Insect Juvenile Hormone Activity of Alkyl (2*E*,4*E*)-3,7,11-Trimethyl-2,4-dodecadienoates. Variations in the Ester Function and in the Carbon Chain

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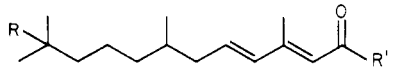
Bioassay data for some analogues of the alkyl (2*E*,4*E*)-3,7,11-trimethyl-2,4-dodecadienoates on the yellow-fever mosquito (*Aedes aegypti*), the greater wax moth (*Galleria mellonella*), the yellow mealworm (*Tenebrio molitor*), the house fly (*Musca domestica*), the pea aphid (*Acyrthosiphon pisum*), and the tobacco budworm (*Heliothis virescens*) are presented and discussed. Variations in the ester function discussed in this paper include *S*-alkyl thioates, *N*-alkylamides, and α,β:γ,δ-unsaturated ketones. The effects on the juvenile hormone activity of substituents in the carbon chain of the dodecadienoates are discussed in detail.

The alkyl (2*E*,4*E*)-3,7,11-trimethyl-2,4-dodecadienoates (e.g., **2** and **17**) (Henrick, 1972; Henrick and Siddall, 1972, 1975c; Henrick et al., 1973) are potent insect growth regulators (IGR's) with juvenile hormone activity (Menn and Beroza, 1972; Slama et al., 1974; Staal, 1975; Menn and Pallos, 1975) and in related papers we have discussed synthetic methods for the preparation of each of the four stereoisomers (Henrick et al., 1975b) and also general stereoselective synthetic routes to these compounds (Henrick et al., 1975a,c). The ability of several of these 2,4-dienoate analogues to interfere with the metamorphosis of the larvae and pupae of many insect species has been extensively studied. For example, methoprene [trademark Altosid IGR; ZR 515; isopropyl (2*E*,4*E*)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate (**17**)] is highly effective in controlling (by the disruption of metamorphosis) many Diptera such as the mosquito species *Aedes aegypti* (Jakob, 1972; Henrick et al., 1973) and *Aedes nigromaculis* (Schaefer and Wilder, 1972, 1973); the house fly, *Musca domestica* (Jakob, 1973; Plapp and Vinson, 1973; Henrick et al., 1975b; Morgan et al., 1975); the stable fly, *Stomoxys calcitrans* (Wright and Bowman, 1973; Harris et al., 1974); black flies (Cumming and McKague, 1973); the face fly, *Musca autumnalis* (Miller and Uebel, 1974); the horn fly, *Haematobia irritans* (Harris et al., 1974); the apple maggot, *Rhagoletis pomonella* (Pree, 1974); the mediterranean fruit fly, *Ceratitis capitata* (Daoud and Sehnal, 1974); and aquatic midges (Mulla et al., 1974). Also the metamorphosis of the cockroach, *Nauphoeta cinerea* (Radwan and Sehnal, 1974), can be disrupted.

The ester **2** (hydroprene, trademark Altozar IGR; ZR 512) is highly active on many insect species of the families Lepidoptera, Coleoptera, and Homoptera. Examples are the potato aphid (Benskin and Perron, 1973) and several other aphid species (Kuhr and Cleere, 1973); mealybugs and soft scale pests of foliage plants (Hamlen, 1975); the cockroach, *Nauphoeta cinerea* (Radwan and Sehnal, 1974); and pests of stored grain (moths, beetles, and weevils; Strong and Diekman, 1973). The 2-propynyl ester **8** (kinoprene; trademark Enstar IGR; ZR 777) shows considerable promise in controlling homopterous insect species such as the greenbug, *Schizaphis graminum*; the green peach aphid, *Myzus persicae* (Nassar et al., 1973); the citrus mealybug, *Planococcus citri* (Staal et al., 1973); the longtailed mealybug, *Pseudococcus longispinus*; hemispherical scale, *Saissetia coffeae*, and *Phenacoccus solani* (Hamlen, 1975); the pea aphid, *Acyrthosiphon pisum* (Table I); and the greenhouse whitefly, *Trialeurodes vaporariorum*.

We have previously briefly discussed some modifications of the structure of methyl 10,11-epoxyfarnesoate leading to the alkyl 3,7,11-trimethyl-2,4-dodecadienoates and have presented some bioassay data for a few selected analogues (Henrick et al., 1973, 1975b). We describe here some detailed structure–biological activity relationships for this class of juvenile hormone analogs.



2, R = H; R′ = OCH_2CH_3 (ZR 512)
8, R = H; R′ = $OCH_2C{\equiv}CH$ (ZR 777)
17, R = OCH_3; R′ = $OCH(CH_3)_2$ (ZR 515)
35, R = OCH_3; R′ = SCH_2CH_3 (ZR 619)
49, R = OCH_3; R′ = $NHCH_2CH_3$ (ZR 618)
65, R = OCH_3; R′ = CH_2CH_3 (ZR 1917)

RESULTS AND DISCUSSION

Alkyl (2*E*,4*E*)-3,7,11-Trimethyl-2,4-dodecadienoates. The bioassay data for some racemic alkyl, alkenyl, and alkynyl esters on several insect species are given in Table I. The esters were prepared from the corresponding 2*E*,4*E* acids via the acyl chlorides as described previously (Henrick et al., 1973, 1975a). The 2*E*,4*E* stereoisomers of these dienoates show considerably higher biological activity than the other three possible stereoisomers (Henrick et al., 1973, 1975b) and all of the compounds discussed in this paper have the *E* configuration at the 4-ene double bond and either predominantly or almost exclusively the *E* configuration at the 2-ene double bond. There is an asymmetric carbon atom at C-7 in these compounds and there are considerable differences in the biological activity of the (+)- and (−)-enantiomers of some of these dienoates. For example, the (*S*)-(+)-enantiomers of **2** and **17** [prepared from (*S*)-(−)-dihydrocitronellal and (*S*)-(−)-7-methoxycitronellal, respectively] show considerably higher juvenile hormone activity against most insect species studied than do the corresponding (*R*)-(−)-enantiomers (Henrick et al., 1976). All of the compounds discussed in this paper are racemic, unless otherwise specified in the tables.

The dependence of the juvenile hormone activity in different insect species on the nature of the ester group is apparent from the results given in Table I. For Diptera (*Aedes aegypti* and *Musca domestica*) and for *Tenebrio molitor* the isopropyl ester analogues show the highest biological activity, whereas for Lepidoptera (*Galleria*

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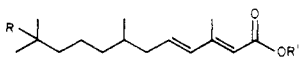
Table I. ID_{50} Values for Esters of (2*E*,4*E*)-3,7,11-Trimethyl-2,4-dodecadienoic Acids on Sensitive Synchronized Instars[a,b]



