, Romaňuk and Šorm (11), we isolated the pure *trans*-dichloro acid and converted it to a number of pure *trans* derivatives. The mother liquors from the *trans* acid were shown by nmr to be a mixture of *cis* and *trans* acids plus some minor impurities. This mixture was also converted via the acid chloride to the appropriate amide derivatives. As seen on this figure, the products obtained from the crude dichloro acid were significantly more active than the materials obtained from the pure *trans* acid. Whether this is due to an inherent activity of the *cis* isomer, the activity of some as yet unidentified minor component in the mixture, or a synergistic effect between the *cis* and *trans* derivatives is not known. If the increased

activity is due to an unidentified minor component then this substance must indeed be extremely potent as we do not believe that any single impurity is present in excess of 1–2% in the crude mixture. The dichloro amide derivative analogous to the *Cecropia* hormone is shown in the last two lines. Neither of these compare in activity to the corresponding farnesol derivatives. This could well be due to the fact that there is a much more complex mixture of isomers present in these substances which could lead to masking effects on the most potent materials.

Figure 12

TENEBRIO MOLITOR SCREENING OF DICHLORO AMIDES



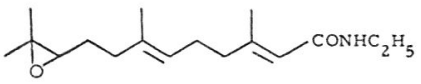
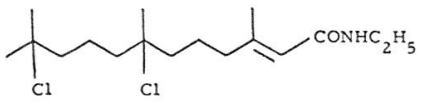
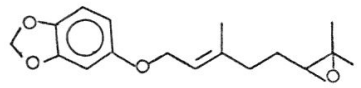
			% RESPONSE AT TEST DOSE (μg/g)			
R	R'	Isomer	100	10	1	0.1
H	OC_2H_5	t	100	6	-	-
H	OC_2H_5	c & t	100	100	80	0
H	NHC_2H_5	t	100	100	100	95
H	NHC_2H_5	c & t	100	100	100	100[a]
H	$N(C_2H_5)_2$	t	100	100	11	-
H	$N(C_2H_5)_2$	c & t	100	100	100	89
CH_3	OC_2H_5	c & t	100	100	53	-
CH_3	NHC_2H_5	c & t	100	100	43	-

[a] 100% RESPONSE AT 10^{-3} μg/g

During the course of our work on screening these juvenile hormone mimics we tested a number of oily carriers to see whether such a formulation would enhance the activity of the hormonal agent. As seen in Figure 13, we could enhance the activity of the epoxy amide one order of magnitude by using mineral or olive oils at a level of 10% in the acetone solution. I might add that a control solution containing only the oil in acetone was totally inactive in our screen. The enhancement of activity of the dichloro amide was much more dramatic. Pure acetone solutions gave total response only at doses of 1 μg/gram. All of the oils enhanced the activity of this material with the most dramatic enhancement being observed with coconut oil or with squalene. Also on this slide is shown the methylenedioxy geranyl ether derivative described by Bowers (12) and cited as one of the most active juvenile hormone compounds in the literature to date. Again, the activity of this material could be somewhat enhanced with certain oily carriers.

Figure 13

EFFECT OF OILY CARRIER IN FORMULATION
LOWEST DOSE (μg/g) FOR 100% RESPONSE

Compound	None	Mineral	Coconut	Olive	Squalene
	10^{-3}	10^{-4}	10^{-3}	10^{-4}	10^{-3}
	1.0	0.1	10^{-2}	0.1	10^{-3}
	0.1	10^{-2}	10^{-2}	0.1	10^{-2}

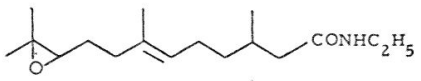
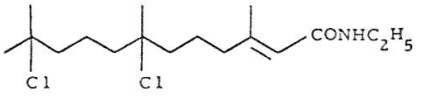
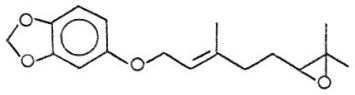
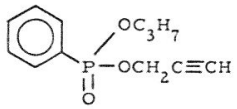
Use of synergists in insecticide formulations is well known. The synergist usually is a compound inactive in its own right but which will markedly enhance the effectiveness of the toxicant. Potentiation effects also are observed in which two active ingredients in combination frequently will be more potent than a similar dose of either component alone. In order to test for these effects, we examined combinations of materials with known juvenile hormone activity. In Figure 14 I have repeated the minimum dose required for 100% response with the epoxy amide, the dichloro amide and the Bowers compound. Also included is a phosphonate ester, a synergist under development by our Niagara Chemical Division. Dr. Bowers had observed some juvenile hormone activity for this material in the *Tenebrio* screen (13), but as you can see, at a very low level of activity.

