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Synthesis and Laboratory Evaluation of 1-(2,6-Disubstituted benzoyl)-3-phenylureas, a New Class of Insecticides. II. Influence of the Acyl Moiety on Insecticidal Activity

Kobus Wellinga, Rudolf Mulder, and Jan J. van Daalen*

The insecticidal properties of a number of 1-acyl-3-phenylureas were evaluated with larval stages of Aëdes aegypti L., Pieris brassicae L., and Leptinotarsa decemlineata Say. Only mono- and di-ortho-substituted benzoyl derivatives showed interesting larvicidal activities. For compounds with the common formula
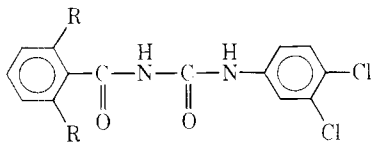
the order of effectiveness was R = H, OH, OCH₃. C₂H₅ < CH₃ < Br ≪ Cl < F. The most powerful toxicant proved to be 1-(2,6-difluorobenzoyl)-3-(4-trifluoromethylphenyl)urea. Together with 1-(4-chlorophenyl)-3-(2,6-dichlorobenzoyl)urea (PH 60-38), a second chemical has been chosen for further development, namely 1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl)urea (PH 60-40). A short survey is given of the properties of both PH 60-38 and PH 60-40.

In part I of this series of articles (Wellinga et al., 1973) we concluded that 1-(4-chlorophenyl)-3-(2,6-dichlorobenzoyl)urea (PH 60-38) was the most promising larvicide out of a series of 157 1-(2,6-dichlorobenzoyl)-3-phenylureas. In the present article we report the synthesis and laboratory evaluation of another series of 1-acyl-3-phenylureas, where acyl in most cases represents substituted benzoyl, with the 2,6-dichlorobenzoyl moiety excluded.

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. Nuclear magnetic resonance spectra were recorded in deutero-dimethyl sulfoxide solution on a Varian HA 100 spectrometer. Chemical shifts are reported in parts per million (δ) downfield from the internal reference tetramethylsilane. All melting points have been determined on a Kofler hot stage apparatus because of severe decomposition at higher temperatures.

All compounds referred to in this paper were prepared according to the methods already described (Wellinga et al., 1973). Method B (Figure 1) especially proved to be of great value because of the simplicity of the procedure and the high purity of the products obtained.

Most of the amides RC(=O)NH₂ or the corresponding acids and nitriles are described in the literature (e.g., Koopman and Daams, 1965). In the following examples only some particular cases are recorded.

Preparation of 2,6-Difluorobenzamide. To a solution of 172.0 g (1.0 mol) of 2,6-dichlorobenzonitrile in 300 ml of dry sulfolane was added 290.0 g (5.0 mol) of finely powdered potassium fluoride. While being stirred vigorously, the mixture was heated at 230–235° for 8 hr. After cooling to 80°, the reaction mixture was poured into 2 l. of water. The resulting suspension was extracted three times with dichloromethane. In order to remove the sulfolane the combined dichloromethane extracts were washed thoroughly with water. After drying, the solvent was removed and the residual oily liquid distilled to give 109.2 g of 2,6-difluorobenzonitrile (78.5%), bp 81–83° (12 mm), mp 30–31°. 2,6-Difluorobenzonitrile was easily hydrolyzed to the corresponding amide in 90% sulfuric acid at 70°, mp 143–145°.

Anal. Calcd for C₇H₅F₂NO (157.12): C, 53.51; H, 3.21; F, 24.18; N, 8.91. Found: C, 53.5; H, 3.4; F, 23.9; N, 9.1.

