Synthesis and Laboratory Evaluation of 1-(2,6-Disubstituted benzoyl)-3-phenylureas, a New Class of Insecticides. I. 1-(2,6-Dichlorobenzoyl)-3-phenylureas

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Upon the discovery of the powerful larvicidal properties of 1-(2,6-dichlorobenzoyl)-3-(3,4-dichlorophenyl)-urea (DU 19111), a large number of structural analogs were prepared. Their insecticidal properties were evaluated with larval stages of *Aëdes aegypti* L., *Pieris brassicae* L., and *Leptinotarsa decemlineata* Say. Many of these compounds proved to be excellent insecticides, bringing about the same symptoms as DU 19111. These symptoms are indicative of a disturbance of the process of cuticle deposition, resulting in abortive moult. Within the series of 1-(2,6-dichlorobenzoyl)-3-phenylureas, the 3-(4-chlorophenyl)-derivative (PH 60-38) appeared to be the most promising compound for several fields of application.

In a recent report from our laboratory (van Daalen *et al.*, 1972), a new insecticidal compound was introduced, namely 1-(2,6-dichlorobenzoyl)-3-(3,4-dichlorophenyl)-urea (DU 19111). This compound proved to be a powerful stomach toxicant for the larvae of several insect species. Its mode of action appeared to be without precedent, in that the larvae usually survived ingestion of the compound seemingly unharmed until their next moult was due. During the process of moulting, however, they would perish, probably due to severe cuticle damage. In view of these symptoms and of the unsusceptibility of the adult stages of the insect species tested, it was surmised that DU 19111 interfered with the process of cuticle deposition. Recently histological evidence (Mulder and Gijswijt, 1973) has confirmed this assumption.

In the present communication we report the synthesis of a series of 1-(2,6-dichlorobenzoyl)-3-phenylureas, 157 in all, and their evaluation as potential insecticides. Part II of this paper (Wellinga *et al.*, 1973) will show that other substitution patterns of the benzoyl moiety give rise to products with little or no insecticidal properties.

CHEMICAL METHODS

Microanalyses were carried out in the Analytical Department of the Institute for Organic Chemistry TNO, Utrecht, the Netherlands, under the supervision of W. J. Buis. The results of these analyses are filed in the microfilm edition of this volume of the journal. Infrared spectra were measured on a Perkin-Elmer 337 spectrophotometer, with KBr pellets. Nuclear magnetic resonance spectra were run on a Varian HA 100 spectrometer in deuterodimethyl sulfoxide solution. Chemical shifts were measured with tetramethylsilane as the internal reference. Because of severe decomposition at higher temperatures, all melting points have been determined on a Kofler hot-stage apparatus.

Three general methods were used for the preparation of the various compounds (Figure 1). The following examples are typical of the preparations performed.

Method A. *Preparation of 1-(2,6-Dichlorobenzoyl)-3-(3,4-dichlorophenyl)-urea (II:46; DU 19111), According to Speziale and Smith (1962).* A suspension of 95.0 g of 2,6-dichlorobenzamide (0.50 mol) in 250 ml of dry 1,2-dichloroethane was treated with 56.0 ml (0.65 mol) of pure oxalyl chloride. As soon as the initial reaction slowed down, the mixture was heated under reflux for 18 to 24 hr. The solvent was distilled off at reduced pressure and the remaining syrup was distilled to give 100.0 g (92.6%) of 2,6-dichlorobenzoylisocyanate [bp 71–72° (0.2 mm)]. Next a solution of 32.4 g of 2,6-dichlorobenzoylisocyanate (0.15 mol) in 100 ml of dry benzene was added, with stirring, to a solution of 24.3 g of 3,4-dichloroaniline (0.15 mol) in 200 ml of dry benzene. The temperature was kept below 40°. After 2 hr the resulting crystals were collected, washed with benzene, and dried, yielding 54.1 g (95.5%) of compound II:46. An analytically pure sample was obtained by recrystallization from acetonitrile. Nmr δ 7.98 (1, s, aromatic), 7.54 (5, m, aromatic), 10.39 (1, s, $\mathrm{CON}\mathit{H}\mathrm{C_6H_5}$), 11.60 (1, s, $\mathrm{CON}\mathit{H}\mathrm{CO}$). Ir 3220 (wm), 3110 (m), 2945 cm^{-1} (m) ($-\nu_{\mathrm{NH}}$); 1705 cm^{-1} (s) ($-\nu_{\mathrm{C=O}}$); 1590 (s), 1550 (s), 1500 (s), 1270 (s), 1230 cm^{-1} (s) (coupled CONH vibrations).

Anal. Calcd for $\mathrm{C_{14}H_8Cl_4N_2O_2}$ (mol wt, 378.05): Cl, 37.51; N, 7.41. Found: Cl, 37.5; N, 7.4.

