Quantitative Structure–Activity Relationship of Insect Juvenile Hormone Mimetic Compounds

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Received September 7, 1983

Juvenile hormone mimetic activities on *Aedes aegypti* (yellow-fever mosquito) and *Tenebrio molitor* (yellow mealworm) of compounds having (2*E*,4*E*)-3,7,11-trimethyl-2,4-dodecadienone structures were comparatively and quantitatively analyzed in terms of their physicochemical structural parameters and by regression analysis. They were structurally composed of three classes, ester and thiol ester derivatives, amides, and ketones, depending on the C_1 substituents. The results indicated that the steric dimensions and the hydrophobicity of the whole molecule are important factors in governing the activity through these classes as well as through both insect species. The effects of the structure of the C_1 and C_{11} substituents, the two ends of the chain molecule, are specific to the insect. The length along the bond axis of the C_1 substituents is significant and the hydroxy and alkoxy functions attached to the C_{11} atom favor the activity on *A. aegypti*, whereas with *T. molitor* the width of the C_1 substituents in the direction perpendicular to the bond axis is significant and the position-specific hydrophobicity of the C_1 moiety enhances the activity. The activity is also affected differently by the compound types. The amide and ketone series of compounds are more active than the corresponding ester type of compounds on *T. molitor*, while the favorable types on *A. aegypti* are the ester and ketone derivatives. Correlation equations formulated for 85 active compounds on *A. aegypti* and 84 compounds on *T. molitor* led us to draw a hypothetical "mode of action" model for each species, which visualizes the overall similarity as well as the species differences of the interaction site or the receptor and may show the structural conditions necessary for activity.

Since the discovery of the insect juvenile hormone JH I,[1] followed by JH II,[2] JH III,[3] and JH 0,[4] many analogous compounds have been prepared and tested for their activity on the metamorphosis of the larvae and pupae of many insect species to explore the structures that confer the activity. They are structurally divided roughly into two classes, terpenoid and nonterpenoid types. Isopropyl (2*E*,4*E*)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate (methoprene)[5] and 2-propynyl (2*E*,4*E*)-3,7,11-trimethyl-2,4-dodecadienoate (kinoprene)[6,7] are compounds of the first type and have been developed to obtain higher potency as well as more field stability than that of the naturally occurring mother compounds. One representative of the nonterpenoid type is ethyl 2-(4-phenoxyphenoxy)-ethyl carbamate,[8] which is more active than methoprene on *Culex pipiens*.[9] *S,S'*-Diisobutyl *N*-ethyl-*N,N'*-ethylenebis(thiocarbamate) has also been shown to possess outstanding activity in the mealworm *Tenebrio molitor* morphogenetic assay.[10] Some chrysanthemic acid esters reportedly show significant morphogenetic activity on the barred stainer bug, *Dysdercus fasciatus*, when compared with several known terpenoid compounds.[11] Other compounds in the nonterpenoid class are not always conspicuous for activity, but they have novel structures. Active compounds hitherto reported and having a great deviation from the terpenoid skeleton are the peptide derivatives ethyl L-isoleucyl-L-alanyl-*p*-aminobenzoate[12] and ethyl pivaloyl-L-alanyl-*p*-aminobenzoate,[13] and *N*-[4-(benzyloxy)benzyl]anilines,[14] compounds of high aromatic content.

The number of effective nonterpenoid compounds is relatively small, but they provide possibilities in the development of useful compounds without the deficiencies like poor field stability and costly synthesis of compounds having the integrity of the terpenoid structure. Recent developments in quantitative structure–activity studies have shown that this is a useful tool to investigate the structural correspondence between different types of compounds having the same type of activity, for example, that between N^6-substituted adenines and *N,N'*-diphenylureas, both agonists of the plant hormones called cytokinins,[15] and that between the terpenoid sweeteners perillartines and sweet L-aspartyl dipeptides.[16] The results suggest the possibility that the information on the structure vs. activity relationship of one class of compounds can be transposed to other types of compounds. The necessary condition for this is probably that the analysis is performed on the basis of the whole molecule rather than on the effects of substituents at one particular position or those of the structural variations at only a part of the molecule.

Among the compounds hitherto known to have JH mimetic activity, the (2*E*,4*E*)-3,7,11-trimethyl-2,4-dodecadienoates and related compounds are a class that has been intensively investigated by Henrick and his coworkers[6] and have brought to us valuable insight into the structure vs. activity relationship of the JH mimetic compounds. The structure is systematically varied at both ends of the chain molecule and the total number of compounds tested for activity is highest, as far as we know. Although they are all terpenoids, a similar mode of action

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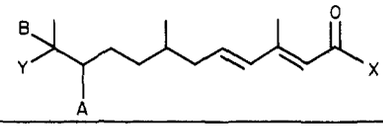
0022-2623/84/1827-1493$01.50/0

Table I. Activity and Physicochemical Parameters of 2,4-Dodecadienones[a]