Preparation of 2-Dimethylamino-6-fluorobenzamide. 2,6-Difluorobenzonitrile (27.8 g, 0.20 mol) was dissolved in 100 ml of acetonitrile. While stirring and cooling to keep the temperature below 30°, dry dimethylamine gas was passed in. After 2 hr the solvent was distilled off at reduced pressure. To the oily residue was added 1 l. of water, after which the pH was adjusted to 9 with a 10% solution of sodium hydroxide. The desired nitrile was iso-
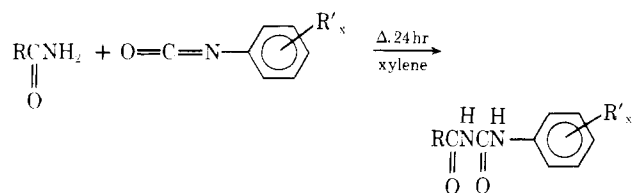
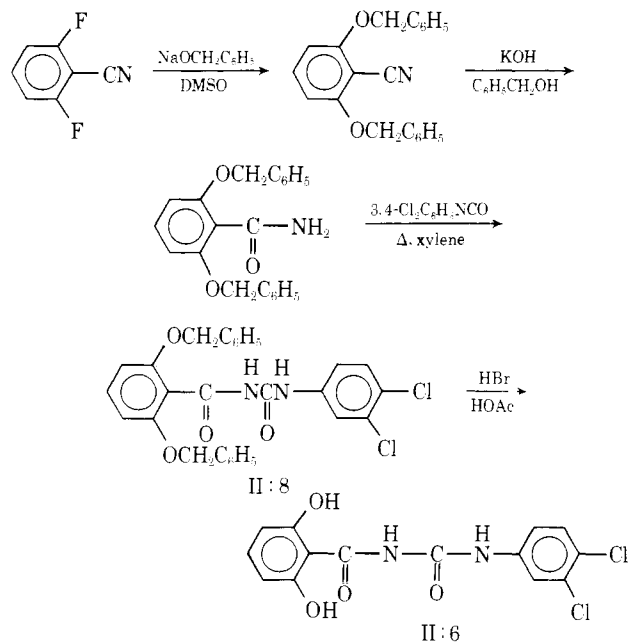**Figure 1.** Preparation of the compounds using Method B.

Figure 2. Preparation of 1-(3,4-dichlorophenyl)-3-(2,6-dihydroxy-benzoyl)urea (II:6).

lated by extracting the water layer three times with dichloromethane. The combined organic layers were washed with water and dried. The solvent was removed and the residual oil distilled, affording 28.8 g of 2-dimethylamino-6-fluorobenzonitrile (87.8%), bp 139–142° (13 mm). This nitrile (16.4 g, 0.10 mol) was dissolved in 120 ml of 80% sulfuric acid and heated in a steam bath for 6 hr. The mixture was poured onto 600 g of crushed ice. The colorless crystals which precipitated after neutralization with a 25% solution of sodium hydroxide were collected, dried, and thoroughly washed with petroleum ether (40–65°), affording 14.1 g (77.5%) of the desired benzamide, mp 152–153°.

Anal. Calcd for $C_9H_{11}FN_2O$ (182.19): C, 59.33; H, 6.09; F, 10.43; N, 15.38. Found: C, 59.6; H, 6.2; F, 10.5; N, 15.5.

Preparation of 1-(3,4-Dichlorophenyl)-3-(2,6-dihydroxybenzoyl)urea (II:6) This was accomplished according to the scheme shown in Figure 2.

2,6-Dibenzyloxybenzonitrile. To a stirred suspension of 12.4 g of 90% potassium hydroxide (0.20 mol) in 60 ml of DMSO was added 21.6 g (0.20 mol) of benzyl alcohol. After 1 hr, 13.9 g (0.10 mol) of 2,6-difluorobenzonitrile was added, the temperature rising to 90°. The reaction mixture was heated in a steam bath for 3 hr and, after being cooled, was poured into 1 l. of water. The resulting crystals were collected and recrystallized from ethanol, yielding 20.6 g (65.4%) of 2,6-dibenzyloxybenzonitrile, mp 122–123°.

2,6-Dibenzyloxybenzamide. 2,6-Dibenzyloxybenzonitrile (6.3 g, 0.02 mol) and 3.0 g of 90% potassium hydroxide were dissolved in 15 ml of benzyl alcohol and 2 ml of water. The solution was heated to 130° for 3 hr, after which the solvent was distilled off. The residue was treat-

ed with water and the resulting solid collected and dried *in vacuo* at 80°. The crude amide was treated with 20 ml of boiling benzene. After cooling to 30° the crystals were removed by filtration, resulting in 3.1 g of 2,6-dibenzyloxybenzamide, mp 131–132°.