Method B. *Preparation of 1-(4-Chlorophenyl)-3-(2,6-dichlorobenzoyl)-urea (II:5; PH 60-38).* A solution of 95.0 g of 2,6-dichlorobenzamide (0.50 mol) and 84.4 g of 4-chlorophenylisocyanate (0.55 mol) in 1000 ml of dry xylene was refluxed for 24 hr. After cooling, the crystals formed were collected, washed with xylene and petroleum ether (40–60°), and finally dried, affording 155.3 g (90.5%) of compound II:5, mp 225°. Crystallization from acetic acid raised the melting point to 234°. Nmr δ 7.61 (2, d, aromatic), 7.33 (2, d, aromatic), 7.48 (3, s, aromatic), 10.40 (1, s, $\mathrm{CON}\mathit{H}\mathrm{C_6H_5}$), 11.54 (1, s, $\mathrm{CON}\mathit{H}\mathrm{CO}$). Ir 3240 (m), 3080 (m), 2970 cm^{-1} (m) ($-\nu_{\mathrm{NH}}$); 1700 cm^{-1} (s) ($-\nu_{\mathrm{C=O}}$); 1600 (s), 1550 (s), 1500 (s), 1270 (s), 1230 cm^{-1} (s) (coupled CONH vibrations).

Anal. Calcd for $\mathrm{C_{14}H_9Cl_3N_2O_2}$ (343.60): Cl, 30.95; N, 8.15. Found: Cl, 30.8; N, 8.4.

Method C. *Preparation of 3-(4-Chlorophenyl)-1-(2,6-dichlorobenzoyl)-1-methylurea (II:30).* Methyl iodide (4.7 g, 0.033 mol) was added, with stirring, to a solution of 10.3 g of 1-(4-chlorophenyl)-3-(2,6-dichlorobenzoyl)-urea (0.03 mol) and 2.06 g of 90% potassium hydroxide (0.033 mol) in 40 ml of DMF. The mixture was stirred at room temperature for 24 hr and then poured into water. The resulting precipitate was collected and dried, yielding 10.3 g (96.0%) of compound II:30, mp 126°. Crystallization from ethyl acetate gave pure II:30, mp 128°. Nmr: a DMSO-d_6 solution showed the presence of two rotamers, due to hindered rotation. Rotamer A: δ 7.4–7.7 (7, m, aromatic), 3.48 (3, s, $\mathrm{NCH_3}$), 11.10 (1, s, NH). Rotamer B: δ 7.4–7.7 (7, m, aromatic), 3.10 (3, s, $\mathrm{NCH_3}$), 9.78 (1, s, NH). Ratio A:B = 1:1. In $\mathrm{CDCl_3}$, only rotamer A was present: δ 7.55 (2, d, aromatic), 7.29 (2, d, aromatic), 7.36 (3, s, aromatic), 3.18 (3, s, $\mathrm{NCH_3}$), 11.32 (1, s, NH). Ir 3240 cm^{-1} (m) ($-\nu_{\mathrm{NH}}$); 1720 cm^{-1} (s) ($-\nu_{\mathrm{C=O}}$); 1545 (s), 1360 (s), 1215 cm^{-1} (s) (coupled CONH vibrations).

Anal. Calcd for $\mathrm{C_{15}H_{11}Cl_3N_2O_2}$ (357.63): Cl, 29.74; N, 7.83. Found: Cl, 29.8; N, 7.9.

Preparation of Some of the Ring-Closed Products. 1-(4-Chlorophenyl)-3-(2,6-dichlorobenzoyl)-hydantoin (II:25).

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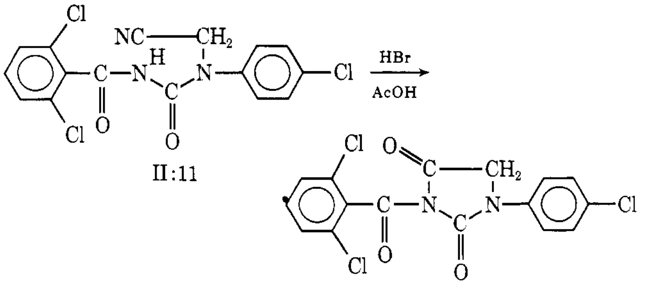


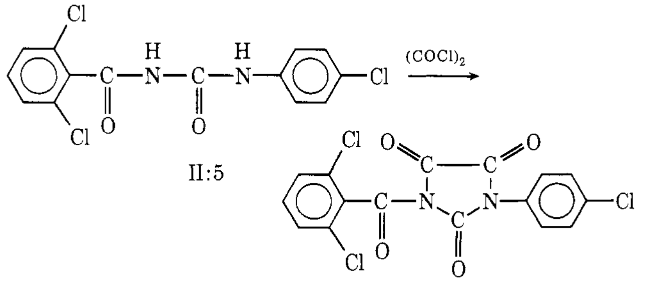
II:11

II:25

1-(4-Chlorophenyl)-1-cyanomethyl-3-(2,6-dichlorobenzoyl)-urea (25.2 g, 0.066 mol) was dissolved in 100 ml of acetic acid containing 25% of hydrogen bromide. The mixture was stirred at room temperature for 6 hr and poured into 500 ml of water. The precipitate was collected and recrystallized from acetic acid to give 21.1 g (83.3%) of compound II:25. Nmr δ 7.62 (2, d, aromatic), 7.38 (2, d, aromatic), 7.47 (3, s, aromatic), 4.66 (2, s, $COCH_2N$). Ir 1800 (s), 1760 (s), 1715 cm^{-1} (s) $(-\nu_{C=O})$; 1240 cm^{-1} (s); 1150 cm^{-1} (s).

