Thiazolylureas: Effects on Larval Growth and Development in the Fall Armyworm and Tobacco Budworm

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Thiazolylurea, 5-[[(2-thiazolylamino)carbonyl]amino]-1,3-benzenedicarboxylic acid dimethyl ester (1), prolonged larval development when fall armyworm larvae were reared on a larval diet containing 100 ppm of the compound. Prolongation of development caused size and weight increases in both larvae and pupae surviving treatment. Larval survival was also lowered at this dose, with insects dying as prepupae or morphologically aberrant larval–pupal intermediates. Thiazolylurea 1 elicited similar growth and development effects in the tobacco budworm but was not as toxic to larvae. Structure–activity relationships were determined by testing 37 analogues of 1 against the fall armyworm. Comparisons between compounds were made on the basis of pupal weight indices. Compound 7, the diisopropyl ester analogue of 1, was the most effective compound against the fall armyworm, with growth-regulating effects observed at a dietary concentration as low as 1 ppm.

Antifertility effects in insects associated with benzoyl-substituted ureas (Grosscurt, 1978), thiourea (Borkovec, 1966; Hall et al., 1979), and related compounds (Borkovec, 1966; DeMilo and Fye, 1976) have provided a basis to investigate other ureides for similar activity. In that context, we evaluated a thiazole-substituted urea 1 (Figure 1; 5-[[(2-thiazolylamino)carbonyl]amino]-1,3-benzenedicarboxylic acid dimethyl ester) and found that while 1 lacked reproduction inhibitory effects, it strongly influenced the growth and development of fall armyworm (*Spodoptera frugiperda* (J. E. Smith)) larvae that were reared on a dietary mixture of 1.

The thiazole ring is clearly a prominent structural feature of 1, and although certain thiazole-substituted ureas or thioureas are reported to have herbicidal (Gobain, 1966), insecticidal (Kano et al., 1977), acaricidal (Kano et al., 1977), antileukemic (Zee-Cheng and Cheng, 1979) and viricidal (Akihama and Okude, 1967) properties, little is known regarding their ability to disrupt normal growth and development of insects. We report here the influences of 1 on larval growth and development in two lepidopterans: the fall armyworm and the tobacco budworm (*Heliothis virescens*). We also report structure–activity relationships derived from tests in the fall armyworm with 1 and 37 of its analogues.

MATERIALS AND METHODS

Synthesis of Chemicals. New compounds listed in Tables I and II gave satisfactory (±0.4% of theory) combustion analyses for carbon and hydrogen. Analyses were performed by Galbraith Laboratories, Knoxville, TN. Melting points are uncorrected. Although acetonitrile was the recrystallization solvent of choice for most compounds, ethanol, methanol, and ethyl acetate were occasionally used.

Because 2-isocyanatothiazole readily cyclodimerizes during its synthesis (Gizycki and Oertel, 1968), its obvious use as a precursor for the synthesis of some of the thiazolylureas had to be avoided (Figure 1, path b). However, 1 and related thiazolylureas (Table I) were readily synthesized by treating the appropriately substituted phenyl isocyanate with the corresponding aminothiazole (Figure 1, path a). Sulfur analogues 5 and 9 (Table I) were prepared from 2-aminothiazole and the appropriately substituted phenyl isothiocyanate in pyridine solvent. Ureas in Table II were prepared in a manner similar to those in Table I, i.e., by treatment of 4 (Figure 1) with the appropriate heteroarylamine. Synthesis of thiourea 40 (Table II) was analogous to methods used for 5 and 9.

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Most of the isocyanates used to prepare ureas in Table I were obtained from commercial sources. Isocyanate 4 and closely related isocyanates (i.e., diethyl and diisopropyl analogues were synthesized (Carbolabs, Inc., New Haven, CT) by treatment of the appropriate aniline precursor with excess phosgene in ethyl acetate (Shriner et al., 1963). Melting points (°C) for isocyanates: 104–106, 4; 27 and 63–64, diethyl and diisopropyl analogues, respectively. Synthetic methods for the aniline precursors and other key compounds and their intermediates follow.