No.	R	R′	*Aedes aegypti*, ppm	*Galleria mellonella*, μg/pupa	*Tenebrio molitor*, μg/pupa	*Musca domestica*, μg/prepupa	*Acyrthosiphon pisum*, % active ingredient in spray	*Heliothis virescens*, ppm in medium
1	H	CH_3	0.15	0.050	1.6	100		0.84
2[c]	H	CH_2CH_3	0.007 8	0.040	0.25	18	0.003 9	0.30
3	H	$CH_2CH_2CH_3$	0.016	1.7	0.54	>100	0.005 6	50
4	H	$CH(CH_3)_2$	0.001 9	0.28	0.026	2.2	0.035	3.8
5	H	$CH_2CH(CH_3)_2$	0.025	27	0.047	>100	0.064	>100
6	H	$CH(CH_3)CH_2CH_3$	0.018	5.3	0.040	25	0.031	>100
7	H	$C(CH_3)_3$	>0.1	>100	29	22		7.4
8[d]	H	$CH_2C{\equiv}CH$	0.23	0.64	1.3	>100	0.000 95	3.0
9	H	$CH_2C{\equiv}CCH_3$	0.30	30	2.2	>100	0.045	190
10	H	$CH_2CH{=}CH_2$	0.020	0.47	0.86	>100	0.003 0	41
11	H	C_6H_5	0.40	16	10	>100		>100
12	H	$CH_2C_6H_5$	10	>100	>100	>100		>100
13	CH_3O	CH_3	0.020	1.3	36	>100		1.2
14	CH_3O	CH_2CH_3	0.002 0	0.17	8.9	5.0	0.000 056	0.20
15	CH_3O	$CH_2CH_2CH_3$	0.003 1	12	7.0	28	0.001 5	1.0
16	CH_3O	$CH_2CH_2CH_2CH_3$	0.031	>100	38	56	0.031	>100
17[e]	CH_3O	$CH(CH_3)_2$	0.000 17	5.7	0.0040	0.0035	0.005 4	0.77
18	CH_3O	$CH_2CH_2CH(CH_3)_2$	0.37	>100	52	>100	>0.1	100
19	CH_3O	$CH(CH_3)CH_2CH_3$	0.002 3	10	0.0070	0.32	>0.01	>100
20	CH_3O	$C(CH_3)_3$	0.001 5	100	0.050	0.78		
21	CH_3O	$CH_2C{\equiv}CH$	0.20	2.5	14	>100	0.000 38	6.3
22	CH_3O	$CH_2CH_2C{\equiv}CH$	0.010	4.7	25	100	0.002 1	17
23	CH_3O	$CH_2CH{=}CH_2$	0.017	28	12	5.0	0.000 25	14
24	CH_3O	$CH_2CH{=}CHCH_3$	0.035	>100	1.8	3.5	0.038	69
25	CH_3O	$CH(CH_3)CH{=}CH_2$	0.003 3	>100	0.013	2.5	0.028	17
26[f]	CH_3O	C_3H_5	0.002 4	2.8	0.40	0.35	0.002 1	2.3
27[g]	CH_3O	C_4H_7	0.002 6	5.2	0.52	2.7	0.003 5	2.8
28[h]	CH_3O	C_5H_9	0.018	>100	0.016	3.4	0.10	>100

[a] All of the esters described in this table are racemic compounds. [b] Bioassays were performed as previously described (Henrick et al., 1973, 1975b). [c] Hydroprene (trademark Altozar IGR; ZR 512). [d] Kinoprene (trademark Enstar IGR; ZR 777). [e] Methoprene (trademark Altosid IGR; ZR 515; Henrick and Siddall, 1975c). [f] Cyclopropyl ester. [g] Cyclobutyl ester. [h] Cyclopentyl ester.

mellonella and *Heliothis virescens*) the ethyl ester analogues usually have the highest activity. For the pea aphid the ethyl, allyl, and 2-propynyl esters show high activity. The 2-propynyl esters (e.g., **8** and **21**) produce additional interesting effects on aphids other than the morphogenetic effects scored in Table I (Nassar et al., 1973; Staal et al., 1973). The juvenile hormone activity decreases rapidly in all of these six insect species when the ester group contains more than four carbon atoms. The phenyl (**11**) and benzyl (**12**) esters show low activity. The cyclopropyl ester **26** shows, in general, lower activity than the isopropyl ester **17** (except for the pea aphid) and the cyclopentyl ester **28** shows comparatively low activity except on *Tenebrio molitor*. Recently it has been reported by Mori et al. (1975) that for a series of alkyl 10,11-epoxyfarnesoates, the juvenile hormone activity on *Bombyx mori* is highest for the ethyl ester (with the ethyl > methyl ≥ *n*-propyl > *n*-butyl > *n*-pentyl).

S-Alkyl Thioates and *N*-Alkylamides. The bioassay data for some thiocarboxylic esters and for some amides are given in Table II. The racemic *S*-ethyl thioates **30** and **35** show high activity on all of the six insect species. The *S*-ethyl ester **35** shows higher juvenile hormone activity than the *S*-isopropyl ester **36** on *Aedes aegypti* but in *Tenebrio molitor* this situation is reversed. The *S*-ethyl 11-hydroxy ester **39** [(−)-enantiomer; optical purity ca. 0.53] and the 11-acetoxy ester **40** [(−)-enantiomer; optical purity ≥0.75] show high activity on Lepidoptera (*Galleria mellonella* and *Heliothis virescens*). The (+) isomers of **39** and **40** (and the racemic mixtures) would be expected to show higher activity (cf. Henrick et al., 1976).

The *N*-ethyl- and *N*,*N*-diethyldienamides show, in general, the highest biological activities (Table II) of the primary *N*-alkylamide analogues. The unsubstituted amide **48** was quite inactive (cf. Wigglesworth, 1969b; Cruickshank and Palmere, 1971). The racemic *N*-ethyl-11-methoxyamide **49** has high activity on all six of the insect species with particularly good juvenile hormone activity on *Tenebrio molitor*. Previously we noted (Henrick et al., 1973) that for alkyl 6,7-dihydrofarnesoate analogues, a 10,11-double bond generally reduces the biological activity compared with the morphogenetic activity of the corresponding 10,11-dihydro carboxylic ester analog. Comparison of the racemic *N*-ethyl 10,11-olefin (**56A**) with the corresponding 10,11-dihydro (**42**) analogue demonstrates that this correlation also applies, in general, to the amide analogues. The analogues **57** and **58** are (−)-enantiomers (optical purity ca. 0.53) and therefore their activity cannot be compared directly with that of the racemic amides **47** and **53** (cf. Henrick et al., 1976).

In a series of *N*-alkyl- and *N*,*N*-dialkyl-10,11-epoxy-3,7,11-trimethyl-2,6-dodecadienamides (and related analogues), the *N*-ethylamides showed the highest juvenile hormone activity on *Tenebrio molitor* (Cruickshank, 1971; Cruickshank and Palmere, 1971). The morphogenetic activity in this series was found to fall off rapidly with

Table II. ID_{50} Values for *S*-Alkyl Esters and *N*-Alkylamides derived from (2*E*,4*E*)-3,7,11-Trimethyl-2,4-dodecadienoic Acids on Sensitive Synchronized Instars[a]

