Compounds Related to Juvenile Hormones. IX. Activity of Citronellylamine and Citronellol Derivatives on the Yellow Mealworm and the Large Milkweed Bug

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Alkyl and phenyl esters of citronellyl-, methylcitronellyl-, and ethylcitronellyl carbamic acids and the analogous β-substituted aminocrotonic acids were prepared and tested for juvenile hormone activity on the yellow mealworm, *Tenebrio molitor* L., and the large milkweed bug, *Oncopeltus fasciatus* (Dallas). The same esters of citronellylcarbonic and β-(citronelloxy)crotonic acids were also prepared and tested. Generally the nitrogen-containing compounds were more active than the oxygen analogs. Variation in activity as a function of structure is discussed.

In reviewing the compounds we have studied (Sonnet *et al.*, 1971, and earlier papers cited therein) and those reported in the literature by other workers (Suchy *et al.*, 1968; Masner *et al.*, 1968; Bowers, 1969; Jarolim *et al.*, 1969; Ruegg and Schmialek, 1969; Wigglesworth, 1969; Mori and Matsui, 1970) one is impressed by the variety of structures which can cause the physiological activity termed "juvenilization" in various insect species. Moreover, the terminal functional group can be considerably varied without great loss of activity in the yellow mealworm, *Tenebrio molitor* L. (Table I).

If a chemical transformation is to be wrought upon the juvenilizing molecule as the basis of its biological activity, then one would expect at least a superficial resemblance of the various functional groups in the active compounds. A chemical reaction which all active compounds studied to date could conceivably undergo is oxidation of the chain adjacent to the aforementioned variable functionality. Such a step requires the presence of an oxidizable hydrogen atom on either the 7 or 8 position counting from the epoxide oxygen (Table I). The first three compounds have either allylic or allylic plus α-oxygen stabilization for an incipient radical formed by such an oxidation at site 7 or 8. The remaining compounds have a tertiary acetal hydrogen atom and an NH at site 8.

In order to assess the requirement of such a hydrogen atom, compounds could be prepared bearing substituents at these sites in order to modify activity. Synthetically, the easiest compounds to deal with in this regard are the carbamates, such as the last compound in Table I. We therefore prepared a series of carbamates and enamino esters in which the NH of site 8 was methodically replaced by NCH_3 and NC_2H_5. We also changed the heteroatom from N to O. Because of the bivalent nature of oxygen, no hydrogen atom could be present at site 8. Thus a series of carbonates and enol ether esters (β-alkoxycrotonates) was synthesized. This paper reports their preparation, their activities, and a comparison of activity as a function of structure.

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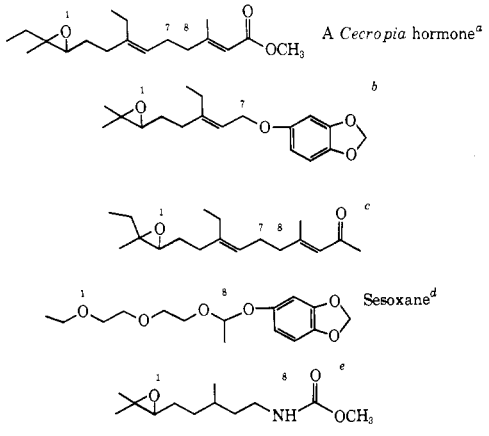
EXPERIMENTAL

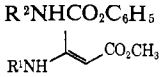
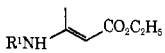
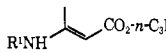
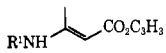
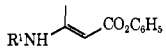
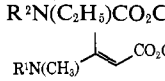
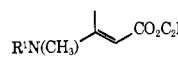
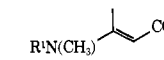
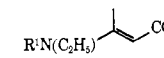
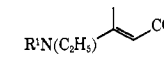
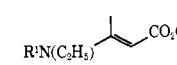
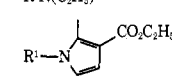
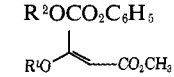
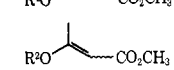
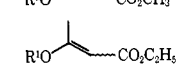
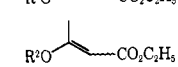
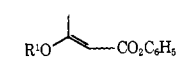
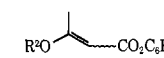
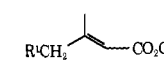
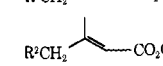
Infrared spectra were obtained with a Perkin-Elmer Model 137 infrared spectrophotometer. Nuclear magnetic resonance spectra were measured with a Varian T-60 instrument with CCl_4 as the solvent and TMS as the internal standard. Thin-layer chromatography was performed with plates coated with silica gel G that were most often developed with 5% methanol–benzene using iodine visualization. Gas chromatography was performed with an Aerograph Model A-700