1-(2,6-Dibenzyloxybenzoyl)-3-(3,4-dichlorophenyl)-urea (II:8). A solution of 2,6-dibenzyloxybenzamide (6.7 g, 0.02 mol) and 3,4-dichlorophenylisocyanate (3.8 g, 0.02 mol) in 50 ml of xylene was boiled for 24 hr. After cooling the resulting precipitate was collected and washed with benzene. To remove the solvent the compound was heated at 90° *in vacuo*, affording 9.8 g (94.0%) of the urea II:8, mp 163–164°.

Anal. Calcd for $C_{28}H_{22}Cl_2N_2O_4$ (521.42): C, 64.49; H, 4.26; Cl, 13.60; N, 5.38. Found: C, 64.1; H, 4.3; Cl, 13.6; N, 5.4.

1-(3,4-Dichlorophenyl)-3-(2,6-dihydroxybenzoyl)urea (II:6). Compound II:8 (5.2 g, 0.01 mol) was heated at 60° for 4 hr in 15 ml of acetic acid containing 45% hydrogen bromide. After being cooled to 25° the mixture was poured into 200 ml of water. The precipitate was collected, washed with water, and dried to yield 3.2 g (93.8%) of compound II:6, mp >280°.

Anal. Calcd for $C_{14}H_{10}Cl_2N_2O_4$ (341.16): C, 49.29; H, 2.95; Cl, 20.79; N, 8.22. Found: C, 49.6; H, 3.1; Cl, 20.7; N, 8.0.

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-acyl-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.
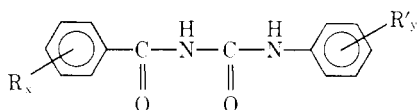
Pieris brassicae L. (**Large Cabbage White**). Potted cabbage seedlings were sprayed with a suspension of the toxicant until runoff. The suspensions contained, respectively, 100, 30, 10, 3, etc., ppm of the compound. When dry, the plants were placed in plastic cylinders provided with ten third-instar 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

The test results and nmr data of the present series of 1-acyl-3-phenylureas are listed in Tables I–III. The concentrations applied to determine the effectivities against larvae of *Aëdes aegypti* L. were, respectively, 1, 0.3, 0.1, 0.03, etc., ppm. With the tests against larvae of *Leptinotarsa decemlineata* Say and *Pieris brassicae* L. suspensions of the compounds were used containing 100, 30, 10, 3, etc., ppm, respectively. The effect of each of the concentrations tried is denoted by one of the following symbols: + for 90–100% mortality; ± for 50–89% mortality; and − for 0–49% mortality.

Table I. Insecticidal Activities of

Compound no.	R_x	R'_y	Aëdes aegypti L.	Pieris brassicae L.	Leptinotarsa decemlineata Say	Mp, °C
1	H	3,4-Cl$_2$	—	—	—	252
2	2-Cl	3,4-Cl$_2$	±±±—	+±±—	—	209
3	2-Br	3,4-Cl$_2$	±±±—	++—	—	217
4	2-OH	3,4-Cl$_2$	—	—	—	211
5	2-OCH$_3$	3,4-Cl$_2$	—	+±—	±—	170
6	2-OCH$_2$C$_6$H$_5$	4-Cl	—	—	—	185
7	4-Cl	3,4-Cl$_2$	—	—	—	±270
8	4-OCH$_3$	3,4-Cl$_2$	—	—	—	239
9	4-NO$_2$	3,4-Cl$_2$	—	—	—	±270
10	2,4-Cl$_2$	3,4-Cl$_2$	—	—	—	223
11	2-Cl, 4-NO$_2$	3,4-Cl$_2$	—	±—	—	239
12	3,4-Cl$_2$	3,4-Cl$_2$	—	—	—	±275
13	2,4,5-Cl$_3$	4-Cl	—	—	—	222
14	2,3,6-Cl$_3$	3,4-Cl$_2$	—	—	—	234
15	2,6-Cl$_2$, 4-OH	3,4-Cl$_2$	—	—	—	260
16	2,6-Cl$_2$, 4-OCH$_3$	3,4-Cl$_2$	—	—	—	215
17	2,6-Cl$_2$, 3-NO$_2$	3,4-Cl$_2$	—	—	—	±270
18	2,4,6-(CH$_3$)$_3$	3,4-Cl$_2$	—	—	—	228