Anal. Calcd for $C_{16}H_9Cl_3N_2O_3$ (383.62): Cl, 27.73; N, 7.30. Found: Cl, 27.9; N, 7.3.

1-(4-Chlorophenyl)-3-(2,6-dichlorobenzoyl)-parabanic Acid (II:27).



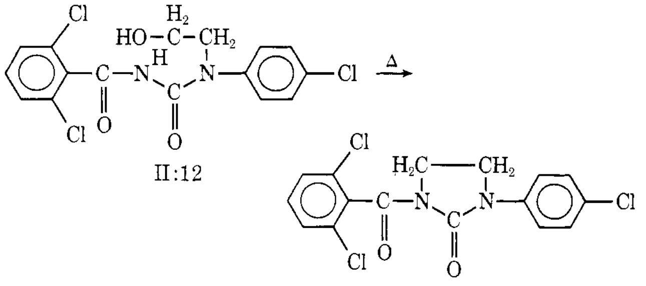
II:5

II:27

1-(4-Chlorophenyl)-3-(2,6-dichlorobenzoyl)-urea (10.3 g, 0.03 mol) and 3 ml of oxalyl chloride (0.035 mol) were dissolved in 100 ml of 1,2-dichloroethane and boiled for 24 hr. The solvent was distilled off and the residue was treated with petroleum ether (60–80°). The crystals formed were recrystallized from benzene, yielding 8.0 g (66.6%) of compound II:27. Nmr δ 7.57 (2, d, aromatic), 7.46 (2, d, aromatic), 7.53 (3, s, aromatic). Ir 1850 (m), 1800 (s), 1730 cm^{-1} (s) $(-\nu_{C=O})$; 1305 cm^{-1} (s); 1235 cm^{-1} (s).

Anal. Calcd for $C_{16}H_7Cl_3N_2O_4$ (397.60): Cl, 26.75; N, 7.04. Found: Cl, 26.6; N, 6.9.

1-(4-Chlorophenyl)-3-(2,6-dichlorobenzoyl)-2-imidazolidone (II:24).



II:12

II:24

1-(4-Chlorophenyl)-3-(2,6-dichlorobenzoyl)-1-(2-hydroxyethyl)-urea (3.00 g, 0.007 mol) was heated at 200° for 10 min. One crystallization from ethanol yielded 1.0 g (35.1%) of compound II:24. Nmr δ 7.58 (2, d, aromatic), 7.40 (2, d, aromatic), 7.48 (3, s, aromatic), 4.08 (4, s, NCH_2CH_2). Ir 1740 (s), 1670 cm^{-1} (s) $(-\nu_{C=O})$; 1380 cm^{-1} (s); 1300 cm^{-1} (s).

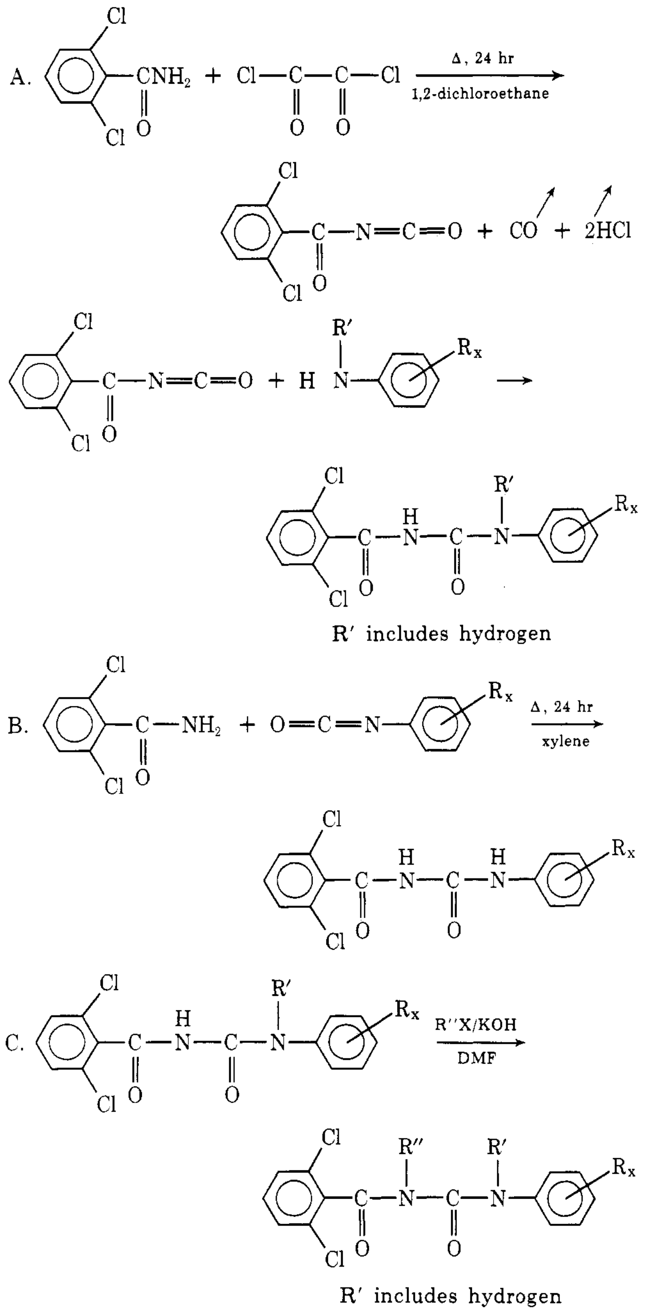
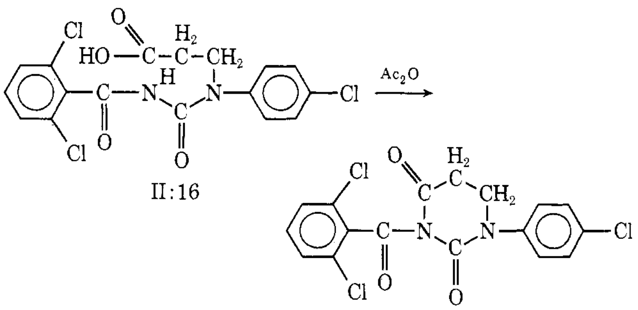