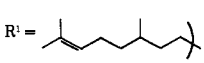
Table I. Examples of Compounds Active in the Yellow Mealworm, *Tenebrio molitor*

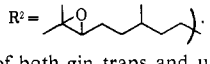


[a] Röller *et al.* (1967). [b] Bowers (1969). [c] Schwarz *et al.* (1970a). [d] Bowers (1968). [e] Schwarz *et al.* (1970a).

Table II. Ratings of Juvenile Hormone Activity of Site 8-Substituted Mimics Applied Topically to Pupae of the Yellow Mealworm and Nymphs of the Large Milkweed Bug[a]

Entry no.	Structure[b]	Average rating[c] *T. molitor* L.	Average rating[c] *O. fasciatus* D.
1	$R^1NHCO_2CH_3$	2.6[d]	0.0
2	$R^2NHCO_2CH_3$	4.0	3.0
3	$R^1NHCO_2C_2H_5$	4.0	2.6[d]
4	$R^2NHCO_2C_2H_5$	4.0	3.0
5	R^1NHCO_2-*n*-C_3H_7	4.0	1.4
6	R^2NHCO_2-*n*-C_3H_7	4.0	3.0
7	$R^1NHCO_2C_3H_3$[e]	4.0	2.6
8	$R^2NHCO_2C_3H_3$	4.0	3.0
9	$R^1NHCO_2C_6H_5$[f]	3.6	2.8
10	$R^2NHCO_2C_6H_5$	4.0	3.0
11		4.0	0.3
12		3.0	2.0
13		3.0	0.0
14		3.0	2.4
15		0.4	0.2
16	$R^1N(CH_3)CO_2CH_3$	0.0	0.0
17	$R^2N(CH_3)CO_2CH_3$	1.3	3.0
18	$R^1N(CH_3)CO_2C_2H_5$	3.1[d]	3.0
19	$R^2N(CH_3)CO_2C_2H_5$	0.0	3.0
20	$R^1N(CH_3)CO_2C_6H_5$	0.8	0.0
21	$R^2N(CH_3)CO_2C_6H_5$	3.0	1.8
22	$R^1N(C_2H_5)CO_2CH_3$	0.2	0.7
23	$R^2N(C_2H_5)CO_2CH_3$	3.4	2.5
24	$R^1N(C_2H_5)CO_2C_2H_5$	0.0	0.8
25	$R^2N(C_2H_5)CO_2C_2H_5$	3.8	3.0
26	$R^1N(C_2H_5)CO_2C_6H_5$	3.0	2.0
27	$R^2N(C_2H_5)CO_2C_6H_5$	4.0	3.0
28		0.2	0.0
29		0.0	0.0
30		0.0	0.0
31		3.8	0.0
32		3.0	1.2
33		0.0	0.0
34		0.8	3.0
35	$R^1OCO_2CH_3$	0.0	0.0
36	$R^2OCO_2CH_3$	0.0	0.0
37	$R^1OCO_2C_2H_5$	0.2	0.4
38	$R^2OCO_2C_2H_5$	0.0	0.0
39	$R^1OCO_2C_6H_5$	0.0	0.2
40	$R^2OCO_2C_6H_5$	0.0	0.0
41		3.0	1.2
42		3.0	3.0
43		3.7	2.8
44		3.0	3.0
45		1.3	2.0
46		0.2	2.0
47		0.2	2.0
48		1.6	3.0

R^1 =  ;

R^2 =  .

