Synthesis and Insecticidal Activity of Substituted 1-Phenyl-3-benzoylureas and 1-Phenyl-3-benzoyl-2-thioureas

Ching-Chieh Yu* and Ronald J. Kuhr

The insecticidal activity of various substituted 1-phenyl-3-benzoylureas and 1-phenyl-3-benzoyl-2-thioureas was determined by allowing seedcorn maggot larvae, *Hylemya platura* (Meigen), to feed on lima bean seeds treated with the synthesized chemicals. The most toxic ureas were those containing a 2,6-difluorobenzoyl moiety combined with a 3,4-dichloro, 4-chloro, 4-trifluoromethyl, or 4-nitrophenyl moiety. Thioureas were less active than corresponding ureas, but similar substitution on the aromatic rings produced parallel effects with both groups. A correlation between Hammett's σ constant for phenyl substituents and toxicity suggested that electron-withdrawing groups were important in conferring insecticidal activity.

A new class of insect stomach poisons, the substituted 1-phenyl-3-benzoylureas, was recently discovered by van Daalen et al. (1972). The precise mode of action of these compounds has not been conclusively established, but it is apparent that the poisons interfere with the formation and/or deposition of cuticle chitin during larval moults (Ishaaya and Casida, 1974; Post et al., 1974; Post and Mulder, 1974). One of the most promising materials, compound TH-6040 [1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl)urea], is currently under development by Thompson-Hayward Chemical Company for control of mosquitoes, flies, and certain agricultural pests.

During a search for seed treatments effective against damage caused by seedcorn maggots, *Hylemya platura* (Meigen), we found that TH-6040 was quite toxic to larvae. Thus, we extended our study to include other analogues in an attempt to find more effective maggot toxicants.

MATERIALS AND METHODS

Chemicals. Compounds **1–23** in Table I were synthesized by refluxing the appropriate benzamide and phenyl isocyanate in xylene (Wellinga et al., 1973a,b). Compounds **24–40** in Table II were prepared by mixing the selected benzoyl chloride with ammonium thiocyanate in acetone, and the resulting benzoyl isothiocyanate was subsequently allowed to react with the required aniline (Rasschaert et al., 1968). Melting points (uncorrected) are listed in Tables I and II. Chemicals which had not been reported previously in the literature were recrystallized several times from acetone or 95% ethanol until analytically pure (based on thin-layer chromatography using 0.25-mm silica gel GF-254 plates developed in benzene or benzene–ether, 1:1). Other chemicals were crystallized only once and washed with xylene and petroleum ether before use. NMR spectra obtained with a Varian HA-100 spectrometer using deuterated dimethyl sulfoxide (for **1–23**) or deuterated acetone (for **24–40**) as solvent verified the assigned structures (Supplementary Tables I and II) (see paragraph at end of paper). Elemental analyses of carbon and hydrogen (Galbraith Laboratories, Inc.) for new compounds also agreed with theoretical values, the average deviations being ±0.38% for carbon and ±0.05% for hydrogen (Supplementary Table III).

Bioassay. Dry lima bean seeds were held for 1 hr in acetone solutions of the test materials at various concentrations (Eckenrode et al., 1974). Since compounds **21** and **22** were insufficiently soluble in acetone, a small amount (less than 2%) of dimethyl sulfoxide was added to bring the crystals into solution. Mortality of larvae fed on seeds treated with 2% Me_2SO demonstrated no significant difference as compared with seeds treated with acetone alone. For synergism studies, test materials were dissolved in acetone containing 0.5% piperonyl butoxide (P.B.). Three-day-old larvae of the seedcorn maggot, *Hylemya platura* (Meigen), were allowed to feed on the treated seeds for 10 days before larval mortality was determined. The LC_{50} values were obtained by plotting log molar concentration against probit percent mortality.

RESULTS AND DISCUSSION

Table I summarizes the results for substituted ureas. The range of insecticidal activity covered more than three orders of magnitude and in some cases activity was synergized by P.B. This suggests that these compounds may have been partially metabolized by the mixed-function oxidases of the larvae. Metabolic destruction may have also been responsible for differences in toxicity of TH-6040 to resistant and susceptible houseflies (Cerf and Georghiou, 1974).

Optimum activity was obtained when the benzoyl moiety was substituted in the 2 and 6 positions with fluorine atoms. Other substituents, such as 2-Cl or 2,6-Cl_2, were also effective, but further changes in the ring abolished most insecticidal activity. These findings agree with those of Wellinga et al. (1973a,b) and imply definite electronic and steric requirements for the benzoyl part of the molecule.

On the phenyl nucleus, the most effective additions were 3,4-Cl_2, 4-Cl, 4-CF_3, and 4-NO_2. Structure–activity relationships were evaluated using both electronic (Hammett's σ constant) and hydrophobic (Hansch's π constant) characteristics of the phenyl substituents according to the values cited by Hansch et al. (1973).