5-Aminoisophthalic Acid Dimethyl Ester (3). 5-Aminoisophthalic acid (2; 18.1 g, 0.1 mol) was added to methanol (250 mL) containing anhydrous HCl (30.1 g, 0.826 mol). After the mixture was refluxed for 24 h, the solvent was removed in vacuo and the residue neutralized by adding a 2 M K_2CO_3 solution (250 mL). The free base was extracted with CH_2Cl_2 (3 × 200 mL), and the extracts were combined, washed with saturated brine, and dried ($MgSO_4$). Removal of the solvent and recrystallization of the residue from MeOH gave 3: 14.6 g, 70%; mp 180–181 °C (lit. mp 176–178 °C (Martin, 1954)). Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30. Found: C, 57.49; H, 5.33.

5-Aminoisophthalic acid diethyl ester was prepared analogously to 3: yield 51%; mp 119–120 °C (benzene). Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37. Found: C, 61.00; H, 6.37.

5-Aminoisophthalic acid diisopropyl ester was prepared analogously to 3: yield 54%; mp 130–131 °C (benzene). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.35; H, 7.22. Found: C, 63.55; H, 7.27.

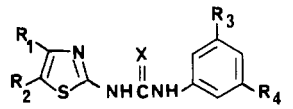
5-[[(2-Thiazolylamino)carbonyl]amino]-1,3-benzenedicarboxylic Acid Dimethyl Ester (1). To a solution of 4 (17.75 g, 0.05 mol) in acetonitrile (100 mL) was added 2-aminothiazole (5.0 g, 0.05 mol) in acetonitrile (150 mL). After the mixture was allowed to stand for 30 min, the precipitated product was collected by filtration. Recrystallization from acetonitrile and then ethanol afforded 1: 7.1 g, 42%; mp 249–250 °C dec.

3,5-Dicarbomethoxyphenyl Isothiocyanate. To a chilled (ca. 5 °C) mixture of water (1 L), CH_2Cl_2 (1 L), $NaHCO_3$ (25.2 g, 0.3 mol), and thiophosgene (9.2 mL, 0.12 mol) was added over 1 h a solution of 3 (20.9 g, 0.1 mol) in CH_2Cl_2 (1.1 L). After addition, the chilled mixture was stirred for 45 min. The CH_2Cl_2 layer was separated, washed with 3 N HCl (2 × 250 mL) and 10% $NaHCO_3$ solution (2 × 250 mL), and dried ($MgSO_4$). The solvent was removed and the residue recrystallized from heptane to give the isothiocyanate: 22.3 g, 80%; mp 116–117 °C.

5-[[(2-Thiazolylamino)thiocarbonyl]amino]-1,3-benzenedicarboxylic Acid Dimethyl Ester (5). To a solution of 3,5-dicarbomethoxyphenyl isothiocyanate (1.25 g, 4.97 mmol) in pyridine (10 mL) was added 2-aminothiazole (0.5 g, 5.0 mmol). After the mixture was allowed to stand 18 h at 25 °C, the mixture was poured into water (50 mL) and the product collected by filtration. Recrystallization from ethanol gave the product: 1.24 g, 71%; mp 182–183 °C dec. Anal. Calcd for $C_{14}H_{12}N_3O_4S_2$: C, 47.85; H, 3.73. Found: C, 48.05; H, 3.79.

5-[[[(Aminothiocarbonyl)amino]carbonyl]amino]-1,3-benzenedicarboxylic Acid Dimethyl Ester (41). To a solution of 4 (7.05 g, 30 mmol) in dry dioxane (3.5 mL) was added thiourea (2.28 g, 30 mmol). The thiourea dissolved, and within a few minutes a solid precipitated from solution. The mixture was stirred at ambient temperature for 1 h and the product collected