[a] All compounds were applied as acetone solutions at 10 μg/μl/pupa (nymph) to five animals. [b] . [c] With *T. molitor*, 0 = perfect adult, no JH activity; 1 = retention of either gin traps or urogomphi; 2 = retention of both gin traps and urogomphi; 3 = same as 2; also retention of pupal cuticle around area of treatment; 4 = second pupa; retention of all pupal characteristics. With *O. fasciatus*, 0 = perfect adult, no JH activity; 1 = adult with retention of nymphal coloration in abdomen; 2 = adult with reduced wings and nymphal coloration in abdomen; 3 = second nymph; supernumerary nymph. [d] 30 μg/μl/pupa (nymph). [e] C_3H_3 = $CH{\equiv}CCH_2$; *i.e.*, 2-propynyl. [f] C_6H_5 = phenyl.

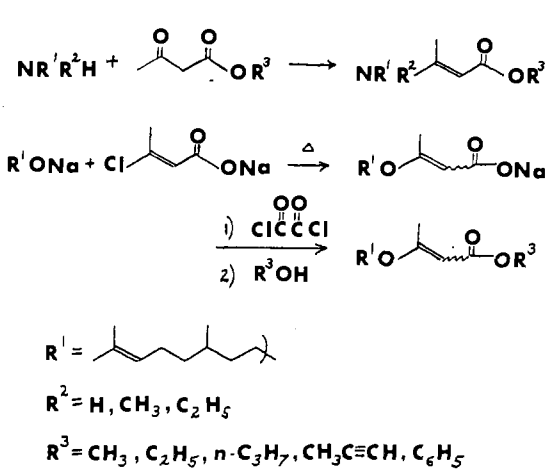
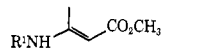
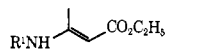
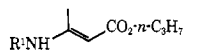
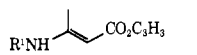
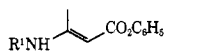
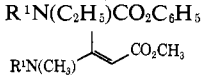
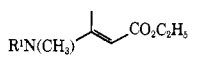
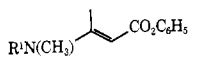
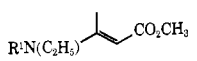
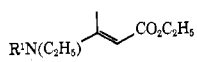
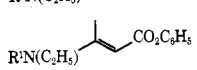
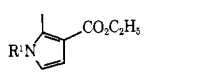
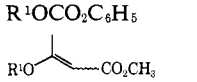
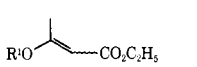
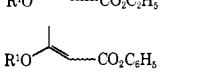
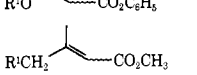


Figure 1. Preparation of enaminoesters and β-citronelloxycrotonates

instrument and various columns. Citronellylamine, bp 44–46° C/0.05 mm (Arigoni and Jeger, 1954), was allowed to react with alkyl and phenyl chloroformates with triethylamine as an acid scavenger to produce the corresponding carbamates (compounds **1**, **3**, **5**, **7**, and **9** in Table II). The chloroformates had been synthesized from the alcohols and phenols with phosgene and triethylamine. In like manner, reaction of citronellol with these same chloroformates and triethylamine produced the carbonates (**35**, **37**, and **38**). Reduction of **3** with LAH gave *N*-methylcitronellylamine, bp 42–44° C/0.025 mm. Acetylation of citronellylamine and analogous reduction yielded *N*-ethylcitronellylamine, bp 41–44° C/0.035 mm. These new amines were converted to carbamates **16**, **18**, **20**, **22**, **24**, and **26**. Condensation of the amines with alkyl and phenyl acetoacetates produced β-aminocrotonates **11–15** and **28–33** (Figure 1). The β-alkoxycrotonates **41**, **43**, and **45** were prepared by heating the sodium salt of β-chlorocrotonic

Table III. Minimum Dose ($\mu g/\mu l$) at Which a JH Activity Rating of 2.0 or Greater Was Obtained on the Yellow Mealworm (I) and the Large Milkweed Bug (II)[a]