Regression analysis produced eq 1 and 2 for the 2,6-dichlorobenzoyl series of compounds as shown:

$$-\log LC_{50}\ (\text{synergized}) = -0.632 + 2.328\sigma$$
$$n = 7,\ R = 0.837,\ S = 0.490\ (F_{1,5} = 11.69,\ P = 0.019) \quad (1)$$

$$-\log LC_{50}\ (\text{synergized}) = -0.495 + 2.512\sigma - 0.252\pi$$
$$n = 7,\ R = 0.846,\ S = 0.534\ (F_{2,4} = 5.04,\ P = 0.082) \quad (2)$$

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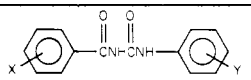
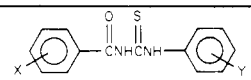
Table I. Insecticidal Activity of Substituted 1-Phenyl-3-benzoylureas against Seedcorn Maggot Larvae



Compd no.	X	Y	LC_{50}, m*M* Alone	LC_{50}, m*M* With P.B	Mp, °C Found	Mp, °C Lit.[a]
1	H	4-Cl	>36	>36	248	
2	2-Cl	4-Cl	0.64	0.32	200-201	
3	2-F	4-Cl	6.1	10.1	190-193	
4	4-Cl	4-Cl	>32	>32	255-256	
5	2,4-Cl_2	4-Cl	>29	>29	192-193	
6	3,4-Cl_2	4-Cl	>29	>29	250-252	
7	2,6-Cl_2	H	>32	8.9	194	196
8	2,6-Cl_2	4-CH_3	>31	36.7	227	242
9	2,6-Cl_2	4-C_2H_5	>29	7.3	223	228
10	2,6-Cl_2	4-CF_3	2.2	0.31	209	214
11	2,6-Cl_2	4-Cl	1.9	0.46	224	225
12	2,6-Cl_2	4-F	1.1	0.60	207	212
13	2,6-Cl_2	3,4-Cl_2	1.8	0.52	229	238
14	2,6-Cl_2	2,3-Cl_2	3.9	3.9	215-217	
15	2,6-F_2	H	17.8	5.4	191-192	
16	2,6-F_2	4-CH_3	17.0	1.7	210-211	
17	2,6-F_2	4-C_2H_5	0.32	0.32	185-186	
18	2,6-F_2	4-CF_3	0.12	0.029	245	255
19	2,6-F_2	4-Cl	0.051	0.0485	230	239
20	2,6-F_2	4-F	0.12	0.13	207-208	
21	2,6-F_2	3,4-Cl_2	0.043	0.029	242	253
22	2,6-F_2	4-NO_2	0.046	0.046	260	
23	2,6-F_2	3-Cl	0.32	0.32	180-181	

[a] Wellinga et al. (1973a,b).

Table II. Insecticidal Activity of Substituted 1-Phenyl-3-benzoyl-2-thioureas against Seedcorn Maggot Larvae



Compd no.	X	Y	LC_{50}, m*M* Alone	LC_{50}, m*M* With P.B.	Mp, °C Found	Mp, °C Lit.[a]
24	H	4-Cl	17.2	24.1	140-142	140-141.5
25	H	4-F	>36.5	36.5	127-128	128-129
26	2-Cl	4-Cl	0.31	0.15	182-184	
27	2-Cl	4-F	45.3	16.8	169-172	
28	2-Cl	2-CH_3, 4-Cl	3.2	2.9	162-164	
29	2-Cl	4-CN	9.5	3.2	186-187	
30	2-F	4-Cl	6.5	1.3	126-127	
31	2-F	4-F	12.0	15.4	106-108	
32	2,6-Cl_2	4-C_2H_5	>28	>28	187-190	
33	2,6-Cl_2	4-Cl	>28	>28	236-237	
34	2,6-Cl_2	4-F	>29	>29	228-229	
35	2,6-Cl_2	2-CH_3, 4-Cl	>27	>27	245	
36	2,6-Cl_2	2-Cl, 4-CH_3	>27	>27	198-199	
37	2,6-Cl_2	3-CF_3	>25	38.1	192-194	
38	2,6-F_2	4-Cl	1.5	0.31	190-192	
39	2,6-F_2	4-F	5.8	2.6	184-185	
40	2,6-F_2	2-CH_3, 4-Cl	>29	>29	178-179	

[a] Schroepl and Pohloudek-Fabini (1969).

and eq 3 and 4 for the 2,6-difluorobenzoyl series of compounds as shown:

$$-\log LC_{50}\ (\text{synergized}) = 0.310 + 1.7673\sigma$$

$$n = 9, R = 0.729, S = 0.591\ (F_{2,4} = 7.94, P = 0.025) \quad (3)$$

$$-\log LC_{50}\ (\text{synergized}) = -0.041 + 1.846\sigma + 0.600\pi$$

$$n = 9, R = 0.819, S = 0.535\ (F_{2,6} = 6.11, P = 0.036) \quad (4)$$

In these equations, n is the number of points (compounds) in the regression analysis, R is the correlation coefficient, S is the standard deviation, and P is the probability point.