Table I. Effects of Variously Substituted Thiazolylureas on Pupal Size in Larval Tests with *S. frugiperda*



compd no.	X	R_1	R_2	R_3	R_4	mp, °C	pupal wt index (PWI)[a]
1	O	H	H	CH_3CO_2	CH_3CO_2	249–250 dec	1.447[b]
5	S	H	H	CH_3CO_2	CH_3CO_2	182–183 dec	1.553[c]
6	O	H	H	$C_2H_5CO_2$	$C_2H_5CO_2$	204 dec	1.350[d]
7	O	H	H	i-$C_3H_7CO_2$	i-$C_3H_7CO_2$	178 dec	1.618[d]
8	O	H	H	H	H	172–173 dec	0.951
9	S	H	H	H	H	173–174 dec	0.938
10	O	H	H	CH_3	CH_3	243 dec	0.951
11	O	H	H	CF_3	CF_3	206 dec	0.943
12	O	H	H	Cl	Cl	244–246 dec	0.927
13	O	H	H	CH_3O	CH_3O	189 dec	0.886
14	O	H	H	CH_3CO_2	H	179.5 dec	1.028
15	O	H	H	$C_2H_5CO_2$	H	177 dec	0.951
16	O	H	H	CH_3CO	H	176 dec	0.918
17	O	H	H	C_2H_5	H	147–148.5 dec	0.986
18	O	CH_3	H	CH_3CO_2	CH_3CO_2	206–207 dec	1.022
19	O	$C_6H_5(CH_2)_2$	H	CH_3CO_2	CH_3CO_2	247–249 dec	1.024
20	O	$C_2H_5OC(O)CH_2$	H	CH_3CO_2	CH_3CO_2	178 dec	0.981
21	O	$C_2H_5CO_2$	H	CH_3CO_2	CH_3CO_2	>270 dec	0.981
22	O	C_6H_5	H	CH_3CO_2	CH_3CO_2	238–242	1.042
23	O	H	NO_2	CH_3CO_2	CH_3CO_2	256–257 dec	1.014
24	O	H	4-$(NO_2)C_6H_4SO_2$	CH_3CO_2	CH_3CO_2	253–255 dec	0.977
25	O	CH_3	CH_3	CH_3CO_2	CH_3CO_2	195–234 dec	1.014
26	O	C_6H_5	C_2H_5	CH_3CO_2	CH_3CO_2	246–248 dec	0.981
27	O	C_6H_5	$C_2H_5CO_2$	CH_3CO_2	CH_3CO_2	240–241.5	0.921

[a] PWI were calculated at 100 ppm. PWI = average weight of pupae (treated insects) divided by average weight of pupae (untreated insects). Pupal weights were recorded at end of pupation (minimum interval 9 days posttreatment). [b] 70% larval mortality by day 21. [c] Average of two data sets. [d] 90% larval mortality by day 36.

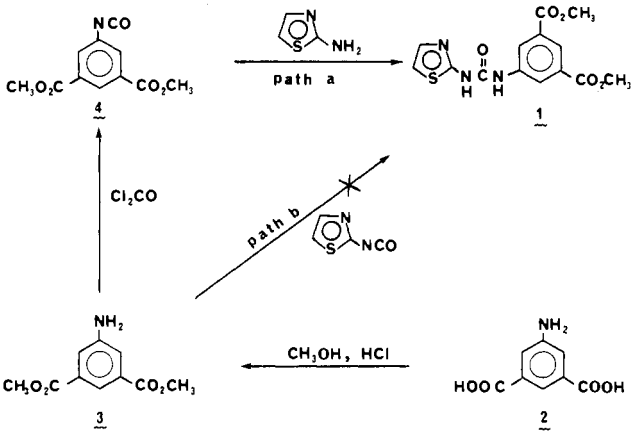


Figure 1. Synthesis scheme.

by filtration. Recrystallization from acetic acid gave **41**: 3.1 g, 33%; mp 210–211 °C dec. Anal. Calcd for $C_{12}H_{13}N_3O_5S$: C, 46.30; H, 4.21. Found: C, 46.46; H, 4.20.

Evaluation of Compounds against *S. frugiperda*. Larvae used in tests were from a laboratory colony (Beltsville strain) and were reared on an artificial diet (Redfern and Raulston, 1970) under a regimen of 27 ± 1 °C, 50 ± 5% RH, and photoperiod 14:10 (L:D). Test compounds were added at the desired rate (ppm) to 100 g of heated (liquified) artificial diet by one of two methods depending on solubility of the compound in a 1:1 (v/v) dimethyl sulfoxide–acetone solution. For soluble compounds, a stock solution of the test compound was prepared (100 μg/μL), and a 100-μL aliquot of the stock solution (or a dilution) was added to the heated diet. For insoluble compounds, the appropriate amount of test compound was blended, by mortar and pestle, with a few grams of wheat germ moistened with 1:1 dimethyl sulfoxide–acetone solution. The slurry was air-dried, and the powder was added to the liquified diet.