Applied concentrations in parts per million

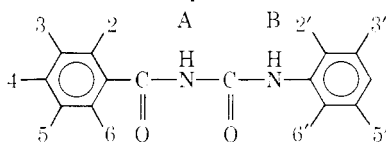Aëdes aegypti L. 1, 0.3, 0.1, 0.03, etc. + = 90–100% mortality
Pieris brassicae L. 100, 30, 10, 3, etc. ± = 50–89% mortality
Leptinotarsa decemlineata Say 100, 30, 10, 3, etc. — = 0–49% mortality

Nmr spectra

Compound no.	H$_2$, δ	H$_3$, δ	H$_4$, δ	H$_5$, δ	H$_6$, δ	Spin system	H$_2'$, δ	H$_3'$, δ	H$_5'$, δ	H$_6'$, δ	Spin system	NH$_A$, δ	NH$_B$, δ	Other compounds, δ
1	7.9–8.2	7.4–7.7	7.4–7.7	7.4–7.7	7.9–8.2	g	7.97		7.58	7.58	f	10.86	10.82	
2		7.4–7.7	7.4–7.7	7.4–7.7	7.4–7.7	e	8.02		7.6	7.6	f	11.32	10.55	
3		7.3–7.8	7.3–7.8	7.3–7.8	7.3–7.8	e	8.02		7.58	7.58	f	11.31	10.52	
4		7.08	7.02	7.80	7.95	e′	8.00		7.58	7.58	f	10.86	10.67	C$_6$H$_4$O*H* 12.06 (s)
5		7.21	7.08	7.57	7.73	e′	7.99		7.56	7.56	f	10.78	10.52	C$_6$H$_4$OC*H$_3$* 3.94 (s)
6		7.16	7.38	7.53	7.86	e′	7.62	7.38	7.38	7.62	h	10.78	10.52	C$_6$H$_4$OC*H$_2$* 5.34 (s)
7	8.02	7.58		7.58	8.02	h	7.96		7.58	7.58	f	10.89	10.70	
8	8.06	7.03		7.03	8.06	h	8.00		7.51	7.51	f	11.02	10.96	C$_6$H$_4$OC*H$_3$* 3.86 (s)
9	8.25	8.32		8.32	8.25	h	7.95		7.52	7.52	f	11.36	10.75	
10		7.64		7.49	7.63	c	7.90		7.51	7.51	f	11.00	10.28	
11		8.40		8.30	7.91	c	7.97		7.56	7.56	f	11.44	10.28	
12	8.28			7.74	8.08	f′	7.98		7.52	7.52	f	10.97	10.64	
13		7.74			7.81	i	7.60	7.32	7.32	7.60	h	11.28	10.39	
14			7.81	7.64		i	7.97		7.57	7.57	f	11.55	10.28	
15		6.89		6.89		i	8.01		7.54	7.54	f	11.38	10.52	
16		7.18		7.18		i	8.01		7.58	7.58	f	11.52	10.45	C$_6$H$_4$OC*H$_3$* 3.88 (s)
17			8.24	7.88		i	7.94		7.56	7.56	f	11.60	10.77	
18		6.92		6.92		i	8.02		7.56	7.56	f	11.10	10.73	C$_6$H$_2$(C*H$_3$*)$_3$ 2.4 (s)

Spin systems

a = AB$_2$ system
b = ABB′ part of ABB′XX′ system
c = ABC system
d = unresolved ABCX system