No.	R	R′	*Aedes aegypti*, ppm	*Galleria mellonella*, μg/pupa	*Tenebrio molitor*, μg/pupa	*Musca domestica*, μg/prepupa	*Acyrthosiphon pisum*, % active ingredient in spray	*Heliothis virescens*, ppm in medium
29[b]	H	SCH_3	0.005 9	0.037	0.15	32	0.042	0.60
30[b]	H	SCH_2CH_3	0.002 2	0.045	0.02 5	2.4	0.000 43	0.55
31[b]	H	$SCH(CH_3)_2$	0.025	0.10	0.01 8	7.8	0.004 5	0.46
32[b]	H	$SCH_2C{\equiv}CH$	0.10	0.71	0.10	84	0.004 6	16
33[b]	H	$SCH_2CH{=}CH_2$	0.12	0.36	0.16	>100	0.002 7	30
34[c]	CH_3O	SCH_3	0.002 7	0.038	0.10	3.2	0.024	1.0
35[c,d]	CH_3O	SCH_2CH_3	0.000 40	0.080	0.10	0.35	0.000 83	0.41
36[c]	CH_3O	$SCH(CH_3)_2$	0.007 2	0.68	0.003 0	0.30	0.001 7	1.7
37[c]	CH_3O	$SCH_2C{\equiv}CH$	>0.10	300	2.3	6.0		29
38[c]	CH_3O	$SCH_2CH{=}CH_2$	0.002 6	2.8	0.47	28	0.000 25	24
39[c,e]	HO	SCH_2CH_3	0.020	0.037	0.11	2.3	>0.01	0.12
40[c,f]	$CH_3C(O)O$	SCH_2CH_3	0.060	0.040	0.50	0.39	>0.01	0.16
41[b,e]	CH_3	SCH_2CH_3	0.037	1.2		2.4	0.003 4	0.11
42[g]	H	$NH{-}CH_2CH_3$	0.060	0.063	0.004 6	0.23	0.032	3.0
43[g]	H	$NH{-}CH(CH_3)_2$	0.028	>100	0.013	0.54	0.025	>100
44[g]	H	$NH{-}CH_2CH(CH_3)_2$	>0.10	>100	70	>100		>100
45[g]	H	$NH{-}CH_2CH{=}CH_2$	0.39	>100	0.013	>100		40
46[g]	H	$N(CH_3)_2$	0.13	0.75	0.053	1.6	>0.01	3.5
47[g]	H	$N(CH_2CH_3)_2$	0.17	0.33	0.006 8	0.21	0.027	3.6
48[h]	CH_3O	NH_2	>0.10	>100	300	>100		>100
49[h]	CH_3O	$NH{-}CH_2CH_3$	0.026	0.11	0.000 33	0.0077	0.03	0.62
50[h]	CH_3O	$NH{-}CH(CH_3)_2$	0.029	80	0.019	0.044	>0.1	50
51[h]	CH_3O	$NH{-}C_3H_5$	0.70	>100	0.056	1.0	>0.1	37
52[h]	CH_3O	$N(CH_3)_2$	0.26	0.40	0.047	0.040		2.0
53[h]	CH_3O	$N(CH_2CH_3)_2$	0.27	0.067	0.001 0	0.030	>0.1	0.48
54[f,h]	HO	$NH{-}CH_2CH_3$	>0.10	1.10	0.001 7	0.22		
55[e,g]	CH_3	$NH{-}CH_2CH_3$	3.7	4.7	0.010	6.5		25
56A	10,11-Olefin	$NH{-}CH_2CH_3$	0.53	3.2	0.004 4	3.0		28
56B[e]			1.8	100	0.058	46		
57[e]	10,11-Olefin	$N(CH_2CH_3)_2$	>10	>100	5.8	4.2		
58[e]	10,11-Epoxy	$N(CH_2CH_3)_2$	5.10	84	0.043	1.8		>100

[a] The compounds described in this table are racemic unless otherwise specified (footnotes *e* and *f*). [b] Henrick, 1974d. [c] Henrick and Siddall, 1975b. [d] Triprene (ZR 619). [e] (−)-Enantiomer; optical purity ca. 0.53. [f] (−)-Enantiomer; optical purity ≥0.75. [g] Henrick, 1974b. [h] Henrick and Siddall, 1974a.

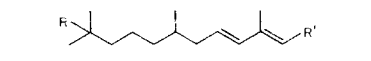
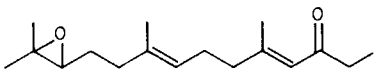
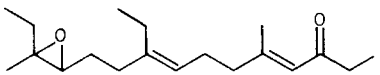
decreasing and increasing (from *N*-ethyl) size of the N substituent. The *N*,*N*-diethylamides in this farnesamide series were considerably lower in activity than were the corresponding *N*-ethylamides (cf. Table II).

α,β:γ,δ-Unsaturated Ketones. In Table III there are presented bioassay data for examples of α,β:γ,δ-unsaturated ketones derived from the 3,7,11-trimethyl-2,4-dodecadienoic acids, and also bioassay data for some related compounds. The conjugated ketones were prepared by reaction of the corresponding dienoic acid with ≥2 equiv of the alkyllithium in diethyl ether at 0°C (Jorgenson, 1970). The dienoic acids, e.g. **72** and **73** (Henrick et al., 1973), show low juvenile hormone activity in all the bioassays, presumably due to the polarity of the carboxylic acid group (cf. Wigglesworth, 1969a). The racemic ethyl ketones **59**, **65**, and **71** show high activity, with the hydroxy ketone **71** showing especially good juvenile hormone activity on lepidopterous species (*Galleria mellonella* and *Heliothis virescens*) and on *Tenebrio molitor*. The *n*-propyl ketones **60** and **66** also have good activity on *Tenebrio molitor*. The other ketones in Table III show somewhat lower activity, in general, on all of the insect species examined. The diazo ketones **64** and **69** show high activity on *Tenebrio molitor* but not on most of the other species examined. The α,β:γ,δ-unsaturated nitriles **74** and **75** show low activity as do the alcohols **76** and **77** and the corresponding acetates (e.g., **78**; cf. Nilles et al., 1973), the alkyl (e.g., **79**, **80**, and **81**) or aryl ethers (e.g., **82**), the thioethers, and the amines (e.g., **83**). The ester **84** with one extra carbon atom between the diene system and the ester (cf. **1**, Table I) has low activity.

The methyl ketone analogues corresponding to the ethyl ketones **85** and **86** had been previously reported to be highly active against *Tenebrio molitor* (Schwarz et al., 1970, 1974b; see also Wright and Spates, 1971). The ethyl ketone **85** has been shown to possess high activity against the red flour beetle *Tribolium castaneum* and the confused flour beetle, *T. confusum* (Amos et al., 1974), and to have greater or equal juvenile hormone activity than the corresponding *n*-propyl ketone and higher activity than the corresponding methyl or *n*-butyl ketone (see also Nilles et al., 1973).

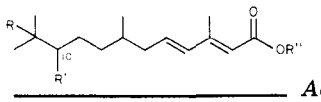
C-10 and C-11 Substituents. Bioassay data are presented in Table IV for ethyl and isopropyl (2*E*,4*E*)-3,7,11-trimethyldodecadienoates with different substituents at C-10 and at C-11. In both the ethyl and the isopropyl 2,4-dienoate ester series, as discussed previously (Henrick et al., 1973), the presence of a terminal epoxide (e.g., **88A**) or of a 10,11-double bond (**87A** and **101A**) reduces the biological activity against some insect species compared with that observed for the 10,11-dihydro compounds (**2** and **4**, respectively) (cf., however, the statements of Slama et al., 1974, p 203). In this context some of the previous comparisons made by us may be inaccurate as the samples of **87**, **88**, and **101** used (Henrick et al., 1973, 1975b) were not racemic as stated, but were (−)-enantiomers (optical purity ca. 0.53), i.e. **87B**, **88B**, and **101B** (Table IV). All of the other compounds previously described (Henrick et al., 1973, 1975b) were racemic analogues. The analogue **102** with an 11-ene (exo-

Table III. ID_{50} Values for $\alpha,\beta:\gamma,\delta$-Unsaturated Ketones and Other Diene Analogs on Sensitive Synchronized Instars[a]