					activity						physicochemical parameters[b]					
					A. aegypti, pI_{50}, mM			*T. molitor*, pI_{50}, μmol/pupa								
no.	X	Y	A	B	obsd	calcd[c]	ΔpI_{50}	obsd	calcd[d]	ΔpI_{50}	L_x	W_x	D	B_x	log P	$\pi_{x'}$
1	OMe	Me	H	H	3.23	3.51	−0.28	2.20	1.43	0.77	3.98	2.86	6.36	0.00	6.20	0.39
2	OEt	Me	H	H	4.53	4.32	0.21	3.03	2.81	0.22	4.80	3.36	7.65	0.00	6.74	0.93
3	O-*n*-Pr	Me	H	H	4.24	4.18	0.06	2.71	3.11	−0.40	6.05	4.30	8.87	0.00	7.28	1.47
4	O-*i*-Pr	Me	H	H	5.17	5.04	0.13	4.03	4.11	−0.08	4.80	4.11	7.65	1.25	7.15	1.34
5	O-*i*-Bu	Me	H	H	4.07	4.13	−0.06	3.80	3.30	0.50	6.05	4.30	8.87	0.00	7.69	1.88
6	O-*sec*-Bu	Me	H	H	4.21	4.84	−0.63	3.87	4.38	−0.51	6.05	4.30	8.87	1.25	7.69	1.88
7[e,f]	O-*t*-Bu	Me	H	H	(<3.46*)	5.00		(1.01)	4.31	−3.30	4.80	4.11	7.65	1.25	7.56	1.75
8	$OCH_2C{\equiv}CH$	Me	H	H	3.08	3.60	−0.52	2.33	1.90	0.43	6.58	2.86	8.34	0.00	5.86	0.05
9	$OCH_2C{\equiv}CCH_3$	Me	H	H	2.99	2.65	0.34	2.12	2.55	−0.43	7.40	3.33	9.63	0.00	6.40	0.59
10	$OCH_2CH{=}CH_2$	Me	H	H	4.14	4.07	0.07	3.51	2.69	0.82	6.22	4.42	8.77	0.00	6.73	0.92
11[e]	OPh	Me	H	H	(2.89)	5.18	−2.29	1.50	1.88	−0.38	5.74	5.89	8.80	1.58	7.67	1.86
12[f]	OCH_2Ph	Me	H	H	1.52	1.14	0.38	(<0.52*)	3.04		8.20	2.87	9.57	0.00	7.87	2.06
13[f]	OH	Me	H	H	1.26	1.41	−0.15	(<0.45*)	−1.34		2.74	1.93	5.15	0.00	5.95	0.14
14	OMe	OMe	H	Me	4.15	4.18	−0.03	0.89	1.67	−0.78	3.98	2.86	7.73	0.00	5.00	0.39
15	OEt	OMe	H	Me	5.17	4.94	0.23	1.92	2.69	−0.77	4.80	3.36	9.02	0.00	5.54	0.93
16	O-*n*-Pr	OMe	H	Me	5.00	4.77	0.23	1.65	2.66	−1.01	6.05	4.30	10.20	0.00	6.08	1.47
17	O-*i*-Pr	OMe	H	Me	6.26	5.80	0.46	4.89	4.11	−0.78	4.80	4.11	9.02	1.25	5.95	1.34
18	O-*n*-Bu	OMe	H	Me	4.02	3.80	0.22	0.93	1.68	−0.75	6.86	4.79	11.52	0.00	6.62	2.01
19	O-*sec*-Bu	OMe	H	Me	5.15	5.56	−0.41	4.67	4.05	0.62	6.05	4.30	10.24	1.25	6.49	1.88
20	O-*t*-Bu	OMe	H	Me	5.33	5.89	−0.56	3.81	4.44	−0.63	4.80	4.11	9.02	1.25	6.36	1.75
21	O-*i*-amyl	OMe	H	Me	2.96	3.82	−0.85	0.81	0.56	0.25	6.86	5.54	11.52	0.00	7.03	2.42
22	$OCH_2C{\equiv}CH$	OMe	H	Me	3.18	3.82	−0.64	1.34	1.23	0.11	6.58	2.86	9.71	0.00	4.66	0.05
23[f]	$O(CH_2)_2C{\equiv}CH$	OMe	H	Me	4.51	4.24	0.27	(<1.11*)	−1.39		5.93	5.81	11.27	0.00	5.20	0.59
24	$OCH_2CH{=}CH_2$	OMe	H	Me	4.26	4.50	−0.24	1.41	2.11	−0.70	6.22	4.42	10.14	0.00	5.53	0.92
25	$OCH_2CH{=}CHMe$	OMe	H	Me	3.96	3.51	0.45	2.25	1.74	0.51	7.04	4.44	11.43	0.00	6.07	1.46
26	$OCH(Me)CH{=}CH_2$	OMe	H	Me	4.99	5.35	−0.37	4.39	3.57	0.82	6.22	4.42	10.14	1.25	5.94	1.33
27	O-c-Pr	OMe	H	Me	5.11	5.18	−0.07	2.89	3.10	−0.21	5.00	3.88	9.03	0.23	5.71	1.10
28	O-c-Bu	OMe	H	Me	5.09	5.10	−0.01	2.79	2.73	0.06	5.56	4.64	9.96	0.00	6.44	1.83
29[e]	O-c-C_5H_4	OMe	H	Me	(4.27)	5.58	−1.31	4.32	3.76	0.56	5.56	4.64	9.69	0.76	7.01	2.40
30[f]	OH	OMe	H	Me	1.22	2.23	−1.01	(<0.43*)	−0.63		2.74	1.93	6.52	0.00	4.79	0.18
31	OEt	Me	H	Cl	4.55	4.29	0.26	3.50	2.79	0.71	4.80	3.36	7.65	0.00	6.44	0.93
32[f]	OEt	OH	H	Me	5.02	4.44	0.58	(~0.54*)	2.19		4.80	3.36	7.74	0.00	4.65	0.93
33[g]	OEt	OAc	H	Me	3.84	3.31	0.53	2.28	2.37	−0.09	4.80	3.36	10.18	0.00	5.57	0.93
34	OEt	OEt	H	Me	5.71	4.96	0.75	2.77	2.48	0.29	4.80	3.36	10.24	0.00	6.08	0.93
35[g]	OEt	SMe	H	Me	3.19	3.63	−0.44	2.24	2.79	−0.55	4.80	3.36	9.56	0.00	6.36	0.93
36[f,g]	OEt	OCONHEt	H	Me	2.25	2.48	−0.23	(<0.55*)	0.35		4.80	3.36	12.64	0.00	5.65	0.93
37[g]	OEt	Me	H	Me	3.88	3.68	0.20	2.50	2.81	−0.31	4.80	3.36	7.65	0.00	7.15	0.93
38	OEt	Et	H	H	3.99	4.28	−0.29	3.47	2.81	0.66	4.80	3.36	9.19	0.00	7.81	0.93
39[f]	OEt	Me	OH	H	3.45	3.58	−0.13	(<0.45*)	2.16		4.80	3.36	7.65	0.00	4.65	0.93
40[e]	OEt	Me	OMe	H	(<4.47*)	4.04		2.54	2.57	−0.03	4.80	3.36	7.65	0.00	5.54	0.93
41[f,g]	OEt	Me	SEt	H	3.15	3.72	−0.57	(1.51)	2.91	−1.39	4.80	3.36	9.19[h]	0.00	6.90	0.93
42[e,g]	OEt	OMe	OMe	Me	(<1.51*)	3.62		1.31	2.09	−0.78	4.80	3.36	9.02	0.00	4.34	0.93
43	OEt	Me	10-ene		3.42	4.24	−0.82	2.38	2.75	−0.37	4.80	3.36	7.65	0.00	6.19	0.93
44	OEt	Me	11-ene		4.10	4.24	−0.14	2.49	2.75	−0.26	4.80	3.36	7.65	0.00	6.19	0.93
45	OEt	Me	10-epoxy		3.41	3.65	−0.24	2.22	2.22	0.00	4.80	3.36	7.65	0.00	4.76	0.93
46[f]	OEt	Me	oxo	H	2.76	3.34	−0.58	(<0.45*)	2.01		4.80	3.36	7.65	0.00	4.30	0.93
47[g]	O-*i*-Pr	Me	H	Cl	5.20	4.39	0.81	3.75	4.11	−0.36	4.80	4.11	7.65	1.25	6.85	1.34
48	O-*i*-Pr	OH	H	Me	6.06	5.40	0.66	4.33	3.70	0.63	4.80	4.11	7.65	1.25	5.06	1.34
49[g]	O-*i*-Pr	OAc	H	Me	4.30	4.16	0.14	3.81	3.78	0.03	4.80	4.11	10.18	1.25	5.98	1.34
50[g]	O-*i*-Pr	OCHO	H	Me	5.06	4.10	0.96	4.43	3.95	0.48	4.80	4.11	8.96	1.25	5.40	1.34
51	O-*i*-Pr	OEt	H	Me	6.15	5.76	0.39	4.51	3.84	0.67	4.80	4.11	10.24	1.25	6.49	1.34
52	O-*i*-Pr	O-*i*-Pr	H	Me	5.97	5.79	0.18	3.01	3.87	−0.86	4.80	4.11	10.24	1.25	6.90	1.34
53[e,g]	O-*i*-Pr	SMe	H	Me	(<4.51*)	4.39		3.77	4.12	−0.35	4.80	4.11	9.56	1.25	6.77	1.34
54[g]	O-*i*-Pr	OCONHEt	H	Me	3.18	3.32	−0.14	1.79	1.76	0.03	4.80	4.11	12.64	1.25	6.06	1.34
55[g]	O-*i*-Pr	Me	H	Me	3.55	4.35	−0.80	3.53	4.06	−0.53	4.80	4.11	7.65	1.25	7.56	1.34
56	O-*i*-Pr	Me	OMe	H	4.97	4.89	0.08	3.82	3.99	−0.17	4.80	4.11	7.65	1.25	5.95	1.34
57[e,g]	O-*i*-Pr	OMe	OMe	Me	(<3.53*)	4.61		3.88	3.64	0.24	4.80	4.11	9.02	1.25	4.75	1.34
58[e,g]	O-*i*-Pr	OMe	OH	Me	(<3.51*)	3.95		2.61	3.04	−0.43	4.80	4.11	9.02	1.25	3.86	1.34

Table I (Continued)