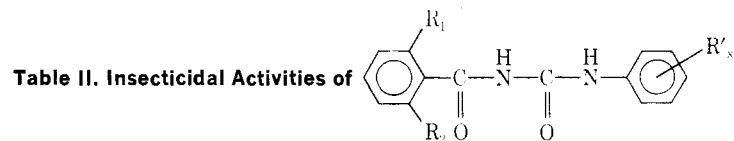e = unresolved ABCD system
e′ = resolved ABCD system
f = degenerated ABX system
f′ = ABX system

g = unresolved ABB′CC′ system
h = AA′BB′ system
i = AA system

Table II. Insecticidal Activities of

Com-pound no.	R_1	R_2	R'_x	Test results			Mp, °C
				Aëdes aegypti L.	Pieris brassicae L.	Leptinotarsa decemlineata Say	
1	CH₃	CH₃	4-Cl	+−	+++++−	++−	191
2	CH₃	CH₃	3,4-Cl₂	±−	+++±±−	−	197
3	CH₃	CH₃	4-CF₃	++±−	−	+++±−	185
4	C₂H₅	C₂H₅	4-Cl	−	−	−	195
5	C₂H₅	C₂H₅	4-CF₃	−	−	−	194
6	OH	OH	3,4-Cl₂	−	−	−	>280
7	OCH₃	OCH₃	3,4-Cl₂	±−	−	−	232
8	OCH₂C₆H₅	OCH₂C₆H₅	3,4-Cl₂	−	−	−	164
9	Cl	OH	4-Cl	−	−	−	200
10	Cl	OCH₂C₆H₅	4-Cl	−	−	−	175
11	F	N(CH₃)₂	4-Cl	−	+++±−	−	161
12	Cl	NO₂	3,4-Cl₂	++−	±−	−	249
13	Cl	Cl	4-Cl	+++++−	+++++++−	++±−	236
14	F	F	4-Cl	++++++±−	+++++++++−	+±−	239
15	F	F	4-Br	++++++±−	++++++++++	++±−	247
16	F	F	3,4-Cl₂	++++++++	+++++++−	+−	253
17	F	F	4-CF₃	++++++++	+++++++++±	++±±−	255
18	F	F	4-i-C₃H₇	+++−	+++++−	++±−	196
19	F	F	4-n-C₄H₉	+++++−	+++++++−	+±−	193
20	F	F	4-t-C₄H₉	+++±−	++++++++−	++±±−	214
21	F	Cl	4-Cl	+++++±−	++++++++−	±±−	182
22	F	Cl	4-CF₃	+++++±−	++++++++−	+±−	220
23	F	Br	4-Cl	+++++−	++++++++−	+−	184
24	F	Br	3,4-Cl₂	+++++−	++++++++−	+±−	238
25	F	Br	4-CF₃	++++++−	+++++++±−	++±−	218
26	Cl	Br	4-Cl	++++−	+−	++−	228
27	Cl	Br	3,4-Cl₂	+++++−	++±−	±±−	240
28	Cl	Br	4-CF₃	+++++±−	+++++±−	++±−	212
29	Br	Br	3,4-Cl₂	±±±±−	++±−	−	250

Applied concentrations in parts per million

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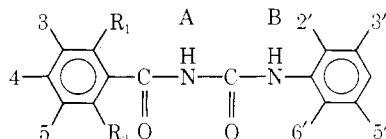Pieris brassicae L. 100, 30, 10, 3, etc.   ± = 50–89% mortality
Leptinotarsa decemlineata Say 100, 30, 10, 3, etc.   − = 0–49% mortality