No.	 R	R′	*Aedes aegypti*, ppm	*Galleria mellonella*, μg/pupa	*Tenebrio molitor*, μg/pupa	*Musca domestica*, μg/prepupa	*Acyrthosiphon pisum*, % active ingredient in spray	*Heliothis virescens*, ppm in medium
59	H	$C(O)CH_2CH_3$	0.024	0.070	0.003 2	0.54		0.050
60	H	$C(O)CH_2CH_2CH_3$	0.038	0.90	0.005 3	3.6	0.029	2.6
61	H	$C(O)CH_2CH(CH_3)_2$	0.22	>100	0.20	>100		77
62	H	$C(O)C_6H_5$	>0.1	>100	0.08 9	56		140
63	H	$CH_2C(O)CH_2CH_3$	0.034	>100	>100	>10		>100
64	H	$C(O)CHN_2$	>0.1	0.52	0.001 9	3.2		>100
65	CH_3O	$C(O)CH_2CH_3$	0.0015	0.084	0.000 46	0.25	0.055	0.036
66	CH_3O	$C(O)CH_2CH_2CH_3$	0.028	2.6	0.000 55	0.72		0.48
67	CH_3O	$C(O)CH_2CH(CH_3)_2$	0.044	>100	0.10	4.0		100
68	CH_3O	$C(O)CH(CH_3)CH_2CH_3$	>0.1	>100	0.088	2.6		74
69	CH_3O	$C(O)CHN_2$	0.024	0.49	0.000 22	2.6		>100
70[b]	CH_3	$C(O)CH_2CH_3$	>0.1	0.50	0.021	3.2		0.72
71	HO	$C(O)CH_2CH_3$	0.064	0.0061	0.000 24	0.18		0.032
72	H	CO_2H	13	>100	>100	>100		>100
73	CH_3O	CO_2H	16	>100	>100	>100	>0.1	>100
74[c]	H	$C\equiv N$	>0.1	>100	4.8	>100		>100
75[d]	CH_3O	$C\equiv N$	>0.1	>100	32	>100		>100
76	H	CH_2OH	5.1	>100	>100	>100	>0.01	>100
77	CH_3O	CH_2OH	2.1	>100	>100	>100	>0.1	>100
78	CH_3O	$CH_2OC(O)CH_3$	3.1	>100	100	>100	>0.01	>100
79	H	CH_2OCH_3	3.8	6.7	22	>100	>0.1	>100
80	CH_3O	CH_2OCH_3	>1	>100	9.2	>100	>0.1	56
81	H	$CH_2OCH_2CH_3$	>10	4.6	3.7	>100		80
82	H	$CH_2OC_6H_5$	>10	>10	>100	>100	>0.1	>100
83[e]	H	$CH_2NH—CH_2CH_3$	>10	90	2.8	33	>0.01	>100
84	H	$CH_2C(O)OCH_3$	>0.1	49	4.9	>100		>100
85			0.0037	0.58	0.002 9	0.34		
86			0.0086	0.0061	0.000 93	>1.0		3.0

[a] The compounds described in this table are racemic unless otherwise specified (footnote *b*). [b] (−)-Enantiomer; optical purity ca. 0.53. [c] Henrick, 1973. [d] Henrick and Siddall, 1973c. [e] Henrick, 1974c.

Table IV. Ethyl and Isopropyl (2*E*,4*E*)-3,7,11-Trimethyldodecadienoates with Various Substituents at C-10 and C-11; ID_{50} Values on Sensitive Synchronized Instars[a]



No.	R	R′	*Aedes aegypti*, ppm	*Galleria mellonella*, μg/pupa	*Tenebrio molitor*, μg/pupa	*Musca domestica*, μg/prepupa	*Acyrthosiphon pisum*, % active ingredient in spray	*Heliothis virescens*, ppm in medium
	R″ = CH_2CH_3							
2	H	H	0.007 8	0.040	0.25	18	0.003 9	0.30
87A	10,11-Olefin		0.10	0.62	1.1	11		1.7
87B[b,c]			0.25	1.3	8.0	60		3.2
88A	10,11-Epoxy		0.11	1.2	1.7	1.1		4.7
88B[b,c]			0.18	2.4	26	23		8.8
89A	Cl	H	0.008 5	0.0087	0.094	1.2		0.15
89B[b]			0.020	0.078	0.85	2.8	0.015	3.2
90A	HO	H	0.002 7	0.0041	~100	2.4		0.035
90B[d]			0.008 1	0.010	>100	2.0	0.021	0.10
91[d]	$CH_3C(O)O$	H	0.047	0.027	1.7	3.0	0.001 6	0.17
14	CH_3O	H	0.002 0	0.17	8.9	5.0	0.000 056	0.20
92	CH_3CH_2O	H	0.000 60	0.17	0.53	0.072		1.0
93[b,e]	CH_3S	H	0.20	0.20	1.8	3.0	0.002 0	2.5
94[d]	EtNHC(O)O	H	2.0	6.2	>100	>100	>0.10	74
95[b]	CH_3	H	0.037	0.60	0.88	4.3		0.39
96	H	HO	0.10	0.37	>100	5.0	>0.010	0.95
97	H	10-Oxo	0.49	1.3	>100	48	>0.010	7.5
98	H	CH_3O	>0.010	0.0060	0.86	3.3		0.028
99[b]	H	CH_3CH_2S	0.23	4.8	10	7.1		170
100[b]	CH_3O	CH_3O	>10	0.39	16	>100		3.4
	R″ = $CH(CH_3)_2$							
4	H	H	0.001 9	0.28	0.026	2.2	0.035	3.8
101A	10,11-Olefin		0.026	5.5	0.059	0.57		82
101B[b,c]			0.066	17	0.35	10	>0.1	>100
102[d]	11,12-Olefin	H	0.010	2.8	0.022	0.29		90
103[b]	Cl	H	0.002 0	0.60	0.056	0.030	0.025	1.9
104A	HO	H	0.000 26	0.054	0.014			0.25
104B[d]			0.001 4	0.40	0.080	0.10	0.050	1.6
105[d]	$CH_3C(O)O$	H	0.017	0.29	0.052	0.27	0.022	0.80
106[d]	HC(O)O	H	0.002 8	0.48	0.012	0.060	0.086	2.4
17	CH_3O	H	0.000 17	5.7	0.0040	0.0035	0.005 4	0.77
107	CH_3CH_2O	H	0.000 23	24	0.010	0.0013		1.0
108	$(CH_3)_2CHO$	H	0.000 36	~100	0.33	0.0034		
109[b,e]	CH_3S	H	>0.010	3.2	0.056	0.36	>0.010	3.1
110[d]	EtNHC(O)O	H	0.24	>100	6.0	2.9	>0.10	>100
111[b]	CH_3	H	0.082	49	0.086	2.8		0.30
112	H	CH_3O	0.003 3	0.33	0.047	2.4		0.45
113[b]	CH_3O	CH_3O	>0.10	>100	0.045	22		>100
114[b]	CH_3O	HO	>0.10	>100	0.80	12		>100

[a] The esters described in this table are racemic unless otherwise specified (footnotes *b* and *d*). [b] (−)-Enantiomer; optical purity ca. 0.53. [c] Henrick et al., 1973, 1975b. These esters were not racemic as previously stated. [d] (−)-Enantiomer; optical purity ⩾0.75. [e] Henrick and Siddall, 1974b.

methylene) double bond (see also **121** vs. **87B**, Table V) shows higher activity than the corresponding 10-ene analogue **101B**. In the ethyl ester series an 11-hydroxy group (cf. **2** with **90A**) gives an increase in juvenile hormone activity on *Galleria mellonella* (see also **71**, Table III). The 11-methoxy group (**14** and **17**) gives a considerable increase in activity relative to 11-H on *Acyrthosiphon pisum* in both ester series, and in the isopropyl ester series there is also a considerable increase in activity on *A. aegypti*, *T. molitor*, *M. domestica*, and *H. virescens*. The 11-ethoxy analogues **92** and **107** also show high activity. In various aromatic terpenoid (substituted geranyl and citronellyl) ether analogues (e.g., Henrick et al., 1970; Sarmiento et al., 1973; Slama et al., 1974, p 432; see also Table VII) the 7-ethoxy analogues, in general, show much higher activity than the corresponding 7-methoxy analogues against insect species such as *T. molitor*. The activity of the 10-hydroxy analogue **96** is somewhat less than that of the corresponding 11-hydroxy analogue **90A**. The 10-oxo (**97**) analogue shows, in general, low activity, whereas, in the ethyl ester series, the *10-methoxy analogue* **98** *shows high juvenile hormone activity on Lepidoptera* (*G. mellonella* and *H. virescens*).