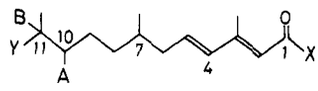
					activity						physicochemical parameters[b]					
					A. aegypti, pI_{50}, mM			*T. molitor*, pI_{50}, μmol/pupa								
no.	X	Y	A	B	obsd	calcd[c]	ΔpI_{50}	obsd	calcd[d]	ΔpI_{50}	L_x	W_x	D	B_x	log P	$\pi_{x'}$
59	O-*i*-Pr	Me	10-ene		4.03	5.02	−0.99	3.67	4.10	−0.43	4.80	4.11	7.65	1.25	6.60	1.34
60[g]	O-*i*-Pr	Me	11-ene		4.44	4.37	0.07	4.10	4.10	0.00	4.80	4.11	7.65	1.25	6.60	1.34
61	SMe	Me	H	H	4.65	3.96	0.70	3.25	2.92	0.33	4.30	3.34	6.95	0.00	7.44	1.63
62	SEt	Me	H	H	5.10	4.30	0.80	4.05	3.57	0.48	5.16	3.97	8.20	0.00	7.98	2.17
63	S-*i*-Pr	Me	H	H	4.07	4.17	−0.10	4.22	4.43	−0.21	5.16	4.49	8.20	1.26	8.39	2.58
64	$SCH_2C{\equiv}CH$	Me	H	H	3.47	2.93	0.54	3.47	2.70	0.77	6.89	3.34	9.09	0.00	5.07	1.29
65	$SCH_2CH{=}CH_2$	Me	H	H	3.39	3.76	−0.37	3.26	2.45	0.81	6.42	5.02	9.41	0.00	7.97	2.16
66	SMe	OMe	H	Me	5.04	4.93	0.11	3.47	3.30	0.17	4.30	3.34	8.32	0.00	6.24	1.63
67	SEt	OMe	H	Me	5.89	5.24	0.65	3.49	3.60	−0.11	5.16	3.97	9.57	0.00	6.78	2.17
68	S-*i*-Pr	OMe	H	Me	4.66	5.24	−0.58	5.04	4.59	0.45	5.16	4.49	9.57	1.26	7.19	2.58
69[e]	$SCH_2C{\equiv}CH$	OMe	H	Me	(<3.51*)	3.93		2.15	2.54	−0.39	6.89	3.34	10.46	0.00	5.90	1.29
70	$SCH_2CH{=}CH_2$	OMe	H	Me	5.10	4.49	0.61	2.06	1.99	0.07	6.42	5.02	10.78	0.00	6.77	2.16
71	NHEt	Me	H	H	3.65	3.21	0.44	4.76	4.47	0.29	4.83	3.42	7.71	0.00	5.24	−0.57
72	NH-*i*-Pr	Me	H	H	4.00	3.38	0.62	4.33	4.80	−0.47	4.83	4.15	7.71	0.00	5.65	−0.16
73[e,f]	NH-*i*-Bu	Me	H	H	(<3.47*)	3.37		(0.62)	5.23	−4.61	6.07	4.36	8.93	0.00	6.19	0.38
74	$NHCH_2$-$CH{=}CH_2$	Me	H	H	2.85	2.92	−0.07	4.33	4.25	0.08	6.25	4.48	8.84	0.00	5.23	−0.58
75	$N(Me)_2$	Me	H	H	3.31	2.36	0.95	3.70	3.20	0.50	4.02	2.90	6.43	0.00	4.94	−0.87
76	$N(Et)_2$	Me	H	H	3.24	3.49	−0.25	4.63	5.19	−0.56	4.83	3.42	7.66	0.00	6.02	0.21
77[f]	NHEt	OMe	H	Me	3.43	3.33	0.10	(5.95)	3.87	2.08	4.83	3.42	9.08	0.00	4.04	−0.57
78	NH-*i*-Pr	OMe	H	Me	4.02	3.64	0.38	4.21	4.32	−0.11	4.83	4.15	9.08	0.00	4.45	−0.16
79	NH-*c*-Pr	OMe	H	Me	2.64	3.37	−0.73	3.74	3.89	−0.15	5.05	3.92	9.09	0.00	4.04	−0.57
80	$N(Me)_2$	OMe	H	Me	3.05	2.61	0.44	3.80	3.04	0.76	4.02	2.90	7.80	0.00	3.74	−0.87
81	$N(Et)_2$	OMe	H	Me	3.08	3.88	−0.80	5.51	4.85	0.66	4.83	3.42	9.03	0.00	4.82	0.21
82[e]	NH_2	OMe	H	Me	(<3.43*)	0.87		0.05	0.74	−0.69	2.93	1.98	6.58	0.00	3.52	−1.09
83	Et	Me	H	H	4.02	3.68	0.34	4.89	4.59	0.30	4.11	2.97	6.54	0.00	6.27	0.46
84	*n*-Pr	Me	H	H	3.84	4.37	−0.53	4.70	5.84	−1.14	4.92	3.49	7.83	0.00	6.81	1.00
85	*i*-Bu	Me	H	H	3.10	2.98	0.12	3.14	3.43	−0.29	4.92	4.21	7.83	0.00	7.22	1.41
86[e]	Ph	Me	H	H	(<3.47*)	2.59		3.52	3.36	0.16	6.28	3.11	7.69	0.00	7.26	1.45
87[e,f]	CHN_2	Me	H	H	(<3.42*)			(5.15)			3.99	3.52	6.67	0.00		
88	Et	OMe	H	Me	5.27	4.34	0.93	5.78	4.79	0.99	4.11	2.97	7.91	0.00	5.07	0.46
89	*n*-Pr	OMe	H	Me	4.02	4.99	−0.97	5.73	5.67	0.06	4.92	3.49	9.20	0.00	5.61	1.00
90	*i*-Bu	OMe	H	Me	3.85	3.73	0.12	3.49	3.38	0.11	4.92	4.21	9.20	0.00	6.02	1.41
91	*sec*-Bu	OMe	H	Me	3.49	3.73	−0.24	3.54	3.52	0.02	4.92	3.49	9.20	0.00	6.02	1.41
92[e,f]	CHN_2	OMe	H	Me	(4.09)			(6.12)			3.99	3.52	8.04	0.00		
93[g]	SEt	OH	H	Me	4.17	4.48	−0.31	3.43	3.59	−0.16	5.16	3.97	8.29	0.00	5.89	2.17
94[g]	SEt	OAc	H	Me	3.75	3.51	0.24	2.83	3.08	−0.25	5.16	3.97	10.72	0.00	6.81	2.17
95[f,g]	SEt	Me	H	Me	3.90	3.52	0.38	nd[i]	3.43		5.16	3.97	8.20	0.00	8.39	2.17
96[e-g]	NHEt	OH	H	Me	(<3.45*)	1.83		(5.22)	3.05	2.17	4.83	3.42	7.80	0.00	3.15	−0.57
97[g]	NHEt	Me	H	Me	1.88	2.73	−0.85	4.45	4.63	−0.18	4.83	3.42	7.71	0.00	5.65	−0.57
98	NHEt	Me	10-ene		2.70	2.91	−0.21	4.78	4.20	0.58	4.83	3.42	7.71	0.00	4.69	−0.57
99[e-g]	$N(Et)_2$	Me	10-ene		(<1.46*)	2.66		(1.70)	5.03	−3.33	4.83	3.42	7.66	0.00	5.47	0.21
100[g]	$N(Et)_2$	Me	10-epoxy		1.78	1.79	−0.01	3.85	4.24	−0.39	4.83	3.42	7.66	0.00	4.04	0.21
101[e,g]	Et	Me	H	H	(<3.42*)	3.09		4.10	4.64	−0.54	4.11	2.97	6.54	0.00	6.68	0.46
102[f]	Et	OH	H	Me	3.62	3.55	0.07	(6.04)	3.75	2.29	4.11	2.97	6.54	0.00	4.18	0.46

[a] When the activity was reported to be lower than a certain value, the activity data are indicated by an asterisk. [b] L_x, the length of the X moiety along the bond axis; W_x, the width perpendicular to the L axis and in the direction in which the skeletal chain extends; D, the summation of the lengths of the X and Y moieties along the axis that passes through the C_1 and C_{11} atoms: B_x, the width toward the C_1-oxo group of the α-branch of ester and thiol ester derivatives; log P, the hydrophobicity of whole molecule; $\pi_{x'}$, the hydrophobicity of the C(Me)=CHCOX moiety. [c] Values were calculated by eq 4. [d] Values were calculated by eq 7. [e] Compounds excluded from the analysis for activity against *A. aegypti*. Their activity data are shown in parentheses. [f] Compounds excluded from the analysis for activity against *T. molitor*. Their activity data are shown in parentheses. [g] Compounds whose activity data are for (−)-enantiomers. [h] The value was estimated considering the longest chain of the compound as $EtS{-}[C_{10}(C_{11}Me_2){-}C_1]{-}X$ and taking the Et of SEt as Y. [i] Activity not detected.

should be at work in other types of compounds if the site of action or the receptor is the same. In this paper, we analyze the activities of this class of terpenoids on *Aedes aegypti* (yellow-fever mosquito) and *Tenebrio molitor* (yellow mealworm) quantitatively in terms of physicochemical parameters. The results indicate that the steric dimensions and hydrophobicity of the molecule are commonly important for activity with both insect species, whereas the effects of variation of the substituents at both ends of the dodecadienone chain are specific. The similarity as well as the dissimilarity of the structural effects on activity is explained in terms of physicochemical interactions with the receptor, and the receptor map drawn for each species, based on these results, is proposed to show a framework in which a compound should fit to be active.

Biological and Physicochemical Parameters. The activity values ID_{50} originally reported by Henrick et al.[6] on *Aedes aegypti* in ppm and *Tenebrio molitor* in μg/pupa were converted to molar and mole units, respectively, and the logarithm of the reciprocal of the molar ID_{50} value, pI_{50}, was used as the biological parameter. All of the compounds are racemic unless otherwise specificed in Table I.

Since the structures of the present series of compounds listed in Table I vary at both ends of the chain molecule, we denoted them by X and Y as shown by Figure 1. The X expresses the substituents at the carbonyl C_1 atom of the dodecadienone skeleton, and the Y is the longest one of the C_{11} substituents in terms of the length L_y along the bond axis. The $Y{-}[C_{11}{-}C_1]{-}X$ thus constitutes the longest



X = OR, SR, NHR, NR_2, Alkyl
Y = OR, SR, OCOR, Me, Et
A = H, OR, SR etc
B = H, Me, Cl

Figure 1. Structure of JH-mimetic, 2,4-dodecadienone derivatives.

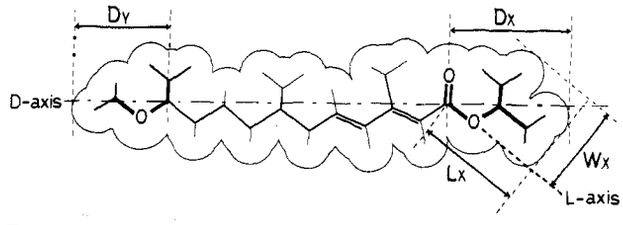


Figure 2. Schematic representation of the steric parameters. The compound used as the model is isopropyl (2*E*,4*E*)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate (17, methoprene). In this and the following figures, the ends of the bars of the molecular model represent hydrogen atoms.

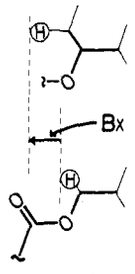


Figure 3. Schematic representation of the steric B_x parameter for ester and thiol ester derivatives.

chain of the molecule. In the case of the Me–C_{11}–C_{10} (SEt) compound **41** in Table I, the longest chain is constituted by EtS–[C_{10}–C_1]–X. Thus the ethyl of the SEt group was taken as Y, considering the sulfur atom as the 11th atom from the C_1 carbon and the parameters of which were used in the actual analyses.