A combination of the epoxyamide and the dichloroamide was found to be very much more active than either component alone. Responses in the *Tenebrio* test were observed down to 10^{-6} μg/gram, a remarkably low level for the activity which we demand in our test. Combinations of 1 and 3 or 2 and 3 did not show significant potentiation. However, 1 and 4, the epoxy amide and the phosphonate, did show slight potentiation effects though nowhere near the degree observed with the epoxy and dichloro derivatives.

With the levels of activity observed in the *Tenebrio* screen, we felt well justified in evaluating these compounds against a rather broad spectrum of insect species. We recognized that a great deal of species specificity had been observed by workers in the field with other compounds. However, we felt that this specificity was one of degree rather

Figure 14

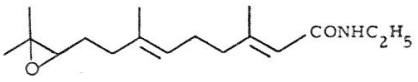
POTENTIATION EFFECTS - TENEBRIO SCREEN

	Compound	Activity μg/g	Combined With	Total Active Ingredient for 100% Response
1.		10^{-3}	2	10^{-6}
2.		10^{-3}		
3.		10^{-2}	1 or 2	10^{-3}
4.		10	1	10^{-4}

than an absolute factor and thus felt confident that we would see some activity against many species with our test compounds. The simplest test which we could set up involved incorporating the active ingredients in stored grain and testing for the growth of a colony of stored grain pests. Figure 15 shows the results with three species of insects : yellow

Figure 15

STORED GRAIN PESTS



SPECIES	% CONTROL OF COLONY AT TEST CONC (PPM) 100	50	10	1	0.1
TENEBRIO MOLITOR	-	-	100	100	100
TRIBOLIUM CONFUSUM	100	100	80	-	
PLODIA INTERPUNCTELLA			NO CONTROL		

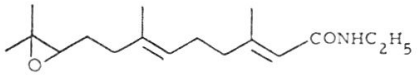
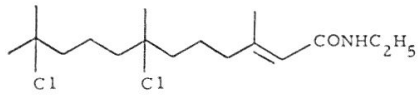
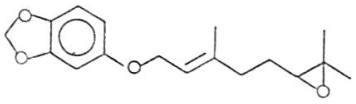
CURRENT CONTROL METHODS: FUMIGANTS, 2 - 4 LBS/1000 CU FT, MALATHION (10 PPM), PYRETHRUM AND SYNERGIST (1 PLUS 10 PPM)

mealworm, confused flour beetle and Indian-meal moth. The flour beetle colonies were controlled at 10 parts/million of the hormonal mimics in the grain and the mealworm at 0.1 ppm, but no control of the *Lepidoptera* species was effected. Current control methods involve use of malathion at 10 parts/million or synergized pyrethrum derivatives at 1 part/million. However, the most prevalent method of stored grain pest control involves fumigation with halogenated hydrocarbons at 2–4 lbs/1000 cu. ft. storage space.

We also have screened our materials against the larvae of houseflies, *Musca domestica*. Results of these tests are shown in Figure 16.

Figure 16

HOUSEFLIES (MUSCA DOMESTICA) -- LARVAE

		% RESPONSE AT TEST DOSE (µg/g)			
		5.0	0.5	0.05	0.005
1.		100	100	60	20
2.		100	70	30	20
3.		100	60	40	20
4.	Combination of 1 and 2	100	100	100	100

LD_{50} µg/g: MALATHION, 12.5; CARBARYL, 17.8; PYRETHRUM 57; DDT, 8-21

The test materials dissolved in acetone plus an oily vehicle were applied topically to the mature larvae. A positive response involved failure of adult flies to emerge from the pupae. Complete control was observed at $^{5}/_{10}$ µg/gram or approximately $^{1}/_{10}$ µg/insect. The 50% control point was approximately $^{5}/_{100}$ µg/gram. The dichloro amide was approximately one order of magnitude less potent and compared in activity to the Bowers compound.