Effect of Unsaturation on Activity. In Table V data are presented which demonstrate the effects, on the juvenile hormone activity, of the location and number of double bonds in ethyl 3,7,11-trimethyldodecanoate. The presence of an *E* 2-ene double bond is essential for morphogenetic activity. Saturated analogues such as ethyl 3,7,11-trimethyldodecanoate have very low activity (cf. Jarolim et al., 1969; Wakabayashi et al., 1969; Nemec et al., 1970; Slama et al., 1970, 1974; Metwally and Sehnal, 1973; Daoud and Sehnal, 1974).

The 2,4-dienoate **2** (Henrick et al., 1973) shows, in general, much higher activity (except on *Musca domestica*) than is observed with the 2,6-dienoate **118**, the 2,10-dienoate **117**, or with any of the trienoates **119**, **120**, **87**, **121**, **122**, and **123**; Table V (cf. Wakabayashi et al., 1969; Metwally and Sehnal, 1973). The 2,10-diene analogues are, in general, more active than the corresponding 2,6,10-triene analogues (Henrick et al., 1973; cf. Wigglesworth, 1969b). Although the 2,6,11-trienoate **120** is less active than the 2,6,10-trienoate **119**, the (−)-2,4,11-trienoate **121** is considerably more active than the corresponding (−)-2,4,-10-trienoate **87B**. The 2,4,6,10-tetraenoate **124** is quite inactive on the insect species in Table V (cf. Jarolim et al.,

Table V. Ethyl 3,7,11-Trimethyldodecanoates with One to Four Trans Double Bonds; ID_{50} Values on Sensitive Synchronized Instars[a]

No.	Substituents	*Aedes aegypti*, ppm	*Galleria mellonella*, μg/pupa	*Tenebrio molitor*, μg/pupa	*Musca domestica*, μg/prepupa	*Acyrthosiphon pisum*, % active ingredient in spray	*Heliothis virescens*, ppm in medium
115	2-Ene	0.062	3.3	2.6	1.4	0.035	100
116	4-Ene	2.8	>100	>100	>100	>100	100
117	2,10-Diene	0.20	6.8	12	2.8	0.029	>100
118	2,6-Diene	0.23	7.1	5.7	30		52
2	2,4-Diene	0.0078	0.040	0.25	18	0.0039	0.30
119	2,6,10-Triene	0.023	~300	4.4	6.4		>300
120	2,6,11-Triene	>0.10	>100	34	67		>100
87A	2,4,10-Triene	0.10	0.62	1.1	11		1.7
87B[b]		0.25	1.3	8.0	60		3.2
121[b,c]	2,4,11-Triene	0.021	0.075	0.86	3.5		5.6
122	2,4,8-Triene	0.012	0.84	3.4	3.1		2.8
123	2,4,9-Triene	>0.1	0.40	5.8	0.63		2.3
124	2,4,6,10-Tetraene	>10	>100	>100	>100		>100
125[d]	11-Methyl-2-ene	0.068	5.0	5.3	1.1	0.026	25
126[e]	11-Chloro-2-ene	0.16	2.2	0.83	0.29	0.0050	10
127[f]	11-Hydroxy-2-ene	0.15	2.3	10	1.8		
128[f]	11-Acetoxy-2-ene	0.17	0.22	>10	0.29		
129[f]	11-Methoxy-2-ene	0.040	33	46	2.1		100
130[f]	10,11-Epoxy-2-ene	0.29	6.7	14	3.7		42
131	11-Chloro-2,6-diene	0.040	4.6	0.50	3.6		
132[f]	11-Hydroxy-2,6-diene	0.20	>100	>100			
133[f]	11-Acetoxy-2,6-diene	0.30	22	12	2.4		
134[f]	11-Methoxy-2,6-diene	>0.1	84	11	>100		>100
135[f]	11-Ethoxy-2,6-diene		280	10	10		>100
136[g]	10,11-Epoxy-2,6-diene	0.14	26	5.5	3.4		>100
137	4,5-Epoxy-2-ene	1.0	>100	>100	17	>0.1	>100
138[h]	4,5-Methano-2-ene	0.23	4.5	2.2	3.2	0.020	30
139[i]	4-Hydroxy-2-ene	0.80	>100	>100	6.4	>0.1	31
140	3-Hydroxy-4-ene	5.6	>100	>100	>100	>0.1	37
141	9,10-Epoxy-2,4-diene	>0.10	7.4	8.7	>100		25
142	6-Methyl-2,4-diene	0.12	0.39	2.7	1.1		0.60
143[j]	7,11-Dichloro-2-ene	6.6	>100	>100	72	0.033	>100
144[k]	7,11-Dimethyl-2-ene	>10	>100	>10	>100		
145	6,7;10,11-Bis(epoxy)-2-ene		>100	>100			
146[l]	7,11-Dimethyl-2,4-diene	25	>100	20	5.4		

[a] All the esters in this table are racemic except for **87B** and **121** (footnote *b*). [b] (−)-Enantiomer; optical purity ca. 0.53. [c] Henrick and Siddall, 1975a. [d] Romanuk et al., 1972b. [e] Siddall and Calame, 1973. [f] Siddall and Calame, 1974. [g] Cruickshank, 1969. [h] Henrick and Siddall, 1973b. [i] Henrick, 1974a. [j] Romanuk et al., 1972a. [k] Siddall, 1972b. [l] Henrick and Siddall, 1973a.

1969; Nemec et al., 1970; Slama et al., 1970; Corey et al., 1971; Mori et al., 1974).

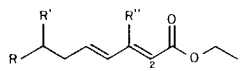
Biological data on compounds with various substituents at C-11 such as a methyl, chloro, hydroxy, acetoxy, methoxy, or a 10,11-epoxy group, in both the 2-enoate and 2,6-dienoate series, are also given in Table V. As noted previously (Henrick et al., 1973; cf., however, the general statement of Slama et al., 1974, p 203), in the 2-enoate series the 10,11-epoxy group (e.g., **130**) decreases the activity compared with that observed with the corresponding 10,11-dihydro analogue (e.g., **115**). In the 2,6-dienoate series, however, there is little difference in activity between such analogues (cf. **118** with **136**) on the insect species examined. The 11-hydroxy and 11-methoxy 2,6-dienoate analogues (**132** and **134**, respectively) have very low biological activity (cf. Wakabayashi, 1969) on comparison with the corresponding substituted 2,4-dienoate analogues (**90A**, **90B**, and **14**, Table IV).