Since preliminary analyses indicated that the steric dimensions are most significant in determining the activity, we examined various steric parameters for their utility in correlations and found that the STERIMOL parameters[17] and their modifications are best in representing the situation. The following parameters were defined and used. L_x is the STERIMOL length parameter of the X end along the bond axis. The original STERIMOL width parameters, B_{1-4}, are calculated on the basis of the zigzag, fully extended conformation, which is thought to be the energy minimum one for simple substituents such as those considered here.[17] In this study, they were slightly modified considering the conformational correspondence of the chain structure, as were defined in our previous studies;[16] namely, the W_x parameter is the width of the X end perpendicular to the L axis and in the direction in which the longest chain of the substituent extends in the fully extended (staggered) conformation, as shown by Figure 2. For benzyl, the benzene ring was twisted 90° from the plane in which the zigzag skeletal chain lies. The width in the reverse direction as well as the thicknesses in the rectangular directions to W_x was defined but was not significant in the analyses. The corresponding length L_y and width W_y parameters for the Y moiety were also insignificant in correlations. The width parameters were calculated geometrically on the basis of the STERIMOL program, which gives coordinates and van der Waals radii of component atoms.[17] The B_x parameter shown by Figure 3 was defined to express the bulkiness toward the carbonyl group of α-substituents in the alcohol moiety of ester derivatives and/or thiol ester derivatives. The reference of the value is shifted to that of the compounds having no α-branch, so that it expresses the length of the protruded part of the α-substituents beyond the α-hydrogen atom.

In addition to the steric parameters of respective ends, the one on the whole molecular basis was used in the correlations, since steric effects of both ends appeared not to be completely independent from but linked with each other to some extent during the analyses. In some typical compounds, the activity tends to vary with the sum of steric dimensions of both ends, other factors being equal. We thus defined the D parameter, which is the summation of the D_x and D_y parameters. D_x is, as shown by Figure 2, the length of the X moiety along the axis that passes through the C_1 and C_{11} carbon atoms in the fully extended, staggered conformation, and D_y is that of the Y moiety. The values for these parameters were calculated geometrically on the basis of the CPK models of the molecules.

The variation in the hydrophobicity of the X moiety is expressed more properly by the π value of the C(Me)=CHCOX moiety, $\pi_{x'}$, than by the aromatic or aliphatic π for X, since it is in conjugation with the α,β-unsaturated carbonyl group. The value was calculated with use of its additive-constitutive nature as below.

For ester derivatives, π[C(Me)=CHCOOR] = log P(CH_2=CHCOOR) − log P(H_2) + π(Me) + F_b, where F_b is the term supplementing the effect of an aliphatic branch.[18] Log P(CH_2=CHCOOR) was calculated with use of available data as log P(CH_3CH=CHCOOH) + [log P(C_6H_5COOR) − log P(C_6H_5COOH)] − π(Me). Because the ester function is in conjugation with a double bond, the hydrophobicity difference between the ester and carboxylic acid was estimated with use of the data of benzoic acid derivatives as above rather than with use of aliphatic acid derivatives.

Similarly, for thiol ester derivatives, π[C(Me)=CHCOSR] = π[C(Me)=CHCOOR] + [log P(O=CS(CH_2)$_2$$CH_2$) − log P(O=CO(CH_2)$_2$$CH_2$)]. For unsubstituted amides, π[C(Me)=CHCONH$_2$] = π[C(Me)=CHCOOMe] + [log P(C_6H_5CONH$_2$) − log P(C_6H_5COOMe)]. For N-monosubstituted amides, π[C(Me)=CHCONHR] = π[C(Me)=CHCOOR] + [log P(C_6H_5CONHR) − log P(C_6H_5COOR)]. For *N*,*N*-dimethyl and *N*,*N*-diethyl amides, π[C(Me)=CHCONMe$_2$] = π[C(Me)=CHCOOMe] + [log P(C_6H_5CONMe$_2$) − log P(C_6H_5COOMe)], π[C(Me)=CHCONEt$_2$] = π(*N*,*N*-dimethyl amide) + 2π(Me). For ketones, π[C(Me)=CHCOR] = π[C(Me)=CHCOOR] + [log P(C_6H_5COR) − log P(C_6H_5COOR)].

In the calculation of log P of C_6H_5COOR, where R is a higher alkyl than Me, the value was estimated by log P(C_6H_5COOMe) + π (an alkyl one carbon unit less than R), and a similar method was applied to the amide and ketone derivatives. The experimental data used were taken from the literature.[18,19]

For the hydrophobicity parameter of the Y end, we used $\pi_{y'}$, which is the value for the Y–C_{11}–C_{10} moiety since some

(17) Verloop, A.; Hoogenstraaten, W.; Tipker, J. *J. Drug. Res.* **1976**, *7*, 165.

(18) (a) Hansch, C.; Leo, A. "Substituent Constant for Correlation Analysis in Chemistry and Biology"; Wiley: New York, 1979. (b) Iwasa, J.; Fujita, T.; Hansch, C. *J. Med. Chem.* **1965**, *8*, 150.

(19) The Pomona College Medicinal Chemistry Data Base.

Table II. Development of Equation 4

const	L_x	L_x^2	D	D^2	log P	(log P)^2	B_x	I_N	I_{OR}	I_{br}	$I_{(-)}$	r	s	$F_{X,Y}$[a]
−6.97	4.13	−0.38										0.50	0.96	$F_{2,82}$ = 13.33
−7.19	4.36	−0.41						−1.26				0.64	0.85	$F_{1,81}$ = 23.52
−7.46	4.34	−0.40						−1.22	0.81			0.74	0.75	$F_{1,80}$ = 24.21
−6.54	3.88	−0.36					0.64	−1.01	0.81			0.79	0.68	$F_{1,79}$ = 16.74
−7.11	4.22	−0.39					0.73	−1.04	0.61		−0.74	0.83	0.63	$F_{1,78}$ = 13.86
−7.54	4.42	−0.41					0.67	−1.12	0.64	−1.13	−0.78	0.85	0.60	$F_{1,74}$ = 9.74
−12.08	4.16	−0.40			1.52	−0.10	0.59	−0.67	0.83	−1.30	−0.77	0.88	0.56	$F_{2,75}$ = 7.51
−16.35	3.65	−0.35	1.08	−0.06	1.90	−0.13	0.57	−0.71	0.86	−1.39	−0.65	0.89	0.53	$F_{2,73}$ = 4.34

[a] F statistic for the significance of the addition of each variable.

Table III. Squared Correlation Matrix for Variables Used in Equation 4

	L_x	D	log P	B_x	I_N	I_{OR}	I_{br}
D	0.34						
log P	0.08	0.02					
B_x	0.00	0.01	0.03				
I_N	0.02	0.04	0.25	0.05			
I_{OR}	0.00	0.12	0.11	0.00	0.00		
I_{br}	0.00	0.00	0.00	0.01	0.01	0.01	
$I_{(-)}$	0.02	0.02	0.01	0.04	0.00	0.12	0.01

compounds have substituents at C_{10} and/or C_{11}. The π value of the Y substituents was mostly taken from the literature.[18,19] For π(OMe), −0.98 was used.[18b] For higher and branched alkoxy groups, π(Me) and F_b were added to π(OMe). The hydrophobicity of the whole molecule, log P, was estimated according to the additive-constitutive nature by $\pi_{x'}$ + log $P(H_2)$ + $\pi_{y'}$ + $\pi(C_4\text{–}C_9)$. The last term, i.e., the π value for the common C_4–C_9 unit, was calculated by $7\pi(CH_3) + F_b$ + [log $P(CH_2{=}CHCH{=}CH_2)$ − log $P(CH_3CH{=}CHCH_3)$], where the term in brackets estimates the extent of decrease in π value due to the conjugation of the C_4 double bond.

The electronic effect considered for the Y moiety is in terms of the Taft's σ^* value estimated according to the literature.[18,20] It is thus directed toward the C_{11} atom. The X or CO–X moiety is divided into six structural types: esters, thiol esters, ketones, and unsubstituted, monosubstituted, and disubstituted amides. The electronic effect of the X substituents varies according to the type of compounds. It is, however, considered nearly constant within a type, since the variation in the X moiety is mostly alkyl. Indicator variables were considered for the effects of each type in the analyses.

Results

Quantitative Structure–Activity Relationships. (A) *Aedes aegypti*. As seen from Table I, the Y moiety of more than half of the compounds in the present series is fixed to Me or OMe, while the structural variation in the X moiety is diverse. Preliminary examination of the structure vs. activity relationship of this type of compounds suggested that esters (**1–6, 8–10, 12, 14–28**), carboxylic acids (**13, 30**), and thiol esters (**61–68, 70**) could be analyzed together. By use of the steric parameters for whole molecule and substituents as defined above and by examination of the improvement in the quality of correlations by adding hydrophobic and electronic parameter terms stepwise as well as systematically, eq 1 was derived as that of the best correlation. In this and the following equations, n is the number of compounds analyzed, r is the multiple correlation coefficient, and s is the standard deviation. The figures in parentheses express the 95% confidence interval.

(20) Taft, R. W. "Steric Effect in Organic Chemistry"; Newman, M. S., Ed.; Wiley: New York, 1955; p 556.

$$\underset{}{\mathrm{pI}_{50}} = \underset{(1.56)}{2.73L_x} - \underset{(0.13)}{0.30L_x^2} + \underset{(1.43)}{2.70D} - \underset{(0.08)}{0.13D^2} + \underset{(2.19)}{3.98\log P} - \underset{(0.17)}{0.30(\log P)^2} - \underset{(8.76)}{27.60} \quad (1)$$

$$n = 36,\ r = 0.94,\ s = 0.45$$

The parameter values are summarized in Table I.

The activity is parabolically related to the length of the X moiety L_x as well as that of the total chain D and to the total hydrophobicity log P, suggesting that there are optimum steric as well as hydrophobic conditions for activity.