After incorporation of the test compound in the heated diet, the mixture was poured into 1-oz plastic cups (8 g/cup) and the cups were cooled to room temperature. One third or early fourth instar was placed in each cup (10 larvae/test concentration). Cups were capped with prepunched lids, and animals were held for the duration of the test under conditions described for rearing.

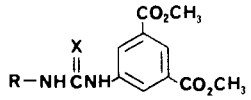
Biological effects were assessed as follows. Treated larvae were examined every 2–3 days, beginning 3 days posttreatment and ending at the terminus of pupation, or before, if death occurred. For test results in Table III, insects were examined at specific intervals of 9, 12, and 15 days posttreatment. Pupae were removed at the terminus of pupation (time varied according to compound), weighed, sexed, and held for adult emergence. Adults that emerged were allowed to mate, and reproduction indices (i.e., fecundity and egg hatch) were qualitatively assessed.

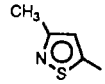
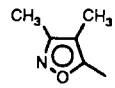
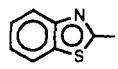
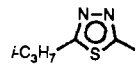
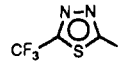
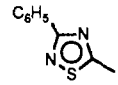
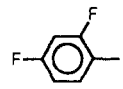
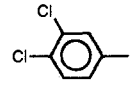
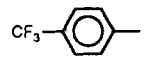
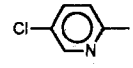
Effects of 1 on Larval *H. virescens*. Animals, obtained as pupae from the Southern Field Crop Insect Management Laboratory, USDA, Stoneville, MS, were allowed to emerge, mate, and lay eggs. Eggs were hatched and reared in individual cups on a modified Adkisson–Vanderzant medium (Adkisson et al., 1960). Compound 1 (50 mg) was dissolved in 1 mL of warm ethanol, and the resulting solution was mixed well with warm liquid diet to a concentration of 50 ppm. Treated diet was dispensed into 1-oz diet cups, and newly hatched larvae were placed in the cups (1/cup). Test animals were maintained at 30 °C with a photoperiod 16:8 (L:D). Newly ecdysed last instars were briefly rinsed with water to remove diet and frass, blotted dry, and weighed. This procedure was repeated each day until larvae pupated.

RESULTS AND DISCUSSION

In initial tests with 1, we found that late third or early fourth stage fall armyworm larvae, reared on a treated diet (100 ppm), molted to more advanced instars, but development was prolonged, size was dramatically increased, and mortality was increased over that observed for controls. Death frequently occurred in prepupal or larval–pupal forms. At lower doses (1–10 ppm), mortality decreased and surviving large larvae molted to proportionately sized pupae and then adults. Again, larval development was prolonged (increase in time appeared proportional to concentration). Topical treatment with 1 (multiple applications) proved ineffective, suggesting in-

Table II. Other Analogues and Their Effects on Pupal Size in Larval Tests with *S. frugiperda*



compd no.	X	R	mp, °C	pupal wt index (PWI)[a]
28	O		250–252 dec	0.967
29	O		221–223	1.309[b]
30	O		243–245 dec	0.991
31	O		249–251 dec	0.995
32	O		261.5–262.5 dec	1.195
33	O		241–242 dec	1.066[b]
34	O		256–258 dec	1.045
35	O		212–213	1.019
36	O		213–214	1.072
37	O		214–214.5	0.986
38	O		255 dec	1.057
39	O		158 dec	1.319[b]
40	S		173–174	1.367[b]
41	O		209–210 dec	0.945

[a] PWI were calculated at 100 ppm. PWI = average weight of pupae (treated insects) divided by average weight of pupae (untreated insects). Pupal weights were recorded at end of pupation (minimum interval, 9 days posttreatment). [b] Average of two data sets.

gestion as the principal mode for compound uptake in these experiments.