Figure 1. Methods of preparation of various compounds.

Anal. Calcd for $C_{16}H_{11}Cl_3N_2O_2$ (369.64): Cl, 28.77; N, 7.58. Found: Cl, 28.8; N, 7.5.

1-(4-Chlorophenyl)-3-(2,6-dichlorobenzoyl)-5,6-dihydrouracil (II:29).



II:16

II:29

1-(4-Chlorophenyl)-3-(2,6-dichlorobenzoyl-1-(2-hydroxycarbonylethyl)-urea (20.8 g, 0.05 mol) and 0.8 g of anhydrous sodium acetate were dissolved in 100 ml of acetic anhydride and heated on a steam bath for 3 hr. The excess of acetic anhydride and acetic acid were distilled off and the remaining solid was recrystallized from acetonitrile, yielding 14.1 g (71.0%) of compound II:29. Nmr δ 7.3–7.5 (7, m, aromatic), 3.92 (2, t, NCH_2), 3.06 (2, t, $COCH_2$). Ir 1755 (s), 1735 cm^{-1} (s) ($-\nu_{C=O}$); 1245 cm^{-1} (s); 1155 cm^{-1} (s).

Anal. Calcd. for $C_{17}H_{11}Cl_3N_2O_3$ (397.65): Cl, 26.75; N, 7.04. Found: Cl, 26.9; N, 7.1.

BIOLOGICAL METHODS

The insecticidal evaluations were usually performed with suspensions made by pouring out quantities of a 10.000-ppm acetonic stock solution into water, with stirring. Compounds insufficiently soluble in acetone were thoroughly milled in laboratory glass mills (Koopmans, 1958).

***Aëdes aegypti* L. (Yellow Fever Mosquito).** Aliquots of 100 ml of tap water containing, respectively, 1, 0.3, 0.1, 0.03, etc., ppm of the 1-(2,6-dichlorobenzoyl)-3-phenylurea, were supplied with 20 1-day-old larvae and kept at 25°. The larvae were fed with malt yeast powder. After 13 days, when the pupae of the untreated insects had hatched, the mortality percentages were calculated with a correction for the natural mortality according to Abbott (1925). There were three replicates per treatment.

***Pieris brassicae* L. (Large Cabbage White).** Potted cabbage seedlings were sprayed with a suspension of the toxicant until runoff. The suspensions contained, respectively, 100, 30, 10, 3, etc., ppm of the compound. When dry, the plants were placed in plastic cylinders provided with ten third-instar caterpillars and kept at 24° and 60–70% relative humidity. There were three replicates per treatment. After 7 days the mortality percentages were calculated according to Abbott's formula.

***Leptinotarsa decemlineata* Say (Colorado Potato Beetle).** Potato shoots, placed in flasks containing tap water, were sprayed with a suspension of the compound until runoff. The concentrations of the suspensions were, respectively, 100, 30, 10, 3, etc., ppm. Upon drying, the shoots were placed in plastic cylinders and provided with ten third-instar larvae. After this the procedure was identical with that applied to the large cabbage white.

RESULTS AND DISCUSSION

In Tables I–IV, the insecticidal effects are recorded of four series of 1-(2,6-dichlorobenzoyl)-3-phenylureas, each representing a different type of substituent in the 3-phenyl ring system. The test results are expressed as follows: + for 90–100% mortality; ± for 50–89% mortality; and − for 0–49% mortality at each of the concentrations tried. A series of these symbols indicates the level of the activity and roughly the slope of the relation between concentration and activity. This method was preferred to LC$_{50}$ values, since some of the compounds showed very little dosage response, whereas with others steep dosage-mortality curves were formed.