A potentiation effect was observed upon combining compounds 1 and 2. At test doses of 5 nanograms/gram no houseflies emerged from the pupae.

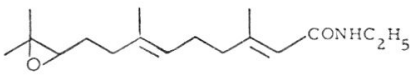
For comparison purposes I have listed the LD_{50} in µg/gram for some representative toxic pesticides ; malathion, a thiophosphate deriva-

tive, has an LD_{50} of 12.5 μg/gram against adult houseflies. The carbamate Sevin ® has an activity of 17.8 μg/gram, and the unsynergized pyrethrums have an LD_{50} of 57 μg/gram. A comparison of these activities indicates that the juvenile hormone mimics could be competitive if a suitable formulation can be developed for spreading in housefly breeding areas.

The most interesting results in our screening were obtained when we tested the amide derivatives against the German cockroach, *Blatella germanica*. These tests were carried out by treating the food with the test agent. Cornstarch was found to be an excellent bait and was treated at 100 parts/million with the test ingredients. Seven adult insects were placed in a cage with the treated food : five adult females carrying egg sacs and two adult males. In Figure 17 we see the results with the

Figure 17

COCKROACHES (BLATELLA GERMANICA)



100 PPM ON STARCH

		Replacement		Colony Development				
	Initial	1st Week	2nd	2nd	3rd	4th	5th	6th
Adults	5 ♀, 2 ♂	3 ♀, 2 ♂	1 ♀		4 ♀†	2 ♂†	1 ♀†	
Nymphs				13*, 3†			6†	4†
		6th	7th	8th	9th		17th	
Adults		5 ♀, 2 ♂	1 ♀, 2 ♂	1 ♀†	3 ♀† 1 ♂†		1 ♀†	
Nymphs				3*, 3†				

Normal ♀ produces 30-40 nymphs

*Hatch † Death

LD_{50} (μg/g): LINDANE 3.8
BAYER 39007 11.0

epoxy amide. During the 1st week that the insects were in the cage, both of the males and 3 of the females died, and were replaced. During the 2nd week 1 additional female died and was replaced. Also during the 2nd week a total of 13 nymphs appeared in the colony. Each normal female German cockroach normally carries an egg sac containing up to 50 eggs from which will appear 30–40 nymphs. The 13 nymphs which did appear therefore represent much less than 10% of a normal hatch. Three of these nymphs died during that 2nd week. During the 3rd week 4 of the adult females died, the 4th week the 2 males died and in the 5th week the surviving adult female died. The remaining

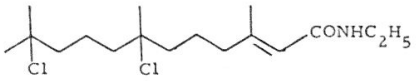
nymphs also died during the 5th and 6th weeks, thus eradicating the colony. At this point, during the 6th week, 5 additional females and 2 additional males were placed in the cage. The following week the 2 males and 1 female died and were replaced; in the 8th week only 3 nymphs appeared and promptly died. One female died that week and 3 females and 1 male died the following week. Over the next 8 weeks the 1 male and 1 female survivor failed to produce any viable eggs. On the 17th week the female died and the sole colony survivor, after 22 weeks, was an adult male.

The egg sacs must be carried by the female German cockroach until the young are about to emerge, if they are to survive. In the presence of the juvenile hormone treated starch these egg sacs frequently were prematurely dropped by the females. Even when the female successfully carried an egg sac until hatch the number of nymphs which appeared was greatly reduced.

Similar results were observed with the dichloroamide as shown in Figure 18. Again, most of the starter adults died during the first week

Figure 18

COCKROACHES (BLATELLA GERMANICA)



100 PPM ON STARCH

		Replacement		Colony Development			
	Initial	1st Week	-	4th	5th	6th	8th
Adults	5 ♀, 2 ♂	4 ♀, 1 ♂		2 ♀†	3 ♀†	2 ♂	
Nymphs				18*	2†	10†	6†
		9th	11th	12th	13th	15th	17th
Adults		5 ♀, 2 ♂	1 ♀		1 ♀†	1 ♀†	
Nymphs				3*			2†
				20th	21st		
Adults				1 ♀†	1 ♀†		
Nymphs				6*	1†		

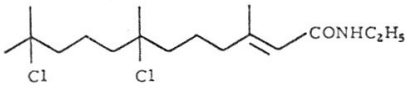
and were replaced. During the 4th week only 18 viable nymphs appeared and by the 8th week all nymphs and surviving adults had died. The colony was reseeded in the 9th week and after struggling for 12 to 13 weeks successfully established itself. However, during this interim period many of the adult females died and only a very small number of nymphs appeared.