Nmr spectra

Com-pound no.	H_3, δ	H_4, δ	H_5, δ	Spin system	H_2', δ	H_3', δ	H_5', δ	H_6', δ	Spin system	NH_A, δ	NH_B, δ	Other compounds, δ
1	7.09	7.24	7.09	a	7.62	7.36	7.36	7.62	h	11.07	10.72	C₆H₃(CH₃)₂ 2.32 (s)
2	7.12	7.26	7.12	a	8.04		7.59	7.59	f	11.20	10.70	C₆H₃(CH₃)₂ 2.30 (s)
3	7.10	7.26	7.10	a	7.70	7.84	7.84	7.70	h	11.22	10.91	C₆H₃(CH₃)₂ 2.30 (s)
4	7.15	7.30	7.15	a	7.64	7.40	7.40	7.64	h	11.16	10.70	C₆H₃CH₂ 2.60 (q); C₆H₃CH₂CH₃ 1.19 (t)
5	7.17	7.36	7.17	a	7.71	7.84	7.84	7.71	h	11.26	10.90	C₆H₃CH₂ 2.62 (q); C₆H₃CH₂CH₃ 1.20 (t)
6	6.48	7.29	6.48	a	7.94		7.52	7.52	f	10.9	10.41	
7	6.73	7.39	6.73	a	8.01		7.56	7.56	f	11.02	10.70	C₆H₃OCH₃ 3.78 (s)
8	6.79	7.2–7.5	6.79	a	8.01		7.57	7.57	f	11.17	10.65	C₆H₃OCH₂ 5.18 (s)
9	6.94	7.28	6.90	c	7.64	7.40	7.40	7.64	h	11.17	10.52	C₆H₅OH 10.48 (s)
10	7.16	7.2–7.5	7.12	c	7.62	7.2–7.5	7.2–7.5	7.62	h	11.32	10.43	C₆H₃OCH₂ 5.22 (s)
11	6.6–6.9	7.2–7.5	6.6–6.9	d	7.66	7.37	7.37	7.66	h	11.24	10.68	N(CH₃)₂ 2.85 (s)

Table II *(Continued)*

Compound no.	H_3, δ	H_4, δ	H_5, δ	Spin system	$H_{2'}$, δ	$H_{3'}$, δ	$H_{5'}$, δ	$H_{6'}$, δ	Spin system	NH_A, δ	NH_B, δ	Other compounds, δ
12	8.07	7.79	8.30	c	7.92		7.56	7.56	f	11.43	10.21	
13	7.48	7.48	7.48	a	7.61	7.33	7.33	7.61	h	11.54	10.42	
14	7.24	7.63	7.24	b	7.62	7.40	7.40	7.62	h	11.45	10.26	
15	7.24	7.63	7.24	b	7.54	7.54	7.54	7.54	h	11.45	10.29	
16	7.23	7.64	7.23	b	7.98		7.56	7.56	f	11.51	10.31	
17	7.26	7.65	7.26	b	7.70	7.82	7.82	7.70	h	11.52	10.50	
18	7.24	7.62	7.28	b	7.46	7.28	7.28	7.46	h	11.38	10.16	$CH(CH_3)_2$ 2.87 (m); $CH(CH_3)_2$ 1.19 (d)
19	7.24	7.63	7.24	b	7.47	7.17	7.17	7.47	h	11.40	1.17	$C_6H_4CH_2$ 2.56 (t); CH_2CH_2 1.1–1.8 (m); CH_3 0.90 (t)
20	7.24	7.63	7.24	b	7.48	7.37	7.37	7.48	h	11.40	10.18	$C(CH_3)_3$ 1.28 (s)
21	7.2–7.6	7.2–7.6	7.2–7.6	d	7.61	7.43	7.43	7.61	h	11.48	10.22	
22	7.2–7.7	7.2–7.7	7.2–7.7	d	7.72	7.84	7.84	7.72	h	11.56	10.44	
23	7.3–7.6	7.3–7.6	7.3–7.6	d	7.64	7.44	7.44	7.64	h	11.51	10.30	
24	7.3–7.7	7.3–7.7	7.3–7.7	d	8.00		7.57	7.57	f	11.56	10.33	
25	7.3–7.7	7.3–7.7	7.3–7.7	d	7.72	7.84	7.84	7.72	h	1160	10.50	
26	7.56	7.47	7.66	c	7.60	7.38	7.38	7.60	h	11.15	10.13	
27	7.60	7.44	7.71	c	8.02		7.58	7.58	f	11.66	10.50	
28	7.61	7.44	7.72	c	7.71	7.85	7.85	7.71	h	11.70	10.64	
29	7.74	7.36	7.74	a	8.02		7.58	7.58	f	11.61	10.46	