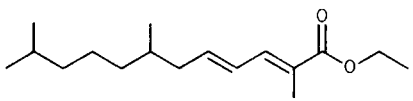
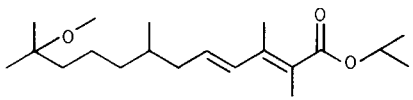
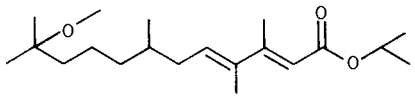
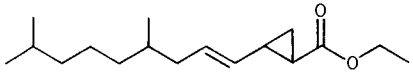
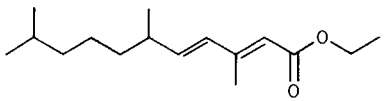
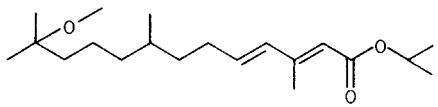
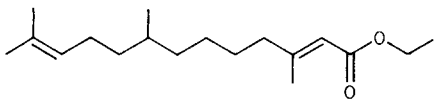
In the ethyl 2,4-dienoate analogue **2**, replacement of the 4-ene double bond by either a 4,5-epoxy (**137**), a 4,5-methano (**138**), or a 4-hydroxy (**139**) group gives analogues with much lower activity on the insect species in Table V with the exception of *M. domestica*. Removal of the 2-ene double bond with retention of the 4-ene double bond as in **116** or **140** gives analogues with negligible juvenile hormone activity. The 9,10-epoxy-2,4-dienoate **141** shows only low activity (cf. the 10,11-epoxy-2,4-dienoate **88A**, Table IV). The 6-methyl analogue **142** shows an increased activity on *M. domestica* in comparison with that observed for **2** but in the other insect species the activity of **142** was somewhat lower.

In the alkyl 3,7,11-trimethyldodecenoate analogues the placement of an extra substituent (such as a chloro, methyl, or epoxy group) at C-7 produces analogues such as **143**, **144**, **145**, and **146** which show low activity on the insect species in Table V. However, such 7,7-disubstituted analogues do show very high activity on hemipteran insects of the families Pyrrhocoridae and Lygaeidae such as *Pyrrhocoris apterus*, *Dysdercus cingulatus*, and *Lygaeus equestris* (Slama et al., 1970, 1974; Henrick et al., 1970; Sorm, 1971; see also Wigglesworth, 1969b; Jarolim et al., 1969; Nemec et al., 1970; Cruickshank, 1971; Cruickshank and Palmere, 1971; Metwally and Sehnal, 1973; Ruzicka et al., 1974).

Variations in the Carbon Chain. In Table VI there are listed some ethyl (2*E*,4*E*)-2,4-dienoate analogues containing variations in the carbon chain. Analogues lacking all the methyl branches have very low activity (cf. Wakabayashi et al., 1969) and compounds such as **147**, **148**, and **155** which possess only the 3-methyl branch still have low activity (cf. Bell et al., 1973). Analogues such as **149** which possess branches at C-3 and at C-11 but not at C-7 show some activity but not as high as the 3,7,11-trimethyl-2,4-dienoates (e.g., **2**). The 7,11-dimethyl analogue

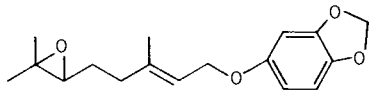
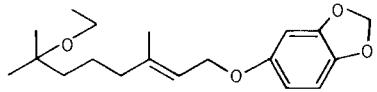
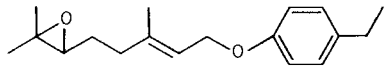
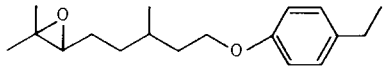
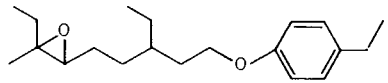
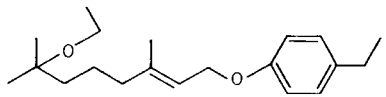
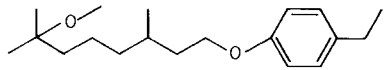
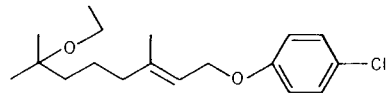
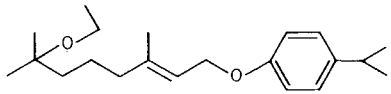
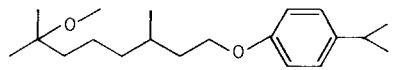
Table VI. Ethyl (2*E*,4*E*)-2,4-Dienoates with Various Alkyl and Aryl Substituents; ID_{50} Values on Sensitive Synchronized Instars[a]



No.	R	R′	R″	*Aedes aegypti*, ppm	*Galleria mellonella*, μg/pupa	*Tenebrio molitor*, μg/pupa	*Musca domestica*, μg/prepupa	*Acyrthosiphon pisum*, % active ingredient in spray	*Heliothis virescens*, ppm in medium
147	$CH_3(CH_2)_5$	H	CH_3	3.0	10	54	>100	>0.10	>100
148	$CH_2{=}CH(CH_2)_6$	H	CH_3	>10	100	>100	>100	>0.10	>100
149	$EtCH(CH_3)—(CH_2)_3$	H	CH_3	0.50	0.76	0.19	36		1.1
150	$(CH_3)_2CH—(CH_2)_3$	CH_3	H	4.9	4.4	34	57		40
2	$(CH_3)_2CH—(CH_2)_3$	CH_3	CH_3	0.0078	0.040	0.25	18	0.0039	0.30
151	$(CH_3)_2CH—(CH_2)_3$	CH_3	Et	0.053	5.0	4.4	31		13
152	$EtCH(CH_3)—(CH_2)_3$	CH_3	CH_3	0.030	0.015	0.10	2.9	0.0020	0.14
153	$EtCH(CH_3)—(CH_2)_3$	Et	CH_3	0.094	0.050	0.10	2.5	0.0037	1.4
154[b]	p-$(CH_3)_2CH—C_6H_4$	CH_3	CH_3	>1.0	0.23	70	>100	>0.10	2.0
155	$C_6H_5—CH_2$	H	CH_3	8.2	>200	>100	>100		>100
156	$(CH_3)_2CH—(CH_2)_3$	CH_3	Cl	>0.1	1.6	0.68	>100		3.7
157				>0.01	>100	>100	>100		>100
158				0.0051	80	0.056	0.55		0.66
159				0.041	>100	0.35	1.4		13
160				0.33	6.7	4.2	3.9		4.0
161				2.8	70	84	>100	0.17	>100
162[c]				>0.047	>10	>100	>0.2		>100
163[a]				>1	>100	>100	>100		>100

[a] All of the esters described in this table are racemic except for 163 which is the (−)-enantiomer (optical purity ca. 0.53). [b] Henrick, 1974e. [c] Contains ≤0.5% of 17.