Commercial toxic cockroach baits normally contain $^1/_{10}$ to 1% active ingredient. These hormonal agents therefore show real promise in cockroach control if lab results can be confirmed in the field.

The *N*-ethylepoxyamide and the *N*-ethyldichloroamide have been tested against phytophagous insects at our Niagara Chemical Division laboratory. Both compounds showed significant ovicidal activity on the eggs of the bean beetle and the dichloro amide showed slight ovicidal activity against the eggs of the army worm. Neither compound was effective as an ovicide against the eggs of the milkweed bug. Chemosterilant effects against adults were observed only with the dichloro amide against the milkweed bug. Some activity was observed for the dichloro amide against nymphs of the milkweed bug (Figure 19), but rather

Figure 19

GIANT MILKWEED BUG (ONCOPELTUS FASCIATUS)



TOPICAL APPLICATION

Dosage	Nymphal Mortality	6th Instar Nymph	Adult Mortality	Malformed Adults	Normal Adults
20.0 µg/g[a]	50%	15%	5%	25%	5%[b]
2.0 µg/g	40%	10%	15%	30%	5%
0.20 µg/g	25%	10%	10%	30%	25%
0.02 µg/g	10%	0%	10%	10%	70%
0.5% spray	40%	18%	5%	15%	22%

[a] Insect weight ca. 50 mg

[b] No viable eggs were produced

LD_{50} µg/g:

Pyrethrum	5 - 7
Carbaryl	4 - 8
DDT	ca. 400
Dieldrin	15

high topical doses were required to effect complete control. Spray treatment of nymphs of mixed ages did not effect control. Control of other species by spraying plants containing larval forms was not successful.

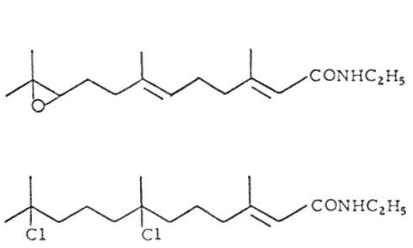
Overall, results with these compounds against phytophagous insects both in our own laboratories and in the laboratories of cooperators have been rather disappointing. The potency of these materials against typical crop pests has been much lower than required when compared to conventional toxicants. Activities such as we have seen against the mealworm in our screening tests would be required to give the hormonal compounds serious consideration. None of the compounds show anything near this magnitude of activity against the phytophagous insects.

Preliminary results have shown positive effects for our compounds against other species of diptera, e.g., *Culex pipiens* and *Stomoxys calcitrans* (14), and some species of ticks (14).

Acute toxicity in mice has been determined for both the epoxy amide and the dichloro amide (Fig. 20). The former exhibited no acute toxic effects ; the latter had an LD_{50} in the region of 5000 mg/kg.

Figure 20

ACUTE MAMMALIAN TOXICITY



	LD_{50}
	>10 g/kg
	ca. 5 g/kg
MALATHION	0.72 - 4.0 g/kg
PYRETHRUM	0.20 - 2.6 g/kg
CARBARYL	500 - 600 mg/kg
DDT	87 - 420 mg/kg

In conclusion, we have prepared two insect growth regulants with significant activity against species of *Coleoptera*, *Orthoptera* and *Diptera*, but apparently with a selection against species of *Lepidoptera*. Many problems remain, however, before compounds of this type can be used commercially. Although high selectivity may be desirable from an ecological point of view, it presents a formidable problem to the pesticide manufacturer who must absorb the high cost of registering each chemical. Reasonably long residual life in the field must be assured to effect each insect at its rather limited susceptible period. Some continued product damage must be tolerated since these compounds do not kill outright, but exert effects during the metamorphosis to pupae or adults.

I wish to acknowledge the very capable assistance of the following colleagues :

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Miss C. M. Miles	Nmr Spectrometry
Mrs. E. O. Johnson	Research Technician
Mr. D. S. Pincus	Biologist

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