The number of the amide derivatives of this type (**71, 72, 74–81**) as well as that of ketones (**83–85, 88–91**) are not sufficient for obtaining a completely reliable correlation for each set. They could be, however, incorporated into eq 1 to give eq 2. The I_N is an indicator variable that takes

$$\underset{}{\mathrm{pI}_{50}} = \underset{(1.54)}{2.97L_x} - \underset{(0.13)}{0.32L_x^2} + \underset{(1.45)}{1.73D} - \underset{(0.08)}{0.08D^2} + \underset{(1.58)}{2.02\log P} - \underset{(0.12)}{0.15(\log P)^2} + \underset{(0.40)}{0.41B_x} - \underset{(0.56)}{0.76I_N} - \underset{(0.67)}{1.43I_{br}} - \underset{(7.51)}{17.61} \quad (2)$$

$$n = 53,\ r = 0.89,\ s = 0.53$$

the value of 1.0 for amides and zero for the others. The negative coefficient shows that the activity of amide compounds is uniformly lower than that of other types of compounds having corresponding structures. The indicator variable term I_{br} is for compounds having a branch at any position in the X moiety of ketone derivatives, the negative coefficient of which shows that their activity is lower than that of the ketones having no branch. In contrast to this, the B_x parameter is incorporated into this equation with the positive coefficient when it is used for the ester derivatives, indicating that the activity of the esters having a bulkier α-branch is higher. The branch effect of the esters became remarkable by including amides and ketones in the analyses. Although the D and its squared term were significant over the 97.5% and 95% levels in the t test, respectively, a somewhat high internal correlation was observed between the D and L_x terms, the squared simple correlation coefficient r^2 being 0.58. This is considered to be due to a correlation between D_x and L_x in the set of compounds analyzed and that the variation of the Y moiety, i.e., that of the D_y, is limited to Me and OMe.

To obtain stepwise an insight into the structure–activity profile of the Y moiety, we analyzed the ethyl and isopropyl ester series of compounds **2, 4, 15, 17, 31–39, 41, 43–52, 54–56, 59,** and **60**, which possess various Y substituents. In eq 3 for this set of compounds, the I_{OR} is the indicator variable that takes 1.0 for the compounds whose Y moiety is alkoxy or hydroxy and otherwise zero.

$$\underset{}{\mathrm{pI}_{50}} = \underset{(0.15)}{-0.20D} + \underset{(0.34)}{0.69B_x} + \underset{(0.51)}{1.81I_{OR}} + \underset{(1.30)}{5.27} \quad (3)$$

$$n = 29,\ r = 0.88,\ s = 0.55$$

The D term with the negative coefficient was significant over the 95% level, but the D^2 term was not. This result appears to show that the D value of most of the compounds analyzed are supraoptimum and on the negative slope of the hypothetical parabola. Since the range of the D value in eq 3 is 7.65–12.64, the optimum D value would be lower than 7.7. In eq 1, in which the range of the D value is 6.36–11.52, the optimum D value is calculated to be 10.4. This apparent discrepancy is attributed to the fact that the parabolic curve in terms of D in eq 1 is rather gentle and the optimum D value is located within a rather wide confidence interval. The negative slope of eq 3 is also low. The optimum value thus appears mobile within the compound sets analyzed in eq 1–3. It should be warranted, as described below, by the analyses of the compounds having more variation in structure in terms of D. The insignificance of the log P term in eq 3 seems due to the narrower range of variation of the values, and the parabolic dependence of activity on log P shown by eq 1 is as mild as that on the D.

The somewhat different appearance with respect to the D term between eq 1 and 3 as well as the incomplete eclipse of their overall features is considered to be brought about by the analyses confined to compound sets having structural variation at only one end of the molecule. The situation suggests the necessity of analyzing the structure vs. activity relationship of the whole molecule, for obtaining better insight into the active structure. Efforts were made to analyze a combined set of compounds, based on the information obtained above, giving eq 4 covering those included in eq 1 and 3 plus compounds **93–95**, **97**, **98**, **100**, **102**. The optimum value for L_x is calculated to

$$\begin{aligned} pI_{50} = {} & \underset{(1.26)}{3.65L_x} - \underset{(0.11)}{0.35L_x^2} + \underset{(1.12)}{1.08D} - \underset{(0.06)}{0.06D^2} + \\ & \underset{(1.13)}{1.90 \log P} - \underset{(0.09)}{0.14(\log P)^2} + \underset{(0.25)}{0.57B_x} - \underset{(0.41)}{0.71I_N} + \underset{(0.35)}{0.86I_{OR}} - \\ & \underset{(0.65)}{1.39I_{br}} - \underset{(0.37)}{0.65I_{(-)}} - \underset{(5.21)}{16.35} \quad (4) \end{aligned}$$

$$n = 85,\ r = 0.89,\ s = 0.53$$

be 5.21. The level of significance of the D term is slightly less than 95%, and the optimum D value is 9.00. The squared correlation coefficient between L_x and D parameters is now 0.34 (Table III), which reflects no significant internal correlations, if any. The optimum hydrophobicity is estimated as 6.79 in terms of log P. Of the C_7 enantiomeric pair, the (*S*)-(+)-enantiomer is reported as being considerably more active than the (*R*)-(−)-counterpart.[6,21] In this work, 23 compounds have the (*R*)-(−)-configuration, whereas the rest are a (±)-mixture. The enantiomeric effect was expressed by the indicator variable term $I_{(-)}$, which takes the value of 1.0 for the (*R*)-(−)-isomer and zero for the (±)-mixture. Any particular effects that may be attributed to the electronic σ^* parameter for the Y moiety were not significant.

The pI_{50} value of some compounds was not determined, but their activity was reported to be lower than thee values indicated by the astericks in Table I.[6] These compounds were thus excluded from the analyses, but their predicted values calculated by eq 4 are listed in Table I. The observed activity for compound **7** (X = O-*t*-Bu, Y = Me) is significantly lower than the calculated one. This may be due to the trident *tert*-butyl structure whose bulkiness is not completely reflected by the steric parameters used in the analyses. Similar reasoning may be valid for the observed value being lower than the calculated one of compound **20** having the same O-*t*-Bu substituent as X but a different Y (OMe). With more compounds having variable Y substituents but the common O-*t*-Bu group as X, it may be possible to estimate the factor to lower the activity, plausibly a steric width one. The calculated values for compounds **40**, **42**, **53**, **57**, **58**, **69**, **73**, **82**, **86**, **96**, **99**, and **101** are not so much in conflict with the reported activity and thus eq 4 provides a physicochemical basis for the activity of these compounds. The predicted values for compounds **11** (X = OPh, Y = Me) and **29** (X = O-c-C_5H_9, Y = OMe) always deviated from the observed ones, and they were excluded from the analysis. The conformation of compound **11** may be somewhat deformed by virtue of the bulky benzene ring from that assumed for the determination of the steric parameters, and/or an electronic effect may be operating somewhere at the position that is in conjugation with the aromatic π-system. The choice of the energetically most stable form is difficult for the cyclopentyloxy moiety of compound **29**, and the values of the steric parameters vary with the conformation. Those adopted in Table I may not be the most suitable ones or some additional steric effect(s) due to the bulkier aliphatic ring may decelerate activity. For explaining the activity of these compounds, it is necessary to estimate appropriate steric and/or electronic parameters with a greater number of cognate compounds such as substituted phenyl and cycloalkyl esters. Because of the lack of appropriate hydrophobicity data for the diazo compounds **87** and **92**, they were excluded from the correlation analyses in this study.

Equation 4a includes all of the compounds whose activity was definitely determined. Although the quality of correlation is slightly lower than that of eq 4, the information derived for the structural effect is almost identical between two equations.

$$\begin{aligned} pI_{50} = {} & \underset{(1.41)}{3.54L_x} - \underset{(0.12)}{0.34L_x^2} + \underset{(1.25)}{1.09D} - \underset{(0.06)}{0.06D^2} + \\ & \underset{(1.25)}{2.17 \log P} - \underset{(0.10)}{0.16(\log P)^2} + \underset{(0.27)}{0.40B_x} - \underset{(0.46)}{0.75I_N} + \underset{(0.39)}{0.87I_{OR}} - \\ & \underset{(0.73)}{1.39I_{br}} - \underset{(0.41)}{0.54I_{(-)}} - \underset{(5.81)}{16.77} \quad (4a) \end{aligned}$$

$$n = 87,\ r = 0.86,\ s = 0.59$$

The development of the final, inclusive eq 4 is summarized in Table II and the degree of independence of the variables used is shown in Table III.

(B) *Tenebrio molitor*. Analyses were performed with use of the activity data listed in Table I as the dependent variables. Equation 5 is the best result for the ester (**1–6**, **8–11**, **14–22**, **24–29**) and thiol ester (**61–70**) derivatives having the Me or OMe group at the Y end. The activity

$$\begin{aligned} pI_{50} = {} & \underset{(3.08)}{6.30W_x} - \underset{(0.34)}{0.81W_x^2} - \underset{(0.23)}{0.27D} + \underset{(0.52)}{0.67\pi_{x'}} + \underset{(0.45)}{0.97B_x} - \underset{(5.96)}{7.64} \\ & (5) \end{aligned}$$

$$n = 35,\ r = 0.88,\ s = 0.63$$

is parabolically dependent on the width of the X moiety, and compounds having hydrophobic X substituents exhibit higher activity as indicated by the positive coefficient of the $\pi_{x'}$ term. The B_x is significant for both ester and thiol ester derivatives in this equation for *T. molitor*.