Similar growth and development effects caused by 1 were found in the tobacco budworm. Figure 2 shows a weight-change profile for the last (fifth) larval instar of the tobacco budworm, resulting from rearing newly hatched larvae on a diet containing 50 ppm 1. Interestingly, treated insects achieved their maximum weight (ca. 40% higher than controls) at approximately the same time in development as controls, but the expected weight decline prior to pupation was not as steep as that for controls. Moreover, the digging and buried periods were markedly increased: 150% and 250%, respectively. Similar to the fall armyworm, budworm pupae and adults surviving larval treatment were considerably larger than controls. However, dead insects were often found as prepupae or morphologically aberrant larval–pupal forms. In contrast to the fall armyworm, larval mortality was usually low.

Structure–activity relationships for thiazolylureas were derived in fall armyworm larval tests with 37 analogues

Table III. Effects on Growth and Development of Third- and Fourth-Stage *S. frugiperda* Treated in Larval Diet with Selected Thiazolylureas and Analogues

compd no.	concn, ppm	% larvae reaching pupal stage at indicated posttreatment day 9	12	15	pupal wt index (PWI)[a]	% adult emergence
1	100	0	0	30[b]	1.447	10
	10	0	100		1.406	50
	1.0	90[c]	90	90	1.146	90
5	100	0	40	100	1.500	70
	10	50	100		1.211	100
	1.0	90	100		1.093	90
6	100	0	0	0[d]	1.350[e]	0
	10	0	0	0[f]	1.504[e]	0
	1.0	0	100		1.254	100
	0.1	30	100		1.049	100
7	100	0	0	0[g]	1.618[e]	10
	10	0	0	0[h]	*i*	0
	1.0	0	60	90	1.365	70
	0.1	60	100		1.061	100
14	100	100			1.028	100
39	100	20	100		1.208	100
	10	80	100		1.117	100
	1.0	100			1.021	90
40	100	0	100		1.267	100
	10	80	90	90	1.154	90
	1.0	100			1.021	100
29	100	0	80	100	1.329	80
	10	90	100		1.058	100
32	100	50	100		1.204	90
	10	80	100		1.054	100
	control[j]	100				100

[a] PWI = average weight of treated pupae divided by average weight of untreated pupae. [b] 70% mortality, day 21. [c] 10% mortality, day 8. [d] 90% mortality, day 36. [e] Pupae malformed. [f] 80% mortality, day 28. [g] 90% mortality, day 30. [h] 100% mortality, day 30. [i] Not calculated, 100% mortality. [j] Average weight of control pupae, 246 mg.

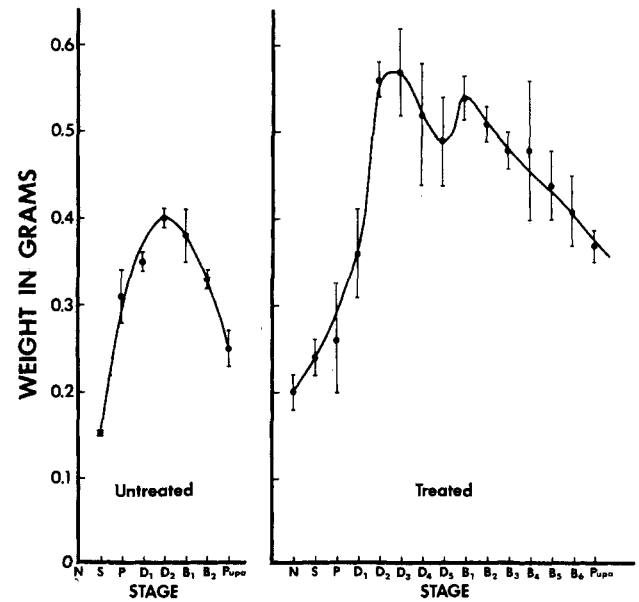


Figure 2. Weight and development time changes in the last larval instar of *H. virescens* caused by thiazolylurea 1. Treatment involved rearing first instars on 50 ppm 1 in diet. Behavioral/morphological markers in last larval instar: N, newly molted; S, slim; P, puffy; D, digging; B, buried; P, newly eclosed pupa. Sample size: 4–17 animals/data point. Bars indicate SEM.