Table I shows the results with alkyl, aryl, and aralkyl substituents at different sites of the phenyl ring. From this table the following conclusions may be inferred. Alkyl substitution, especially at the para position, led to enhanced activity. Introduction of additional substituents turned out to be unfavorable (I:26,27,32). The optimum size of the substituents varied with the different insect species. While I:4 (4-ethylphenyl) was clearly optimal with *Aëdes*, *Pieris* required a larger substituent, such as in I:11 (4-*n*-butylphenyl) and I:17 (4-*tert*-butylphenyl) for optimal effect. But with *Leptinotarsa* I:7 (4-isopropylphenyl) appeared to be optimal. Substitution at one or both of the nitrogen atoms of the molecule decreased the activity drastically. With *Aëdes*, activity vanished entirely; with the two other species it was greatly lowered, the 4-*tert*-butyl derivatives (I:17 and I:18) forming a notable exception. The most plausible explanation for this effect is that N-substituted compounds are intrinsically ineffective, with any insecticidal effect observed reflecting dealkylation. Substitution of the alkyl moieties attached to the ring was pernicious, but for one spectacular exception, the trifluoromethyl function. A concentration of 0.001 ppm of compound I:39 (4-CF$_3$-phenyl) proved to be sufficient to control all the larvae of the yellow fever mosquito. Even when attached to the meta position (I:38), this group afforded considerable activity. Another striking result was that both these compounds were virtually ineffective with larvae of the Colorado potato beetle. Again, 4-halogenphenyl and 4-benzyl radicals as substituents at the para position gave rise to products with high larvicidal activities towards *Aëdes* and *Pieris*. Once again *Leptinotarsa* was the exception (I:43–49).

From Table II, presenting the test results of all halogen derivatives, the following conclusions may be drawn. Within this series the 4-chlorophenyl (II:5) and the 3,4-dichlorophenyl (II:46) derivatives appeared to be the most effective. Whereas 2,6-disubstitution in the benzoyl moiety of the basic molecule appeared to be essential for larvicidal effectiveness (Wellinga *et al.*, 1973), insecticidal activity was virtually abolished when the same substitution pattern was applied to the phenyl group of the aniline moiety (II:38,45). It is noteworthy that II:34 (4-bromophenyl) was inactive with *Aëdes* and II:35 (4-iodophenyl) showed hardly any activity with all three insect species; surprisingly, II:42 (2-fluoro-4-iodophenyl) and II:43 (3-fluoro-4-iodophenyl) gave excellent results. Substitution at one or both nitrogen atoms again proved detrimental to larvicidal activity. This is demonstrated by comparison of the test results of II:46 with those of II:47, II:50, and II:51. The fair results obtained with II:27, II:28, and II:52 were most probably due to decomposition of the compounds into the corresponding 1-chlorophenyl-3-(2,6-dichlorobenzoyl)-ureas. In these cases it was noticed that the chemicals decomposed slowly when dissolved in aqueous ethanol.

Table III shows the results obtained with derivatives carrying electron donating groups, apart from alkyl and halogen. It is obvious that none of the tabulated compounds was an improvement on the best of the derivatives of Tables I and II.

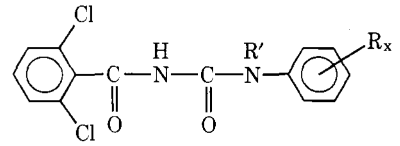
Finally, the results presented in Table IV demonstrate that electron attracting groups, when attached to the phenyl ring, gave rise to products with poor larvicidal effectivity. Exceptions were IV:4, IV:9, and IV:15, but their activities lagged far behind those of I:39 (4-CF$_3$-phenyl).

The toxicological data obtained with these 1-(2,6-dichlorobenzoyl)-3-phenylureas are still scanty. The acute LD$_{50}$ values toward mice are known for six derivatives, namely I:7 (4-isopropylphenyl), I:17 (4-*tert*-butylphenyl), I:39 (4-CF$_3$-phenyl), II:5 (4-chlorophenyl), II:34 (4-bromophenyl), and II:46 (3,4-dichlorophenyl).

When administered orally, all these compounds gave LD$_{50}$ values in excess of 3160 mg/kg, while with intraperitoneal administration all values were higher than 1000 mg/kg. Guppies survived a 7-days' exposure to 10-ppm suspensions of compounds II:5 and II:46. Application of higher rates is of no avail, since the solubilities of none of the compounds tried exceeded 1 ppm.

CONCLUSION

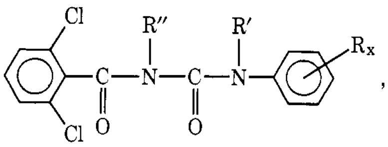
From the economic point of view, 1-(4-chlorophenyl)-3-(2,6-dichlorobenzoyl)-urea (II:5, PH 60-38) appears to be the most promising compound in this series and will therefore be developed as a larvicide against many species