With incorporation of amide (**71**, **72**, **74–76**, **78–82**) and

(21) Henrick, C. A.; Anderson, R. J.; Staal, G. B.; Ludvik, G. F. *J. Agric. Food Chem.* **1978**, *26*, 542.

Table IV. Development of Equation 7

const	W_x	W_x^2	D	D^2	log P	(log P)^2	$\pi_{x'}$	B_x	I_{NR}	I_{br}	r	s	$F_{X,Y}$[a]
−9.00	6.44	−0.82									0.47	1.06	$F_{2,81}$ = 11.25
−11.95	7.46	−0.91							1.43		0.68	0.89	$F_{1,80}$ = 36.95
−10.26	6.64	−0.84						0.85	1.70		0.77	0.78	$F_{1,79}$ = 23.43
−15.44	6.39	−0.78	1.42	−0.09				0.77	1.55		0.80	0.74	$F_{2,77}$ = 6.29
−17.10	6.66	−0.81	1.64	−0.10				0.75	1.82	−1.29	0.83	0.69	$F_{1,76}$ = 10.98
−16.55	5.62	−0.74	1.92	−0.12			0.77	0.77	2.73	−2.31	0.88	0.59	$F_{1,75}$ = 29.33
−23.32	4.63	−0.63	2.58	−0.15	1.76	−0.13	0.61	0.87	2.89	−2.51	0.90	0.54	$F_{2,73}$ = 7.85

[a] F statistic for the significance of the addition of each variable.

Table V. Squared Correlation Matrix for Variables Used in Equation 7

	W_x	D	log P	$\pi_{x'}$	B_x	I_{NR}
D	0.28					
log P	0.20	0.01				
$\pi_{x'}$	0.40	0.20	0.47			
B_x	0.20	0.02	0.04	0.14		
I_{NR}	0.12	0.15	0.15	0.41	0.14	
I_{br}	0.00	0.00	0.01	0.01	0.02	0.14

ketone (**83–86**, **88–91**) derivatives, eq 6 was formulated as shown below:

$$\underset{}{pI_{50}} = \underset{(2.22)}{5.26W_x} - \underset{(0.27)}{0.70W_x^2} + \underset{(1.78)}{2.08D} - \underset{(0.10)}{0.13D^2} + \underset{(1.60)}{1.42 \log P} - \underset{(0.13)}{0.11(\log P)^2} + \underset{(0.49)}{0.75\pi_{x'}} + \underset{(0.43)}{0.90B_x} + \underset{(0.62)}{2.83I_{NR}} - \underset{(0.84)}{2.53I_{br}} - \underset{(8.69)}{20.68} \quad (6)$$

$$n = 53,\ r = 0.92,\ s = 0.60$$

The log P and its squared term are significant over 90% level in this equation. Their insignificance in eq 5 for the ester and thiol ester derivatives appears due to the mild dependence of the activity on log P and narrower range of its variation. The fact that the D^2 term is significant in eq 6 but not in eq 5 indicates that the range of the D value for compounds included in eq 5 is narrower than that for those included in eq 6 and located on the supraoptimal side of the parabolic relationship. The I_{NR} is the indicator variable for the amides and ketones; i.e., it is 1.0 when X = NHR, NR_2, or R and is otherwise zero. The positive sign of the coefficient indicates that the amide and ketone types of compounds are more favorable to the activity of *T. molitor* than the corresponding ester types of compounds. The indicator variable I_{br} for the branched ketone is significant in this equation as it is in eq 2 for *A. aegypti*.

The correlation equation (not shown) for the variation of the Y moiety together with eq 6 indicated that the combined set of compounds could be analyzed as they were in the previous section for the activity on *A. aegypti*. Equation 7 thus obtained covers compounds included in eq 6 and compounds **31–60** and **93–102**, omitting four outliers and five derivatives, the activity of which was not accurately determinable. All of the variables incorporated

$$\underset{}{pI_{50}} = \underset{(1.69)}{4.63W_x} - \underset{(0.21)}{0.63W_x^2} + \underset{(1.14)}{2.58D} - \underset{(0.06)}{0.15D^2} + \underset{(1.13)}{1.76 \log P} - \underset{(0.09)}{0.13(\log P)^2} + \underset{(0.30)}{0.61\pi_{x'}} + \underset{(0.26)}{0.87B_x} + \underset{(0.47)}{2.89I_{NR}} - \underset{(0.71)}{2.51I_{br}} - \underset{(5.96)}{23.32} \quad (7)$$

$$n = 84,\ r = 0.90,\ s = 0.54$$

are significant over the 99% level. The optimum conditions for activity of W_x, D, and log P are calculated to be 3.67, 8.60, and 6.77, respectively. The indicator variable term $I_{(-)}$ for (−)-enantiomers was not significant so far as the present set of compounds is concerned. Table IV shows the development of the final eq 7 and Table V the degree of independence of the variables used. The squared correlation coefficients of D with the component D_x and D_y are 0.45 and 0.55, respectively, the values being very close to those observed for the set of compounds analyzed in eq 4.

Of the compounds whose activity was reported as lower than the values indicated by the asterisks in Table I, the activity of compounds **13**, **23**, **30**, and **36** seems amenable to eq 7. The fact that the activity on *A. aegypti* of the benzyl ester **12** is well explained by eq 4 but that on *T. molitor* is not by eq 7 may mean that the bulky benzyl moiety of the compound is differently allocated on the *T. molitor* receptor with a somewhat different conformation. The activity of the C_{10}-hydroxy compound **39** and the C_{10}-oxo compound **46** is thought to be considerably lower than that predicted, and the reasons are unclear. The activity values pI_{50} of the compounds **7**, **32**, 41, **73**, **77**, **96**, and **102** always deviated from the calculated values during the development of eq 7, and thus they were excluded from the analyses. The activity of compound **7**, having the bulky *t*-Bu function, may be explained by the steric effect similar to that considered in the previous section for the low activity on *A. aegypti*. The deviation of the calculated value from the observed one of compound **41** may be also caused by a steric effect, since it possesses the bulkiest A substituent (*i*-Pr) and the steric parameters considered here do not reflect any of its bulkiness. Compound **73** is the only amide that possesses a branch at the β-position of the side chain. Compounds **96** and **102** have a common feature; i.e., they are the amide and ketone, respectively, having a hydroxy group at the A position and the observed activities are higher than the calculated one. Although the physicochemical basis is obscure, the existence of the hydroxy function at that position may enhance the activity of amides and ketones. It is, however, statistically not meaningful to use a parameter for a compound set having less than a few members, for example, a steric parameter for the branched **73** and an indicator variable for the hydroxy **96** and **102**. As to the rest of the compounds, **32** and **77**, it is hard to find any structural conspicuousness to explain the deviation of the calculated activity from the observed one. Their activity seems rather conflicting with that of the congeneric compounds analyzed, so far as the present data and results are concerned. For example, the activity of the 11-hydroxy compound **48** (X = O-*i*-Pr, Y = OH) is explained by eq 7 but that of the cognate **32** (X = OEt, Y = OH) is not. The actvity of compound **77** (X = NHEt, Y = OMe) is unexpectedly high in comparison with the corresponding **97** (X = NHEt, Y = Me). Further biological as well as chemical studies are thus required for these derivatives. For the majority of compounds, however, the activity data are rationalized by eq 7.

Equation 7a is derived for all compounds including outliers from eq 7, showing a much poorer correlation. The

level of significance of the log P and $(\log P)^2$ terms is below 90%, and they are not presented in the equation.

$$pI_{50} = \underset{(2.69)}{4.85W_x} - \underset{(0.33)}{0.66W_2^2} + \underset{(1.82)}{1.65D} - \underset{(0.10)}{0.10D^2} + \underset{(0.44)}{0.70\pi_{x'}} + \underset{(0.43)}{0.78B_x} + \underset{(0.75)}{2.52I_{NR}} - \underset{(1.18)}{1.99I_{br}} - \underset{(7.90)}{13.79} \quad (7a)$$

$$n = 91,\ r = 0.73,\ s = 0.93$$

Discussion

Equations 4 and 7 show that the hydrophobic effect in terms of log P and the steric factors expressed by D, B_x, and I_{br} are very similar between the two insect species *A. aegypti* and *T. molitor*. The overlaps of the coefficient values of the log P and $(\log P)^2$ terms between two equations indicate the similarity of the transport process(es), while those of the steric D and D^2 terms suggest similar dimensions of the receptor. The D parameter is the sum of the lengths of the X and Y substituents, D_x and D_y. Any sums of other steric parameters, L_x, L_y, W_x, W_y, of both ends were not significant or were less significant. Although the D parameter is defined as the length along the D axis as shown in Figure 2, this does not necessarily mean that the molecule is always fully extended. The common optimum D value is ca. 8.8 Å irrespective of the conformation of the middle part of the molecule. Examination using the CPK model minimizing the strains between bonds as well as the existence of active compounds having a conformationally less flexible structure between the two ends (see discussions below) may, however, support a rather extended middle part as depicted in Figure 2.