Spin systems

a = AB₂ system
b = ABB'XX' system
c = ABC system
d = unresolved ABCX system

e = unresolved ABCD system
e' = resolved ABCD system
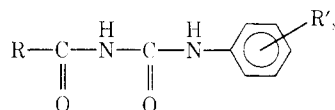f = degenerated ABX system
f' = ABX system

g = unresolved ABB'CC' system
h = AA'BB' system
i = AB system

Table III. Insecticidal Activities of

R—C(=O)—N(H)—C(=O)—N(H)—C₆H₄—R'ₓ

Nmr data

Compound no.	R	R'ₓ	Test results — Aëdes aegypti L.	Test results — Pieris brassicae L.	Test results — Leptinotarsa decemlineata Say	Mp, °C	$H_{2'}$, δ	$H_{3'}$, δ	$H_{5'}$, δ	$H_{6'}$, δ	NH_A, δ	NH_B, δ	Other compounds, δ
1	$(CH_3)_3C-$	3,4-Cl₂	—	±—	—	165	7.97		7.62	7.62	10.90	10.36	$(CH_3)_3$ C 1.27 (s)
2	$(CH_3)_3CCH_2-$	4-Cl	—	—	—	178	7.60	7.37	7.37	7.60	10.74	10.68	CH_2 2.29 (s); $(CH_3)_3$ 1.02 (s)
3	$(i\text{-}C_3H_7)_2C(-CN)-$	4-Cl	—	—	—	200	7.61	7.40	7.40	7.61	10.30	10.16	CH 2.3–2.8 (m); $(CH_3)_2$C 1.03 (d) and 1.10 (d)
4	Cl_3C-	3,4-Cl₂	—	—	—	170	7.93		7.51	7.51	11.34	9.98	
5	Adamantyl-1	3,4-Cl₂	—	—	—	235	7.90		7.47	7.47	10.72	9.70	ad αH 1.95 (m); βH 1.72 (m); γH 2.04 (m)
6	$(C_6H_5)_3C-$	3,4-Cl₂	—	—	—	188	7.95		7.50	7.50	10.61	9.77	C_6H_5 7.1–7.5 (m)

Applied concentrations in parts per million

Aëdes aegypti L. 1, 0.3, 0.1, 0.03, etc.
Pieris brassicae L. 100, 30, 10, 3, etc.
Leptinotarsa decemlineata Say 100, 30, 10, 3, etc.

+ = 90–100% mortality
± = 50–89% mortality
— = 0–49% mortality

The substitution patterns and the substituents of the phenyl ring of the aniline moiety have been chosen on the grounds of the results obtained with the 1-(2,6-dichlorobenzoyl)-3-phenylureas described in part I.

Table I shows the results obtained with a series of 1-benzoyl-3-phenylureas, the benzoyl moiety being substituted with a variety of functional groups. The di-ortho substitution pattern is not surveyed in this table. Within this series only three mono-ortho-substituted derivatives (I:2, 3, and 5) afforded a slight activity. Notably compound I:14 (2,3,6-Cl₃-benzoyl), which strongly resembles one of the most active compounds mentioned in part I, namely 1-(2,6-dichlorobenzoyl)-3-(3,4-dichlorophenyl)urea (DU 19-111), was completely inactive.
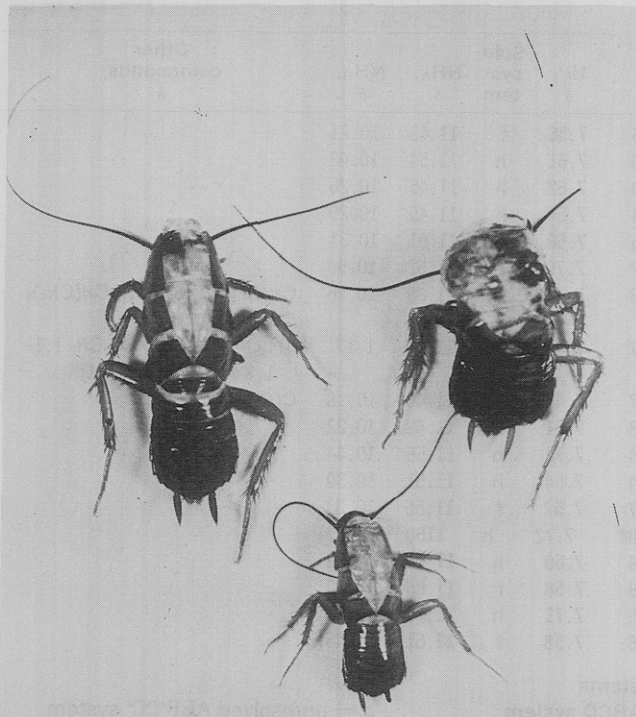
Figure 3. Nymphs of *Periplaneta americana* L. injected daily for 4 successive days with an aqueous suspension containing 1 μg of PH 60-40. Ecdysis was blocked after splitting of the exuvia along the ecdysial line. The nymphs died several days afterwards.