Table VII. ID_{50} Values on Sensitive Synchronized Instars

No.	Structure	*Aedes aegypti*, ppm	*Galleria mellonella*, μg/pupa	*Tenebrio molitor*, μg/pupa	*Musca domestica*, μg/prepupa	*Acyrthosiphon pisum*, % active ingredient in spray	*Heliothis virescens*, ppm in medium
164a	JH III[a]	0.35	12	4.5	>100	>0.1	>100
164b	JH II[a]	0.26	0.13	4.3	>100	0.035	>100
164c	JH I[a]	0.15	0.060	0.70	>100		24
164d	JH 0[a]	1.0	1.0	0.15	>100		>100
165[b]		0.003 2	0.082	0.0050	2.0	0.020	>100
166[c]		0.25	6.3	0.0022	1.7	>0.01	
167[d]		0.000 70	0.072	0.0025	3.0	0.043	~100
168A[e]		0.20	3.2	0.016	3.8		>100
168B[f]		0.019	0.66	0.023	6.4	0.029	>100
169[e,g]		0.057	0.037	0.0024	54		
170[h]		>0.01	>100	0.000 62	>100	>0.01	24
171[e]		0.050	>100	0.37	>100		50
172[i]		5.2	>100	0.006 8	>100		
173[i]		1.7	>100	0.034	>100		>100
174[e]		0.33	>100	7.6	>100	>0.1	>100

175[j]		0.0036	>100	30	0.093	>100
176[k]		0.026	4.5	0.38	25	~100
177[l]		0.017	~10	>100	>100	1.5

[a] Henrick et al., 1975b. [b] Bowers, 1969, 1971a,b. [c] Siddall, 1973; Sarmiento et al., 1973. [d] R-20458 (Stauffer Chemical Co); Pallos et al., 1971; Walker and Bowers, 1973; Menn and Pallos, 1975. [e] Racemic compound. [f] ZR 442; this sample had $[\alpha]^{25}D$ +5.5° (CH_3OH) and was prepared from (+)-citronellol; Jakob, 1972; Strong and Diekman, 1973. [g] Ro 10-3108; Chodnekar et al., 1975. [h] Siddall, 1972a; Sarmiento et al., 1973. [i] Sarmiento et al., 1974a. This sample was supplied by M. Schwarz and had $[\alpha]^{25}D$ −2.7° (CH_3OH). [k] CGA-34303 (Ciba-Geigy Corp); Franke and Traber, 1974; Scheurer and Ruzette, 1974. [l] CGA-13353 (Ciba-Geigy Corp).

150, which lacks the 3-methyl group, has considerably lower morphogenetic activity than does **149**, demonstrating that the C-3 methyl group is more important in these compounds than is the branch at C-7. In contrast to the results found in these 2,4-dienoate compounds, it has been found that for analogues of methyl 10,11-epoxyfarnesoate (i.e., the 2,6-dienoates **164**) the C-3 methyl group is *not* very important. Thus, in the silkworm, *Bombyx mori* (Ohtaki et al., 1972; Kiguchi et al., 1974), and in several other insect species, including *Tenebrio molitor*, *Tribolium castaneum*, and *Galleria mellonella* (Mori, 1971, 1972; Mitsui et al., 1973), the morphogenetic activity was found to be similar for the analogues with H or methyl substituents at C-3 (with the 3-H analogues often showing higher activity). However, for the methyl 10,11-epoxy-2,6-dienoates (i.e., **164**) the removal of the alkyl branch at C-7 did give analogues with much lower juvenile hormone activity on *Bombyx mori* (Ohtaki et al., 1972). Analogues lacking only the C-7 alkyl branch were reported to have some activity on *Tenebrio molitor* but analogues lacking both the C-3 and C-7 branches were inactive on *T. molitor* and on *B. mori* (Takigawa et al., 1975). For analogues of methyl 10,11-epoxyfarnesoate (i.e., **164**) it has also been reported, for a number of insect species including *Tenebrio molitor*, *Tribolium castaneum*, and *Galleria mellonella*, that the lack of alkyl branching at C-11 gave analogues of low morphogenetic activity (Mori, 1971, 1972; Mitsui et al., 1973). Thus, alkyl branching at C-11 is very important in this series of compounds for juvenile hormone activity.

Replacing methyl groups at C-7 and at C-11, in the ethyl ester 2,4-dienoate **2**, with ethyl groups to give **152** and **153** (Table VI) does not produce an increase in the activity, except against *M. domestica*. In contrast, the known natural juvenile hormones, JH I (**164c**) and JH II (**164b**), show much higher topical activity on *Galleria mellonella* than does JH III (**164a**) (Table VII; Henrick et al., 1975b). Also, on *Tenebrio molitor*, JH I (**164c**) shows the highest activity (Henrick et al., 1975b; see also Schwarz et al., 1969) of the three known natural juvenile hormones. The synthetic analogue JH 0 (**164d**), with an ethyl group at C-3, has higher activity on *T. molitor* than does **164c**. However, replacing the methyl group at C-3, in the 2,4-dienoate **2**, with an ethyl group to give **151**, gives a decrease in biological activity against the insect species in Table VI.

164a, R = R′ = R″ = CH_3 (JH III)
b, R = R′ = CH_3; R″ = CH_2CH_3 (JH II)
c, R = CH_3; R′ = R″ = CH_2CH_3 (JH I)
d, R = R′ = R″ = CH_2CH_3 (JH 0)

In the methyl 10,11-epoxyfarnesoate series, the inhibition of metamorphosis in *Bombyx mori* was highest for the analogues with a methyl or H group at C-3, a methyl or ethyl group at C-7, and an *n*-butyl group at C-11 (e.g., methyl 10,11-epoxy-7-ethyl-3,11-dimethyl-2,6-pentadecadienoate; Kiguchi et al., 1974; Nihmura et al., 1974). Similar results were obtained with *Tenebrio molitor* (Mori, 1971, 1972; Ozawa et al., 1973; Mori et al., 1975). With the corresponding ethyl esters, ethyl 10,11-epoxy-3,7,11-trimethyl-2,6-tetradecadienoate was the most active of the analogues tested on *Bombyx mori* (Mori et al., 1975).

The 7-(4-isopropylphenyl) analogue **154** shows moderate juvenile hormone activity on *G. mellonella* but not on the other species tested. The 3-chloro-7,11-dimethyl analogue **156** shows much lower activity than does **2** (cf. Sorm, 1971) and the 2,7,11-trimethyl analogue **157** is even less active than the 7,11-dimethyl compound **150**. The 2,3,7,11-

tetramethyl analogue **158** is less active than the corresponding 3,7,11-trimethyl analogue **17** (Table I) on the first four insect species in Table VI. The 3,4,7,11-tetramethyl analogue **159** shows very low activity on comparison with the activity observed for **17**. The analogue **160** containing a 2,3-methano group in place of the 3-methyl-2-ene grouping has some activity.

The morphogenetic activity of these terpenoid analogues is very dependent on the isoprenoid nature of the carbon chain. Nonisoprenoid 3,6,10-trimethyldienoate analogues, such as **161**, with one less carbon atom between the first two methyl branches show much lower activity (cf. **2**; Table I). The corresponding analogues with one extra carbon atom between the first two methyl branches also have very low activity. For example, whereas the 3,7,11-trimethyldodecadienoate **17** has an ID_{50} of 0.00017 ppm on *Aedes aegypti* (Table I) and 0.0035 μg on *Musca domestica*, the corresponding 3,8,12-trimethyltridecadienoate **162** shows an ID_{50} of >0.047 ppm on *A. aegypti* and >0.2 μg on *M. domestica*. Similar results had been obtained previously by us in the alkyl 2-enoate series. Thus, ethyl (−)-(*E*)-3,8,12-trimethyl-2,11-tridecadienoate (**163**) shows much lower activity than the corresponding (±)-3,7,11-trimethyl analogue **117** (Table V). Thus, in these terpenoid juvenile hormone analogues the 3,7-dialkyl branching is necessary for high morphogenetic activity. It has previously been reported with a number of insect species that the juvenile hormone activity of farnesoate-type analogues is also critically dependent on the spacing between the first two methyl branches. The shortening or lengthening of the carbon chain between C-3 and C-7 by one CH_2 unit generally produces a substantial loss in activity. However, it has been reported that the shortening of the carbon chain between C-7 and C-11 by one CH_2 unit can give analogues which retain activity (Slama et al., 1972; Gelbic and Sehnal, 1973; Sorm, 1971; Ruzicka et al., 1974; Daoud and Sehnal, 1974).