	Unepoxidized compounds[b]	Corresponding epoxidized compounds[b]				
		T. molitor	*O. fasciatus*		*T. molitor*	*O. fasciatus*
1	$R^1NHCO_2CH_3$[b]	>10	>10	2	5	5
3	$R^1NHCO_2C_2H_5$	3	>10	4	0.3	1
5	R^1NHCO_2-*n*-C_3H_7	5	>10	6	1	1
7	$R^1NHCO_2C_3H_3$	5	10	8	1	5
9	$R^1NHCO_2C_6H_5$	1	10	10	0.1	1
11		5	>10			
12		5	10			
13		10	>10			
14		5	10			
15		>10	>10			
16	$R^1N(CH_3)CO_2CH_3$	>10	>10	17	>10	5
18	$R^1N(CH_3)CO_2C_2H_5$	>10	0.3	19	>10	1
20	$R^1N(CH_3)CO_2C_6H_5$	>10	>10	21	1	>10
22	$R^1N(C_2H_5)CO_2CH_3$	>10	>10	23	10	5
24	$R^1N(C_2H_5)CO_2C_2H_5$	>10	>10	25	5	5
26	$R^1N(C_2H_5)CO_2C_6H_5$	1	5	27	1	1
28		>10	>10			
29		>10	>10			
30		>10	>10			
31		>10	>10			
32		>10	>10			
33		1	5			
34		>10	1			
35	$R^1OCO_2CH_3$	>10	>10	36	>10	>10
37	$R^1OCO_2C_2H_5$	>10	>10	38	>10	>10
39	$R^1OCO_2C_6H_5$	>10	>10	40	>10	>10
41		10	>10	42	10	5
43		5	5	44	10	1
45		>10	10	46	>10	10
47		>10	10	48	>10	1
49	Farnesyl methyl ether	2				
50	Synthetic JH (mixture of isomers)	1				
51	Sesamex		5			

[a] The scoring systems for the two species differ and the data here do not yield true measures of relative activity. [b] The entry numbers are those of Table I.

acid (Jones *et al.*, 1960) with sodium citronelloxide. The resulting β-citronelloxycrotonic acid was then converted to the acid halide with oxallyl chloride and then to the ester by treatment with the appropriate alcohol.

The enamino esters were expected to have the geometry shown in Figure 1 (Pizey and Truce, 1964) and the nmr spectrum of, for example, **11** shows a singlet vinyl proton absorption for the enamine unit at 4.32 ppm. This compares well with the value 4.38 found for ethyl β-(propylamino)crotonate (Allen *et al.*, 1966). The isomeric crotonate is expected to show this absorption at lower field. The stereochemistry of the β-alkoxycrotonates is unsettled (Jones *et al.*, 1960).

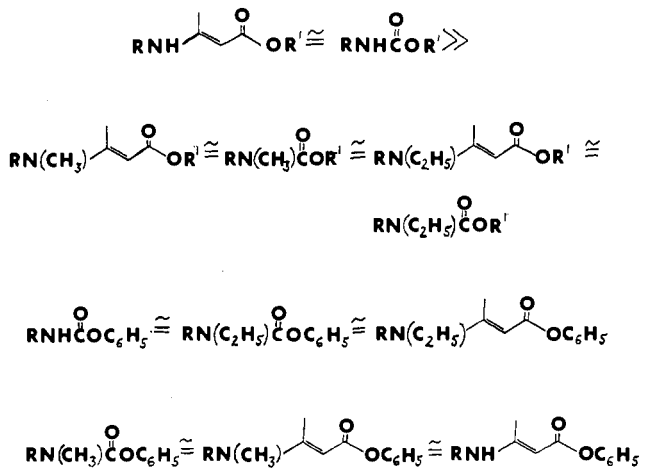


Figure 2. Relative activities in the yellow mealworm, *Tenebrio molitor*

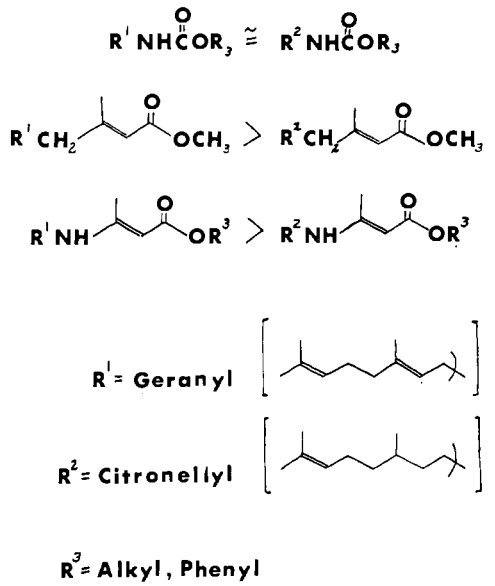


Figure 3. Effect of substitution of geranyl for citronellyl upon JH activity

The epoxides of a number of the compounds described above were prepared with *m*-chloroperbenzoic acid in methylene chloride.