Correlations were good in eq 1 and 3, and incorporation of π values to yield eq 2 and 4 did not significantly improve the correlation at $P \leq 0.05$ (partial F for the π term was 0.215 and 2.534, respectively, for eq 2 and 4). Therefore, the electronic properties of the phenyl substituents (σ) were most influential in conferring activity while contributions from hydrophobic interactions were negligible. A plot of the log LC_{50} (synergized) vs. Hammett's σ constant indicated that an increase in electron-withdrawing power of the ring substituent yielded a corresponding increase in insecticidal activity (Figure 1).

Table II lists the insecticidal activity of the thioureas. These compounds were generally less toxic than the corresponding ureas in Table I. However, optimum additions to the aromatic rings were similar, i.e., addition of 2-Cl or 2,6-F_2 to the benzoyl moiety, and 4-Cl to the phenyl

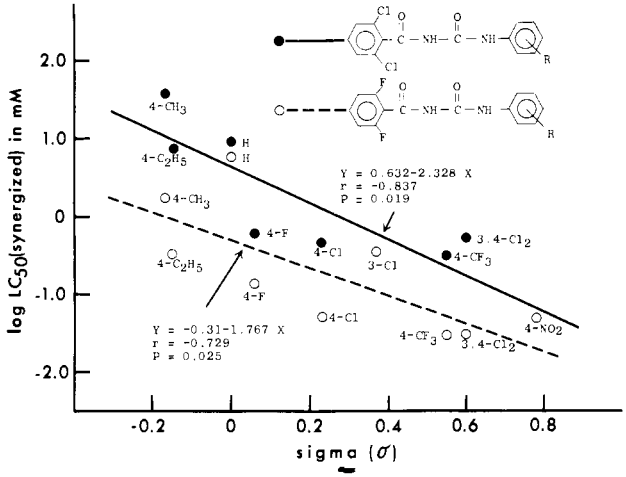


Figure 1. Correlation of insecticidal activity and Hammett's σ constant for substituted 1-phenyl-3-(2,6-dichlorobenzoyl)- and 1-phenyl-3-(2,6-difluorobenzoyl)-ureas.

moiety, produced the most active structures.

ACKNOWLEDGMENT

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Supplementary Material Available: Supplementary Tables I–III describing NMR and elemental analysis data, 4 pages. Ordering information is given on any current masthead page.

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Carbamate Poisoning. Effect of Certain Carbamate Pesticides on Esterase Levels in the Pheasant (*Phasianius colchicus*) and Pigeon (*Columba livia*)

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Pheasants and pigeons were fed with lethal and sublethal doses of six widely used carbamates. Esterase levels were measured quantitatively in liver and brain and also by an electrophoretic method involving histochemical staining. It is suggested that the inhibition of esterase levels demonstrated by the quantitative measurement and the apparent elevation in esterase levels revealed by the electrophoretic method can be used to diagnose poisoning in birds with these compounds.

Previous communications from this laboratory (Bunyan and Taylor, 1966; Bunyan et al., 1968a,b, 1969, 1971) have demonstrated that esterase inhibition can be used for the diagnosis of organophosphorus poisoning in avian species, even under field conditions. Following increasing restrictions on the use of organochlorine pesticides and the concomitant increase in organophosphorus and carbamate pesticide usage, an investigation has now been undertaken into the possible use of the esterase inhibition method for the detection of carbamate pesticide poisoning in birds.

The pesticides chosen for this study include a number in full commercial use and additionally represent a wide range of chemical structures. Selection was also made to include compounds with a broad spread of toxicity, although at the time the experiments were carried out data were limited for avian species. For methiocarb and Zectran LD_{50} values were available for both pheasant and pigeon, but data for aldicarb, aminocarb, and pirimicarb were available only for the chicken. No data for avian species were available for propoxur.

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EXPERIMENTAL SECTION

Animals. The origin of the pheasants and pigeons and their treatment before and after dosing have been described previously (Bunyan and Taylor, 1966; Bunyan et al., 1968a). Relevant data on the birds and the dosage rate are given in Table I.

Pesticides. Six pesticides were chosen for study, namely: aldicarb (2-methyl-2-(methylthio)propionaldehyde *O*-(methylcarbamoyl) oxime), aminocarb (4-dimethylamino-3-methylphenyl methylcarbamate), methiocarb (3,5-dimethyl-4-methylthiophenyl methylcarbamate), pirimicarb (2-dimethylamino-5,6-dimethylpyrimidin-4-yl dimethylcarbamate), propoxur (2-isopropoxyphenyl methylcarbamate), and Zectran (4-di-