Some Other Morphogenetic Analogues. Bioassay data for synthetic samples of the known natural juvenile hormones JH I (**164c**), JH II (**164b**), and JH III (**164a**), and for some other morphogenetic analogues under investigation by various groups, are given in Table VII for comparison purposes. Aromatic terpenoid ethers such as **165** (Bowers, 1969, 1971a,b) and **167** (Pallos et al., 1971; Menn and Pallos, 1975) show high morphogenetic activity on a number of insect species. These 6,7-epoxygeranyl phenyl ethers have, in general, somewhat higher activity than the corresponding 6,7-epoxycitronellyl ethers such as **168** [**168B** is the (+)-enantiomer (ZR 442; Jakob, 1972; Strong and Diekman, 1973); cf. Menn and Beroza, 1972, p 291]. The 7-ethoxygeranyl ethers such as **166** (Siddall, 1973; Sarmiento et al., 1973) and **170** (Siddall, 1972a; Sarmiento et al., 1973) have very high juvenile hormone activity on *Tenebrio molitor* but generally lower activity than the corresponding 6,7-epoxy analogues on the other insect species in Table VII. The arylterpenoid compound **175** has good activity on Diptera and may have promise in controlling a number of species of flies [Schwarz et al., 1974a; (−)-enantiomer supplied by M. Schwarz]. A class of juvenile hormone analogues, represented by the esters **176** and **177**, has recently been reported (Scheurer and Ruzette, 1974; Franke and Traber, 1974).

The laboratory bioassays described in this paper provide a good basis for quantitative structure–activity comparisons of the morphogenetic activity of different compounds. The measured level of activity (dose required to produce 50% inhibition) only applies to carefully synchronized instars and only for the specific morphogenetic process on which the activity was measured. Under field conditions less synchronous populations can be expected which would require some measure of field stability of the compound. Other effects on different developmental stages of insect species are also observed with these compounds and thus the practical efficacy for insect control can only be assessed under field conditions. The field stability of 2,4-dienoates such as **2**, **8**, and **17** is low (e.g., Quistad et al., 1974, 1975; Schooley et al., 1975a,b) compared with most standard insecticides (which also require less synchronous populations for effective control) and can be expected to be less than for analogues such as **175** (Table VII). However, the field persistence of the 2,4-dienoates can be successfully enhanced in many cases by suitable formulation. For example, a commercial slow release formulation (Altosid SR-10) has been developed for **17** for mosquito control (Schaefer and Wilder, 1973).

BIOASSAY PROCEDURES

Bioassays were performed on synchronized sensitive stages of the six insect species. The activities are expressed as ID_{50} or IC_{50} values (dose or concentration required to produce 50% inhibition of metamorphosis). The procedures for bioassay on *Aedes aegypti* (last larval instars), *Galleria mellonella* (fresh pupae), and *Tenebrio molitor* (fresh pupae) have been previously described (Henrick et al., 1973). The bioassay procedures for *Musca domestica* (full grown larvae), *Acyrthosiphon pisum* (2nd and 3rd instar nymphs), and *Heliothis virescens* (larvae) have also been previously described (Henrick et al., 1975b). The graded-response scale was calculated as a percentage of the maximum attainable and plotted against the dose on semilogarithmic paper. The ID_{50} dose was taken from the intersection of this plotted line with the 50% effect level. For each compound, several assays, performed on different days with fresh dilutions, were averaged to obtain the data given in the Tables I–VII.

EXPERIMENTAL SECTION

Preparative thin-layer chromatography was carried out on 1 m × 20 cm plates coated with 1.3 mm of Merck (Darmstadt) silica gel PF-254. NMR spectra were determined on a Varian T-60 spectrometer. Infrared spectra were measured on a Unicam SP 200G spectrophotometer. Mass spectra were measured on a Varian Mat CH-7 spectrometer, at 20 or 70 eV ionization potential. Gas–liquid chromatographic analyses were performed on Model 402 Hewlett-Packard instruments equipped with hydrogen flame ionization detectors. All solvents were dried over activated molecular sieves, and most reactions were carried out under an argon or a nitrogen atmosphere. Elemental analyses were obtained by A. Bernhart, W. Germany. Almost all of the analogues were purified by preparative thin-layer chromatography followed by short-path distillation.

Most of the substances described in this paper are racemic compounds; the prefix (±) is omitted. In the syntheses the starting aldehydes 2,6-dimethyl-5-hepten-1-al, 3,7-dimethyl-1-octanal, 7-methoxy-3,7-dimethyl-1-octanal, 6-methoxy-3,7-dimethyl-1-octanal, 3,7-dimethyl-6-oxo-1-octanal, and 2,3,7-trimethyl-1-octanal were racemic compounds. Two different samples of 7-hydroxy-3,7-dimethyl-1-octanal were used in these syntheses: (a) Laurine (Givaudan Corp), $[\alpha]^{25}D$ ($CHCl_3$) +10.8° [optically pure (*R*)-(+)-7-hydroxycitronellal is reported to have $[\alpha]^{20}D$ ($CHCl_3$) +10° (Skorianetz et al., 1971)] and (b) racemic material from Bush Boake Allen Inc.; the (+)-citronellal had $[\alpha]^{25}D$ (neat) +8.4°; optical purity 0.53 [it has been calculated that optically pure (*R*)-(+)-citronellal has $[\alpha]D$ +16° (O'Donnell and Suth-

erland, 1966)]; and the (+)-citronellol had $[\alpha]^{25}D$ (neat) +3.8° [optically pure (*R*)-(+)-citronellol has $[\alpha]^{25}D$ (neat) +5.5° (Overberger and Kaye, 1967)]. Racemic samples of citronellal and citronellol were also used where indicated.

All the new compounds mentioned in Tables I–VII gave satisfactory elemental analyses (within ±0.4% of the theoretical values) and were characterized also by their NMR, ir, and mass spectra. Selected examples of experimental details and physical constants are given in the Supplementary Material section (microfilm).

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Supplementary Material Available: Synthetic experimental details and physical constants for selected compounds from Tables I–VII (36 pages). Ordering information is given on any current masthead page.

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Novel Nonterpenoid Insect Growth Regulators

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A novel series of aliphatic bisthiolcarbamate insect growth regulators (IGR's) was synthesized in accordance with a generalized molecular model for activity proposed in this paper. These compounds differ significantly in structure from the well-known terpenoid IGR's. One of the new compounds, *N*-ethyl-1,2-bis(isobutylthiolcarbamoyl)ethane, compound XX, which adheres closely to the proposed template showed outstanding activity in the yellow mealworm, *Tenebrio molitor* morphogenetic assay. It was nontoxic to several other insect species and to other nontarget higher organisms including the rat, rabbit, and fish.

Most of the insect growth regulators (IGR's) with juvenile hormone activity which have been synthesized and reported to date are derived from terpenes and sesquiterpenes (Wigglesworth, 1970; Bowers, 1971; Pfiffner, 1971; Menn and Beroza, 1972; Sláma et al., 1974; and Menn and Pallos, 1975).

More recently, several investigators described IGR's which did not retain the integrity of the terpenoid skeleton. These include a report by Zaoral and Sláma (1970) who described several peptide derivatives, more specifically, the ethyl ester of L-isoleucyl-L-alanyl-*p*-aminobenzoic acid which showed a much greater morphogenetic effect on last

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