Table I. Insecticidal Activities of  **where R_x = H, alkyl, and aryl**

Compound no.	R′	R_x	Test results			mp, °C
			Aëdes aegypti L.	*Pieris brassicae* L.	*Leptinotarsa decemlineata* Say	
			R_x = alkyl			
1	H	H	−	++±−	±±−	196
2	CH_3	H	−	−	±−	138
3	H	4-CH_3	++±−	−	−	242
4	H	4-C_2H_5	+++++++−	++±−	−	228
5	H	4-*n*-C_3H_7	+++++−	+++−	±±−	194
6	CH_3	4-*n*-C_3H_7	−	+−	−	146
7	H	4-*i*-C_3H_7	−	+++±−	+++±−	204
8	CH_3	4-*i*-C_3H_7	−	+±−	−	124
9	H	3-cyclopropyl	++−	+++−	±−	208
10	H	4-cyclopropyl	+±±−	++++−	+±±−	208
11	H	4-*n*-C_4H_9	±±−	+++++−	±−	190
12	CH_3	4-*n*-C_4H_9	−	++±−	−	152
13	H	4-*i*-C_4H_9	++++±−	++++−	−	215
14	CH_3	4-*i*-C_4H_9	−	+±−	−	163
15	H	4-sec-C_4H_9	+++−	++++−	±±−	168
16	CH_3	4-*sec*-C_4H_9	−	+±±−	−	131
17	H	4-*t*-C_4H_9	±−	+++++±−	+±−	212
18	CH_3	4-*t*-C_4H_9	−	++++±−	−	158
19	H	4-cyclo-C_6H_{11}	±±−	++−	−	262
20	H	4-*n*-C_8H_{17}	++±−	+±−	±−	124
21	CH_3	4-*n*-C_8H_{17}	−	−	−	112
22	H	4-*n*-$C_{12}H_{25}$	+++±−	+++−	−	117
23	CH_3	4-*n*-$C_{12}H_{25}$	−	−	−	72
24	H	2,3-$(CH_3)_2$	−	−	±±−	238
25	H	2,6-$(CH_3)_2$	−	−	−	230
26	H	3,4-$(CH_3)_2$	±−	±−	−	202
27	H	3,4-$[(CH_2)_4]$	−	+−	±±−	196
28	H	2,3-$[(CH{=}CH)_2]$	−	−	−	240
29	H	3,4-$[(CH{=}CH)_2]$	−	−	−	232
			R_x = alkyl + chloro			
30	H	2-CH_3, 4-Cl	++−	+++−	±−	206
31	H	3-CH_3, 4-Cl	++−	±−	−	194
32	H	3-Cl, 4-CH_3	−	−	±−	228
33	H	2-CH_3, 4,5-Cl_2	−	−	−	265
			R_x = substituted alkyl			
34	H	4-CH_2CN	−	−	−	226
35	H	4-$CH_2N(CH_3)_2$	−	−	−	225
36	H	4-$CH_2\dot{S}CH_3$	±±−	±−	−	214
37	H	2-CF_3	−	−	−	176
38	H	3-CF_3	+++±±−	+++−	±−	230
39	H	4-CF_3	+++++++−	+++++++−	±−	214
40	H	3-(2,2-dichlorocyclopropyl)	−	±−	±−	220
41	H	4-(2,2-dichlorocyclopropyl)	−	++±−	−	245
42	H	4-$C(CH_3)_2CH_2OCH_3$	−	++±−	−	194
			R_x = aryl and aralkyl			
43	H	4-C_6H_5	+++++−	+++−	±−	260
44	H	4-(4-ClC_6H_4)	+++++−	+++±−	±±±−	270
45	H	4-(4-BrC_6H_4)	+++++±−	++++++−	+−	270
46	H	4-(4-$NO_2C_6H_4$)	−	−	−	>300
47	H	4-$CH_2C_6H_5$	+++±−	++++−	−	207
48	H	4-CH_2(4-ClC_6H_4)	+++++−	++++±−	−	204
49	H	4-$CH_2CH_2C_6H_5$	+++±−	++−	−	208

Applied concentrations in parts per million

Aëdes aegypti L. 1, 0.3, 0.1, 0.03, etc.	+ = 90–100% mortality
Pieris brassicae L. 100, 30, 10, 3, etc.	± = 50–89% mortality
Leptinotarsa decemlineata Say 100, 30, 10, 3, etc.	− = 0–49% mortality