Many of the compounds could not be distilled without decomposition and these were therefore purified by column chromatography on alumina. The purity of all compounds prepared was assessed by the combined use of thin-layer and gas chromatographies, and infrared and nmr techniques. They were then tested topically as described previously (Redfern *et al.*, 1970) and rated according to the method of McGovern *et al.* (1971).

RESULTS AND DISCUSSION

Table II lists the compounds prepared and their average ratings when they were applied topically at a rate of 10 μg/μl/pupa (nymph). Quite a number of compounds gave ratings of 3.0 or better on *T. molitor* and so the relative activities are not readily assessed. Table III, which forms the basis of the following discussion, lists the same compounds but gives the minimum dose at which a rating of 2.0 or better was achieved in each test species.

The phenyl citronellylcarbamates were among the most active of the citronellylcarbamates when they were compared with compounds of their own class; *i.e.*, epoxidized *vs.* epoxidized or unepoxidized *vs.* unepoxidized. These two classes have been separated into two columns in Table III to facilitate such a comparison. The methyl esters were slightly less active. The activities of the corresponding enamino esters were roughly similar, perhaps occasionally greater, than those of the carbamates. One distinct exception was the much diminished activity of the phenyl ester **15**. Because of the basicity of the enamino esters we were unable to prepare the epoxides by the usual route.

Replacement of the available H on site 8 by CH_3 gave compounds **16–20**. Both the methyl and phenyl esters showed less activity in both test species than either of their secondary carbamate or their crotonate counterparts. While the ethyl esters, **18** and **19**, showed less activity in *T. molitor*, they were very active in *Oncopeltus fasciatus*, Dallas. This striking inversion of activity (compare **3** and **18**) was brought about by *N*-methylation; *i.e.*, no change in functional group, chain length, or chain flexibility. The phenomenon illustrates the specificity which we have found in our screening efforts.

Because *N*-demethylation is an established biodegradative route which regenerates the NH we sought to remove, we also prepared a series of *N*-ethyl compounds. The methyl and ethyl esters increased in activity (see the epoxides column for comparison between **23** and **17**, and **25** and **19**). The unique activity of **18** against *O. fasciatus*, however, has been lost by replacing CH_3 with C_2H_5. The phenyl ester showed slightly increased activity. The *N*-methyl and *N*-ethyl (citronellylamino)crotonates, **28–32**, showed consistently reduced activity, but the maverick phenyl ester **33** was as active as phenyl citronellylcarbamate **9**. The pyrrole, **34**, although structurally similar to the *N*-methyl enamino ester **32** is chemically very different, of course. The ester function is somewhat more like that of a carbamate than that of an enamino ester. In fact its activity was very much like that of **18**; it showed only low activity in *T. molitor*, but considerable activity against *O. fasciatus*.

The carbonates, **35–40**, showed uniformly low activity. Extending the chain to produce β-citronelloxycrotonates did in fact seem to increase activity. Although no potential oxidation site existed at position 8, some activity was nevertheless found.

The testing data for *T. molitor* is summarized in Figure 2. When R was the citronellyl radical and R^1 was an alkyl group, the carbamates and β-aminocrotonates showed roughly equivalent activity, as would be expected if position 8 were required to have an oxidizable hydrogen atom. The phenyl esters showed a different activity relationship (Figure 2). The low activity of **15** could be ascribed to base sensitivity, since this compound probably eliminates phenol even more readily than do the aryl carbamates. However, the enhanced activity of the two ethylated compounds **26** and **33** cannot be explained by a simple oxidation idea. In particular, the variation in activity between the two insect test species suggests that other structural requirements, namely shape and length, are being superimposed over the primary chemical requirements.

One final observation can be made. In earlier work (Wakabayashi *et al.*, 1969) the importance of the central double bond for maximum activity of the *cecropia*-like structures was demonstrated. The carbamates (Schwarz *et al.*, 1970) and

aryl carbamates (Sonnet *et al.*, 1971) were not significantly enhanced in activity against either of the test species when the citronellyl group was replaced by geranyl (Figure 3). However, a similar substitution in aminocrotonates did increase activity. Perhaps a relationship exists between chain length and requirement for internal stereoregulation. The longer chain makes better use of an internal olefinic link, while the somewhat less flexible shorter chain experiences no real advantage from it.

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