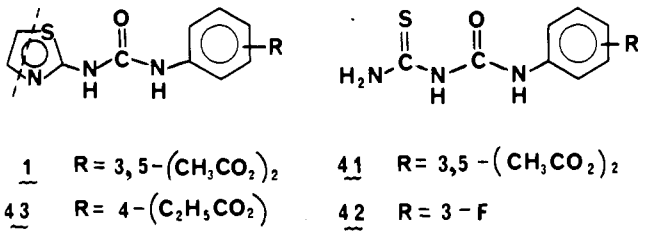


Figure 3. Thiobiurets and other analogues.

of 1. Initial tests to screen compounds for growth-regulating effects were done at 100 ppm, and data are reported in Tables I and II. Active compounds (i.e., PWI ≥ 1.200) were retested under conditions that allowed for more frequent observations at predetermined intervals, and data are reported in Table III.

Data in Table I show that active compounds possessed two ester moieties on the benzene ring (1, 5–7). Replacement of oxygen in the urea moiety of 1 with sulfur (5) increased activity slightly. When both carbomethoxy groups in 1 were replaced with hydrogen (8), methyl (10), chlorine (12), or methoxy (13), activity was lost. To highlight the importance of disubstitution on 1, removal of a single carbomethoxy group gave inactive 14. Analogues with one or more substituents on the thiazole ring were completely ineffective (18–27).

Although replacement of the thiazole ring with isoxazole or thiadiazole provided moderately active compounds 29 and 32, respectively, other heteroaryl systems proved ineffective (Table II). Also ineffective were benzene derivatives 35–37. Noteworthy is activity associated with the nonaromatic thiazoline derivative 39 and its sulfur analogue 40. Despite structural differences between 29, 32, 39, 40, and parent compound 1, morphological effects induced by these analogues were strikingly similar to those induced by 1.

Compound 41 was synthesized because its structure, suggested by a hypothetical cleavage of the thiazole ring in 1 (Figure 3), was analogous to larvicidally effective 42 (100% toxic to fall armyworms at 62.5 ppm) and related monothiobiurets (Hainaut et al., 1975). Despite these reasons, 41 lacked both toxic and growth-regulating effects in the fall armyworm.

Data for two pairs of sulfur–oxygen analogues (1 and 5, 39 and 40) are shown in Table III. Although differences were evident in developmental times for pupation between 1 and 5 at 100 ppm, compounds within each pair had comparable activity. Because of this, only a few sulfur compounds were synthesized for this study. The most effective compounds in Table III were diethyl ester analogue 6 and diisopropyl analogue 7; both prolonged larval development appreciably at 10–100 ppm. At these doses, mortality was high in prepupal or larval–pupal forms, and pupation and adult emergence were severely reduced. Even at 1 ppm, compound 7 elicited a strong effect (PWI = 1.365; 60% pupation 15 days posttreatment).

Compound 1 also affected development of the Indianmeal moth (*Plodia interpunctella* (Hübner)) when early instars were reared on a diet treated with 1. For example, although 1 administered at 100 ppm reduced pupation (ca. 70%) and adult emergence appreciably, it induced malformation of pupae and completely prevented adult emergence at 1000 ppm. Insects completely unaffected by 1 in larval tests were the tobacco hornworm [*Manduca sexta* (L.)] and the house fly (*Musca domestica* L.) at concentrations of 50 and 10 ppm, respectively.

Very little can presently be gleaned from the literature regarding properties of thiazolylureas in other biological systems to suggest how these compounds work as insect growth regulators. Thiazolylurea 43, closely related to 1 (Figure 3), while highly effective in the leukemia P-388 tumor screen (Zee-Cheng and Cheng, 1979) was inactive against the fall armyworm. Similarly, thiourea 9, a dopamine β-hydroxylase inhibitor known to affect catecholamine levels in mouse or rat brains (Johnson et al., 1972), also lacked growth-regulating activity in the fall armyworm. Biological effects observed in our studies (i.e., prolongation of larval development, concomitant weight increases in larval and pupal forms, and morphological aberrations at time of death) are suggestive of hormonal imbalances induced by 1. Data obtained in our laboratory from preliminary studies with 1 in *H. virescens* support this hypothesis. Results of these studies will be published elsewhere.

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