Table II. Insecticidal Activities of  **, where R_x = halogen**

Compound no.	R''	R'	R_x	Test results			mp, °C
				Aëdes aegypti L.	*Pieris brassicae* L.	*Leptinotarsa decemlineata* Say	
				R_x = monohalogen			
1	H	H	2-F	++−	−	−	205
2	H	H	3-F	±±−	±±−	±−	222
3	H	H	4-F	++±−	+++±−	±−	212
4	H	H	3-Cl	−	+±±−	±−	237
5	H	H	4-Cl	+++++−	+++++++−	++±−	236
6	H	CH_3	4-Cl	++−	++++±−	±−	176
7	H	C_2H_5	4-Cl	++−	++++±±−	±−	146
8	H	i-C_3H_7	4-Cl	±−	+++++−	−	195
9	H	n-C_4H_9	4-Cl	+−	+++±−	−	134
10	H	n-C_5H_{11}	4-Cl	+−	++±−	−	138
11	H	CH_2CN	4-Cl	+++±−	++++±−	−	185
12	H	CH_2CH_2OH	4-Cl	−	+±−	−	175
13	H	CH_2CF_3	4-Cl	−	++++−	−	176
14	H	CH_2CH_2CN	4-Cl	±−	+++−	±−	174
15	H	$CH_2CH_2C(=O)NH_2$	4-Cl	±−	+++−	−	205
16	H	CH_2CH_2COOH	4-Cl	−	−	−	183
17	H	$CH_2CH=CH_2$	4-Cl	−	+++±−	±−	128
18	H	$CH_2CBr=CH_2$	4-Cl	−	+++±−	±−	161
19	H	C_6H_5	4-Cl	−	−	−	161
20	H	4-ClC_6H_4	4-Cl	−	−	−	232
21	H	$CH_2C_6H_5$	4-Cl	++−	++±−	−	188
22	H	1-cyclohexenyl	4-Cl	−	−	−	158
23	H	1-cyano-1-cyclohexyl	4-Cl	−	−	−	200
24	CH_2CH_2		4-Cl	−	−	−	215
25	$COCH_2$		4-Cl	±−	+−	−	183
26	CO-1-cyclohexyl		4-Cl	−	−	−	160
27	COCO		4-Cl	++++±±−	++++++±−	±±−	157
28	CH_2OCH_2		4-Cl	++++−	++++±±−	+±−	168
29	$COCH_2CH_2$		4-Cl	−	−	−	214
30	CH_3	H	4-Cl	++++±−	+++++−	−	126
31	CH_3O	H	4-Cl	−	++−	−	100
32	CH_2OCH_3	H	4-Cl	++++−	+++++−	−	122
33	$CH_2C_6H_5$	H	4-Cl	++±−	−	−	126
34	H	H	4-Br	−	++++++−	±±−	236
35	H	H	4-I	−	−	±−	215
				R_x = dihalogen			
36	H	H	2,4-F_2	±−	++++±−	±−	248
37	H	H	2,5-F_2	−	+−	±−	225
38	H	H	2,6-F_2	−	−	−	241
39	H	H	3,4-F_2	±−	+++++−	−	216
40	H	H	3-F, 4-Cl	+++++−	++++++−	±−	225
41	H	H	3-F, 4-Br	−	++++++−	±±−	228
42	H	H	2-F, 4-I	+++++±−	++++++−	−	256
43	H	H	3-F, 4-I	+++++−	+++++−	++±−	220
44	H	H	2,4-Cl_2	+±±−	+++−	±−	238
45	H	H	2,6-Cl_2	−	−	−	244
46	H	H	3,4-Cl_2	+++++±±−	+++++±−	++±−	238
47	H	CH_3	3,4-Cl_2	++±−	++++±−	±±−	178
48	H	C_2H_5	3,4-Cl_2	++±−	++++±−	±−	154
49	H	n-C_5H_{11}	3,4-Cl_2	−	++−	−	160
50	CH_3	H	3,4-Cl_2	++++±−	−	−	182
51	CH_3	CH_3	3,4-Cl_2	++−	++±−	−	131
52	CH_2OCH_2		3,4-Cl_2	++++±−	+++++−	+−	188
53	CH_2OCH_3	H	3,4-Cl_2	++++−	++++−	+±±−	146
54	$CH_2C_6H_5$	H	3,4-Cl_2	+++−	−	−	152
55	OH	H	3,4-Cl_2	−	−	−	203
56	H	OH	3,4-Cl_2	+++++±−	+++±−	−	175
57	H	$COOC_2H_5$	3,4-Cl_2	±−	++−	−	185

Table II *(Continued)*

Compound no.	R″	R′	R_x	Test results: *Aëdes aegypti* L.	Test results: *Pieris brassicae* L.	Test results: *Leptinotarsa decemlineata* Say	mp, °C
58	H	$COCH_3$	3,4-Cl_2	−	++−	−	180
59	H	H	3-Cl, 4-Br	+±−	+++−	++−	240
60	H	H	3-Br, 4-Cl	−	+−	±−	254
61	H	H	3-Cl, 4-I	−	+++−	++−	254
62	H	H	3,4-Br_2	−	+++−	±±−	252
			R_x = trihalogen				
63	H	H	2,5-F_2, 4-Br	+++++−	++++−	−	270
64	H	H	2,4,5-Cl_3	−	++±−	±−	270
65	H	H	3,4,5-Cl_3	−	±−	−	270

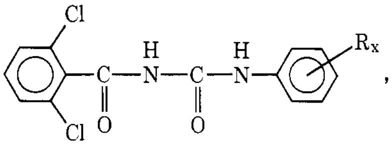
Applied concentrations in parts per million

Aëdes aegypti L. 1, 0.3, 0.1, 0.03, etc. + = 90–100% mortality

Pieris brassicae L. 100, 30, 10, 3, etc. ± = 50–89% mortality

Leptinotarsa decemlineata Say 100, 30, 10, 3, etc. − = 0–49% mortality

Table III. Insecticidal Activities of



, where R_x = electron donating groups

Compound no.	R_x	Test results: *Aëdes aegypti* L.	Test results: *Pieris brassicae* L.	Test results: *Leptinotarsa decemlineata* Say	mp, °C
1	4-$N(CH_3)_2$	−	−	−	266
2	3-Cl, 4-$N(CH_3)_2$	−	−	−	246
3	4-$NHCOCH_3$	−	−	−	220
4	2-OH, 3,5-Br_2	−	−	−	>300
5	3-OH	−	−	−	201
6	4-OH	−	−	−	246
7	3-OCH_3	−	±−	−	194
8	3-OCH_3, 4-Cl	−	−	−	230
9	4-OCH_3	−	−	−	194
10	3-Cl, 4-OCH_3	−	−	−	238
11	3,4-OCH_2O	−	+±−	−	242
12	3,4-$CH_2CH_2CH_2O$ 0.5 C_6H_6	−	−	±±−	198
13	3-$OCOCH_3$	−	−	−	216
14	4-O-(4-ClC_6H_4)	−	+±−	−	205
15	4-O-(2,6-$Cl_2C_6H_3$)	−	−	−	225
16	4-SCH_3	+±−	±−	−	216
17	3-Cl, 4-SCH_3	±−	−	−	242
18	4-S-*n*-C_5H_{11}	+++−	++−	−	130
19	4-SC_6H_5	−	++−	−	196
20	4-S-(2,6-$Cl_2C_6H_3$)	−	−	−	196
21	4-S-(4-ClC_6H_4)	++++−	+++−	+−	159
22	4-S-(2,4,5-$Cl_3C_6H_2$)	−	−	−	275
23	4-S-(4-$NO_2C_6H_4$)	−	−	−	270
24	4-SCN	−	−	−	230