Table II, presenting the di-ortho-substituted benzoylphenylureas, demonstrates the exceptional character of this substitution pattern insofar as halogen atoms are involved. Whereas II:1, 2, and 3 [2,6-$(CH_3)_2$] were moderately active, all substitutions other than with halogen gave rise to products without larvicidal effect. Excellent results were obtained with the derivatives containing one or two fluorine atoms in the ortho position (II:14-25), culminating in II:17 [1-(2,6-difluorobenzoyl)-3-(4-trifluoromethylphenyl)urea]. If the test results of II:14-20 (2,6-F_2-benzoyl derivatives) are compared with those of the corresponding 2,6-dichlorobenzoylureas (described in part I of this paper), it is clear that the former compounds are the more effective larvicides. The differences between the two series are the least pronounced with II:13 (PH 60-38, inserted as reference) and II:14 (the corresponding difluorobenzoyl derivative). In this case the results obtained with *Leptinotarsa* were even better with the dichloro derivative. The order of effectiveness with 1-(2,6-R_2-benzoyl)-3-phenylureas, namely R = H, OH, OCH_3, C_2H_5 < CH_3 < Br ≪ Cl < F, indicates that insecticidal activity is not merely related to the extent of sterical hindrance within the benzoyl moiety but also that electronic effects are involved.

In support of this notion, Table III shows the test results obtained with six sterically highly hindered acylphenylureas. Within this group no insecticidal activity was found. These results once again underline the essen-

tial role of the 2,6-disubstituted benzoyl moiety, with halogen atoms eliciting the largest insecticidal effects by far.

Preliminary toxicological data with mice have been obtained for two representatives of this series, namely II:14 and II:16. The acute LD_{50} values were similar for the two compounds, namely higher than 3160 mg/kg when administered orally, and higher than 1000 mg/kg upon intraperitoneal application.

CONCLUSION AND SUPPLEMENTARY DETAILS

As is shown in Table II, the 1-(2,6-difluorobenzoyl)-3-phenylureas have an extreme larvicidal potency toward *Pieris* and *Aedes*. Compound II:14 (PH 60-40) was chosen to be compared in greenhouse and field trials with PH 60-38 (II:13), already selected as a potential insecticide. PH 60-38 has shown that it possesses promising larvicidal activity on a variety of insect species. In preliminary experiments it was found to be rather stable in soil and water. Further experiments should furnish the information necessary to judge whether this stability is acceptable from the ecological point of view. PH 60-40 is the more effective on larvae of most insect species tested and its stability compares favorably to that of PH 60-38 (Nimmo, 1973).

Besides the insect species mentioned in the tables, larval stages of many other species have proved to be susceptible in laboratory and small-scale field experiments. Among them are various culicine and anopheline mosquitoes, various fly species, lepidopterous species like *Heliothis virescens* Fabr. (Tomerlin, 1973), *Spodoptera exigua* Hübner, *Spodoptera littoralis* Boisd., the coleopterous species *Sitophilus granarius* L. (Wickham, 1973), *Tribolium castaneum* Herbst (Wickham, 1973), and further species like *Schistocerca gregaria* Forsk., *Periplaneta americana* L. (Figure 3), and *Solenopsis* species (Tomerlin, 1973).

Finally it is noteworthy that various phosphate- and dieldrin-resistant insect species proved to be susceptible to both PH 60-38 and PH 60-40.

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