The ester derivatives seem above all susceptible to a hydrolytic attack[22] in *A. aegypti* since the bulky analogues in terms of B_x favor activity. The site of the enzymatic attack on these compounds, probably the carbonyl carbon atom, becomes sterically hindered. The B_x term is significant for both ester and thiol ester derivatives in eq 7, so that they both appear susceptible to the enzymatic attack in *T. molitor*. The slight difference between the species may be attributed to a difference in the potency of the enzyme. This is consistent with the discussion below of the significance of the I_{NR} term in eq 7. The branched and thus bulky ketones, on the contrary, are unfavorable to the activity, as indicated by the I_{br} term with the negative coefficient in each equation. Ketones are considered resistant to hydrolytic attack, so that the result seems to mean that the branch obstructs the proper fit in the receptor.

In eq 4 for *A. aegypti*, one of the important factors is the length of the X substituents, L_x, whereas it is the width parameter, W_x, in eq 7 for *T. molitor*. This is considered to reflect the difference of the receptor shape at the region where the X moiety comes in. Equation 4 suggests the existence of a receptor wall in the L_x direction ca. 5.2 Å, the optimum value, distant from the carbonyl C_1 atom in the *A. aegypti* receptor, whereas it is located in the W_x direction ca. 3.7 Å distant from the L_x axis in the *T. molitor* receptor. Another conspicuous result that shows the species difference of the receptor is that the position-specific hydrophobic effect expressed by the $\pi_{x'}$ term is important for *T. molitor*. The position of the receptor surface where the X moiety is located is considered to be hydrophobic and the receptor surface interacts more strongly with compounds having a hydrophobic X substituents.

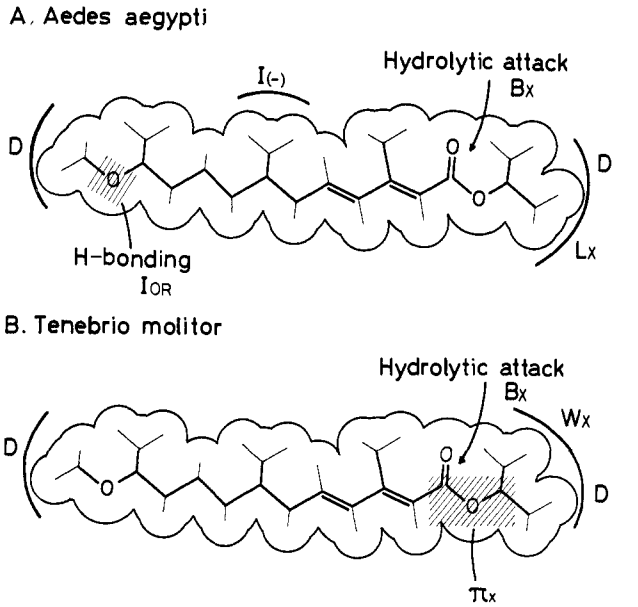


Figure 4. Binding models of 2,4-dodecadienones to *A. aegypti* (A) and *T. molitor* (B) receptors. The solid lines marked D, L_x, W_x, and $I_{(-)}$ are the steric interaction sites or spatial walls suggested by eq 4 and/or 7. The region indicated by the oblique lines in A is the H-bonding site suggested by the I_{OR} term in eq 4, and that in B is the hydrophobic interaction site suggested by the $\pi_{x'}$ term in eq 7. The arrows directed toward the carbonyl group indicate the possible hydrolytic site suggested by the B_x term in eq 4 and 7. The compound used as the model is isopropyl (2*E*,4*E*)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate (17, methoprene).

The positive sign of the I_{NR} term in eq 7 for *T. molitor* may reflect the resistance of the amides to and the impotency of the ketones against hydrolytic attacks that raise the concentration of the active species at the site of action. The insignificance of the term in eq 4 seems to reflect the weaker potency of the hydrolytic enzyme. The resistance of the amide and ketone derivatives to it may be relatively less important for the activity on *A. aegypti*. The physicochemical meaning of the I_N term with the negative coefficient in eq 4 is obscure, but a specific enzyme system to destroy amides may be involved to decelerate activity. The I_{OR} factor that specifically enhances the activity on *A. aegypti* of the C_{11} hydroxy and alkoxy compounds seems to be an electronic one; possibly the basic oxygen atom interacts with an acidic group on the receptor. The basicity of the SR compounds is thought to be weaker. The hydrogen-bonding interaction is position specific or sensitive to the geometry of binding, and this explains the fact that the effect is not operative in the C_{11} ester derivatives **33**, **36**, **49**, **50**, **54**, and **94** where the site of interaction is the carbonyl oxygen atom and in the epoxy ether compounds **45**, **46**, and **100**. The significance of the $I_{(-)}$ term in eq 4 indicates that a spatial wall exists closer to the methyl group at the C_7 atom in the interaction site, probably the receptor site, of *A. aegypti*.

On the basis of the results described above, an inclusive "mode of action" model was drawn for each species. Figure 4A shows the results of eq 4 and Figure 4B the results of eq 7. The affixes D, L_x, W_x, and $I_{(-)}$ indicate the steric interaction sites. The position-specific hydrophobic interaction site is expressed by stripes and affixed by $\pi_{x'}$ in Figure 4B. The hydrogen-bonding interaction site suggested by the I_{OR} term in eq 4 is shown by stripes in Figure 4A. The arrows directed toward the carbonyl group and

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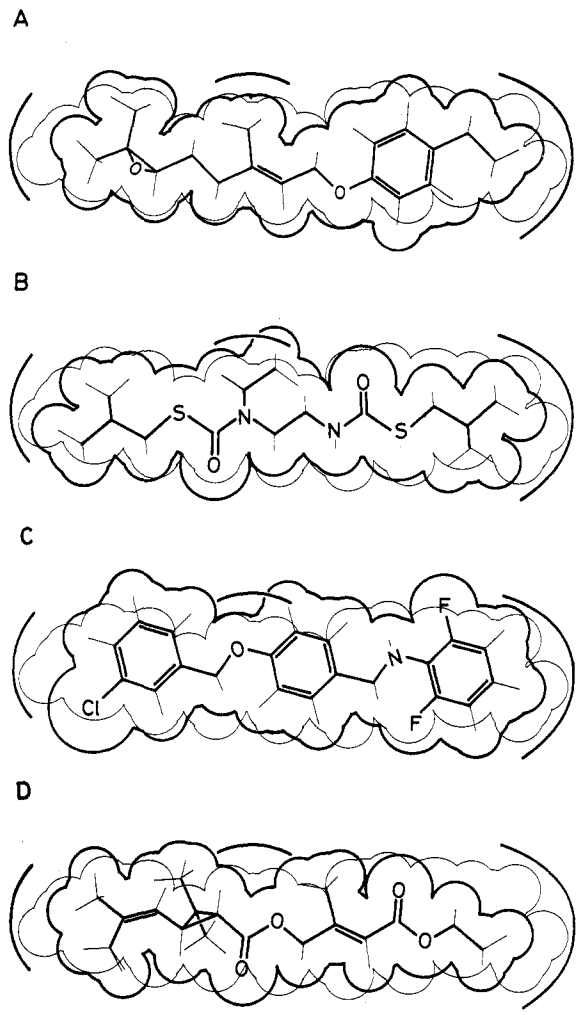

Figure 5. Comparison of the molecular shapes of some JH-mimetic compounds with that of compound 17 (methoprene): A, 6,7-epoxy-1-(4-ethylphenoxy)-3,7-dimethyl-2-octene; B, *S,S'*-diisobutyl *N*-ethyl-*N,N'*-ethylenebis(thiocarbamate); C, *N*-[4-(3-chlorobenzyloxy)benzyl]-2,6-difluoroaniline; D, 1-(ethoxycarbonyl)-2-methylprop-1-en-3-yl chrysanthemate. The contours of the CPK models of these compound are represented by the thick solid line and that of compound 17 (methoprene) by the thin solid line. The spatial walls of the *A. aegypti* and *T. molitor* receptors are also shown inclusively by the solid lines.

affixed by B_x indicate the possible hydrolytic degradation site. The models help in understanding the overall resemblance as well as the species differences of the mode of action.