Applied concentrations in parts per million

Aëdes aegypti L. 1, 0.3, 0.1, 0.03, etc. + = 90–100% mortality

Pieris brassicae L. 100, 30, 10, 3, etc. ± = 50–89% mortality

Leptinotarsa decemlineata Say 100, 30, 10, 3, etc. − = 0–49% mortality

of arthropods. The correctness of this choice has been confirmed by the results of various greenhouse and small-scale field trials.

ACKNOWLEDGMENT

The authors express their gratitude to Truus van der Chijs and Frits W. van Deursen for the interpretation of the recorded spectra. They are grateful also to Lambert C. Post for helpful suggestions concerning the manuscript.

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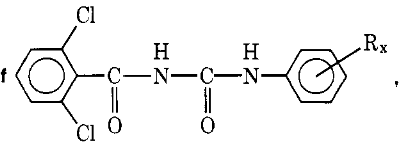
Table IV. Insecticidal Activities of  **, where R_x = electron attracting groups**

		Test results			
Compound no.	R_x	*Aëdes aegypti* L.	*Pieris brassicae* L.	*Leptinotarsa decemlineata* Say	mp, °C
1	$4\text{-}COCH_3$	±−	−	−	212
2	$4\text{-}COC_6H_5$	+−	++±−	±−	198
3	$4\text{-}COOC_2H_5$	−	−	−	197
4	4-CN	+++−	++++±−	±−	248
5	$3,5\text{-}(CN)_2$	±−	+±−	−	255
6	$4\text{-}NO_2$	±−	++±−	±±−	256
7	$3\text{-}Cl, 4\text{-}NO_2$	±−	−	−	>300
8	$3\text{-}CF_3, 4\text{-}NO_2$	−	−	−	>280
9	$3\text{-}NO_2, 4\text{-}CH_3$	−	+++±−	++−	256
10	$2,4\text{-}(NO_2)_2$	−	−	−	260
11	$4\text{-}N^+(CH_3)_3I^-\cdot 1$ aq	−	−	−	250
12	$4\text{-}SO_2CH_3$	−	+±−	−	222
13	$4\text{-}SO_2\text{-}n\text{-}C_5H_{11}$	−	+±−	−	166
14	$4\text{-}SO_2C_6H_5$	−	−	−	238
15	$4\text{-}SO_2\text{-}(4\text{-}ClC_6H_4)$	+++±−	+++±−	−	245
16	$4\text{-}SO_2\text{-}(2,4,5\text{-}Cl_3C_6H_2)$	−	−	−	265
17	$4\text{-}SO_2NH_2$	−	−	−	>270
18	$4\text{-}SO_2N(CH_3)_2$	−	±−	−	232
19	$4\text{-}SO_2N(n\text{-}C_3H_7)_2$	−	−	−	210

Applied concentrations in parts per million

Aëdes aegypti L. 1, 0.3, 0.1, 0.03, etc. + = 90–100% mortality
Pieris brassicae L. 100, 30, 10, 3, etc. ± = 50–89% mortality
Leptinotarsa decemlineata Say 100, 30, 10, 3, etc. − = 0–49% mortality

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Received for review October 31, 1972. Accepted February 5, 1973. Microanalyses results will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JAFC-73-348.

Alkyl 3,7,11-Trimethyl-2,4-dodecadienoates, A New Class of Potent Insect Growth Regulators with Juvenile Hormone Activity

Clive A. Henrick,* Gerardus B. Staal, and John B. Siddall

A new class of insect growth regulators with juvenile hormone activity, including isopropyl 11-methoxy-3,7,11-trimethyl-*trans*-2,*trans*-4-dodecadienoate and ethyl 3,7,11-trimethyl-*trans*-2,*trans*-4-dodecadienoate, has been synthesized and shown to be more potent and more stable than the known natural juvenile hormones. Bioassay data on yellow fever mosquito *(Aedes aegypti)*, greater wax moth *(Galleria mellonella)*, and yellow mealworm *(Tenebrio molitor)* for these and related compounds are given.

Insect growth regulators (IGR's) with juvenile hormone activity (Williams, 1956) may be used to interfere with essential life processes such as metamorphosis and adult emergence. Many insects are remarkably sensitive to the external application of suitable IGR's at certain critical stages in their life cycle. At present, the detailed biochemical consequences of such abnormal treatment are poorly understood; however, the morphological and developmental consequences are largely irreversible and therefore ultimately lethal to the target insects. The effects may be expressed by the occurrence of larval–pupal or

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