It is worthwhile to test the validity of the receptor models on other classes of compounds. In Figure 5A, the CPK model of the rather congeneric but highly active 6,7-epoxy-1-(4-ethylphenoxy)-3,7-dimethyl-2-octene (R-20458)[23] was compared to a model that shows inclusively the receptor contour of both insect species with that of compound **17** (methoprene), a representative member of the present series of compounds. The drawings were made so as to overlap the structurally corresponding 6,7-epoxy end with the Y moiety and the 3-methyl with the 7-methyl of methoprene. As a matter of course, it can be easily accommodated to the receptor model. The structurally more deviated *S,S'*-diisobutyl *N*-ethyl-*N,N'*-ethylenebis(thiocarbamate)[10] was similarly examined to give Figure 5B. The compound that fits well into the inclusive model reportedly exhibits a high morphogenetic activity on *T. molitor*,[10] but the activity data on *A. aegypti* is lacking. The compound is expected to show some activity on *A. aegypti*, if the *N*-ethyl group does not interact so badly with the $I_{(-)}$ wall. The structural resemblance suggests the possibility that the *N,N'*-ethylenebis(thiocarbamate) series of compounds can be analyzed, being collated with the present results. Alternatively, they may be analyzed together with the present series of compounds by defining the steric parameters as applicable for or common through both series. Figure 5C is the result on *N*-[4-(3-chlorobenzyloxy)benzyl]-2,6-difluoroaniline,[14] which possesses a seemingly very different structure and exhibits, although moderately, activity on *T. molitor*. The conformation adopted in Figure 5C is a flat, extended one. Although the benzene rings at both ends may be twisted at the site of action, the compound has a conformationally rigid benzene ring at the center of the molecule. Thus, if one assumes the common target site with the present series of compounds, a rather extended conformation is supposed for the middle part of the 2,4-dodecadienoates. From the drawing, the 2,4-diene part and its vicinity may correspond to the central benzene ring. If the appropriate biological data are available, the structure–activity relationships of both ends may be interpreted and collated with those of this study. As a result, which end corresponds to the X (or Y) moiety may be revealed, providing a deeper insight into the structural essentials that confer the JH activity. Among the insect species tested, which include *A. aegypti* and *T. molitor*, some of the chrysanthemic acid esters have been reported to be JH active only on *Dysdercus fasciantus* (Hemiptera Pyrrhocoridae). In a "bird's-eye view" of a representative of the class, 1-(ethoxycarbonyl)-2-methylprop-1-en-3-yl chrysanthemate (Figure 5D), with a log *P* value of 4.69 calculated from the value of methyl chrysanthemate (3.76)[24] by a method similar to that used for the present compounds, this compound does not appear to be in conflict with the present receptor model. Some unknown factor must be at work, preventing the proper fit to the resembled *A. aegypti* and *T. molitor* receptors.

The examination of the above possibility as well as the problems described remains for future studies. Also remaining is the extension of the study to activities on other insect species.[6] The present results, the mode of action models or the receptor maps, will act as a guide in these phases as well as in exploring the structure vs. activity profiles of other diverse classes of compounds and may be of value in developing a new class of active compounds.

Acknowledgment. This research was supported in part by Grant 58560129 for scientific research from the Ministry of Education. The regression analyses were carried out on a FACOM M-382 computer of the Data Processing Center of this university.

Registry No. 1, 41205-08-7; **2**, 41205-09-8; **3**, 58239-28-4; **4**, 41205-07-6; **5**, 58221-93-5; **6**, 58221-94-6; **7**, 58221-95-7; **8**, 53023-55-5; **9**, 58221-96-8; **10**, 58221-97-9; **11**, 58221-98-0; **12**, 58221-99-1; **13**, 53023-67-9; **14**, 58222-00-7; **15**, 58222-01-8; **16**, 58222-02-9; **17**, 41205-06-5; **18**, 58222-03-0; **19**, 57783-19-4; **20**, 58222-05-2; **21**, 91384-63-3; **22**, 58222-06-3; **23**, 58222-07-4; **24**, 58222-08-5; **25**, 58222-09-6; **26**, 41915-86-0; **27**, 58222-10-9; **28**, 58222-11-0; **29**, 58222-12-1; **30**, 53092-52-7; **31**, 58222-68-7; **32**,

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53023-56-6; **33**, 58222-69-8; **34**, 58222-70-1; **35**, 58222-71-2; **36**, 58222-72-3; **37**, 58222-73-4; **38**, 41096-52-0; **39**, 58222-74-5; **40**, 58239-26-2; **41**, 91384-64-4; **42**, 58222-77-8; **43**, 58222-67-6; **44**, 91384-65-5; **45**, 35529-97-6; **46**, 58222-75-6; **47**, 58222-80-3; **48**, 58222-81-4; **49**, 58222-82-5; **50**, 58222-83-6; **51**, 58222-84-7; **52**, 58222-85-8; **53**, 58222-86-9; **54**, 58222-87-0; **55**, 58222-88-1; **56**, 58222-89-2; **57**, 58222-90-5; **58**, 58222-91-6; **59**, 58222-78-9; **60**, 58222-79-0; **61**, 58222-13-2; **62**, 58222-14-3; **63**, 58222-15-4; **64**, 58222-16-5; **65**, 58222-17-6; **66**, 58222-18-7; **67**, 53023-54-4; **68**, 58222-19-8; **69**, 58222-20-1; **70**, 58222-21-2; **71**, 58222-25-6; **72**, 58222-26-7; **73**, 58222-27-8; **74**, 58222-28-9; **75**, 58222-29-0; **76**, 58222-30-3; **77**, 58222-32-5; **78**, 58222-33-6; **79**, 58222-34-7; **80**, 58222-35-8; **81**, 58222-36-9; **82**, 58222-31-4; **83**, 58222-42-7; **84**, 58222-43-8; **85**, 58222-44-9; **86**, 58222-45-0; **87**, 58222-47-2; **88**, 58222-48-3; **89**, 58222-49-4; **90**, 58222-50-7; **91**, 58222-51-8; **92**, 58222-52-9; **93**, 58222-22-3; **94**, 58222-23-4; **95**, 58222-24-5; **96**, 58222-37-0; **97**, 58222-38-1; **98**, 58222-39-2; **99**, 58222-40-5; **100**, 58222-41-6; **101**, 91423-74-4; **102**, 58222-54-1.

Potentiation of the Tolerogenicity of Benzylpenicilloylated Eicosa-L-lysine by Conjugation with 4-(Hydroxymethyl)benzyl 3β-Cholestanyl Succinate

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It was previously found that amino acid polymers such as oligolysines bearing haptenic groups in high densities efficiently suppress anti-hapten IgE antibody formation. Such conjugates are strong elicitors of anaphylaxis and therefore may not be used for desensitization of drug allergic patients. Here we report on the synthesis and immunological evaluation of benzylpenicilloylated (BPO) eicosa-L-lysines containing none, one, or two lipophilic *p*-(hydroxymethyl)benzyl cholestan-3β-yl succinate (OSuco) groups. The lipophilic derivatives suppress primary as well as ongoing anti-BPO IgE antibody formation in mice much more efficiently than their hydrophilic counterpart. The lipophilic but not the hydrophilic derivatives form stable micelles in water and suppress the antibody formation according to different cellular mechanisms. The relationship between structure, hydrophobicity, and mode of action is discussed.

Drug allergies of the immediate or anaphylactic type, such as, for example, the penicillin allergy, still constitute an unsolved, though more and more urgent problem in medical therapy. It is well established that these allergies are mediated by specific IgE antibodies that are formed against, and recognize the drug or its metabolites in the form of a conjugate with autologous protein(s). Thus, in the case of the penicillin allergy the benzylpenicilloyl (BPO)[1] moiety was shown to be the major antigenic determinant.[2a] One approach to the treatment of allergies would consist in the abrogation of the allergen-specific IgE antibody formation, and several such attempts have been made. Chiorazzi et al.[2b] have reported that primary as well as ongoing anti-BPO IgE antibody formation in mice can be suppressed by injecting BPO-poly(D-Glu,D-Lys). Similarly carbohydrates,[3,4] isologous γ-globulins,[5] or poly(D- or L-lysines)[6] bearing haptenic groups in high densities were found to suppress antibody formation with hapten but not isotype specificity. These compounds were shown to exert their action by interfering with the function of the antibody-forming cells.[2,3,5] It must be noted, however, that these B-cell tolerogens also strongly elicit anaphylaxis in sensitized individuals, thereby limiting their potential therapeutic usefulness.

In previous studies on BPO-oligolysines[6-8] it was found that BPO_{21}-eicosalysine is the smallest homomer that still displays a high tolerogenicity. Having developed a synthesis in solution for BPO_{21}-eicosa-L-lysine, we were interested to study whether the introduction of hydrophobic auxillary groups into this conjugate potentiates its tolerogenicity, such that the required dosage and/or epitope density could be lowered correspondingly.

Several literature reports provide evidence that lipid modification of antigens tends to lower their humoral immunogenicity and often even leads to immune tolerance. Some years ago Dailey and Hunter[9,10] observed that the introduction of dodecanoyl residues into bovine serum albumin (BSA) completely abrogates its humoral *but increases* its cellular immunogenicity. Furthermore, Machida et al.[11,12] demonstrated that the suppressed humoral immunogenicity of dodecanoylated BSA is a consequence of the action of BSA-specific suppressor T cells. A similar effect of lipid modification was reported by Benacerraf and co-workers, who found that palmitoyl conjugated poly(L-Glu,L-Lys,L-Phe) peptides[13] or fowl γ-globulin[14] bind

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(1) Symbols and abbreviations are in accordance with the recommendations of the IUPAC-IUB Commission on Biochemical Nomenclature (*Eur. J. Biochem.*, 74, 1 (1977)). In addition, the following abbreviations are used: Adip, adipinoyl; BPO, benzylpenicilloyl; DCC, dicyclohexylcarbodiimide; DNP, dinitrophenyl; EDAC, *N*-ethyl-*N'*-[3-(dimethylamino)propyl]-carbodiimide hydrochloride; HOBt, 1-hydroxybenzotriazole; HONSu, *N*-hydroxysuccinimide; DCHA·MIA, dicyclohexylammonium (2-methyl-1-indolyl)acetate; OSuco, 4-(hydroxymethyl)benzyl 3β-cholestanyl succinate; PBS, phosphate balanced saline; PCA, passive cutaneous anaphylasix; PVm/BPO, molar penamaldate value per BPO group; BSA, bovine serum albumin; Asc, *Ascaris suum* protein(s); HVE, high-voltage electrophoresis.

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