Analogues of TH-6038 and TH-6040. Growth Regulating Effects on the Fall Armyworm*,.**

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11. TH-6038 と TH-6040 の類縁体の Fall Armyworm 生長に対する効果

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1-(4-chlorophenyl)-3-(2,6-dichlorobenzoyl) urea (TH-6038) と 1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl) urea (TH-6040) 及び，それらの関連化合物を *Spodoptera frugiperda* の 3，4 令幼虫の食餌に混合してその成育阻害を検討した．TH-6038 に，殺幼虫作用があり，他の三化合物が同程度の効力を有することが明らかとなった．

Compounds that prevent adult development by mimicking the effects of juvenile hormones have received a great deal of attention as possible insect control agents. As a result, virtually thousands of compounds, representing a wide variety of chemical structures, have been synthesized and investigated for this type of activity (Menn and Beroza[1]; Sláma *et al.*[2]). A new category of inhibitors of insect development has been reported from the Philips-Duphar Research Laboratories (van Daalen *et al.*[3]; Wellinga *et al*[4,5]). These compounds, substituted 1-phenyl-3-benzoyl urea derivatives, are capable of disrupting the development of immature forms of a large variety of insects, presumably by interfering with cuticle deposition by the treated larvae (Post and Vincent[6]; Post *et al.*[7]). Two highly effective compounds in this category are 1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl) urea (TH-6040, Thompson-Hayward 6040, Dimilin®, I) and 1-(4-chlorophenyl)-3-(2,6-dichlorobenzoyl) urea (TH-6038, Thompson-Hayward 6038, II).

The Philips-Duphar group thoroughly examined the effects of substituents on both the aromatic rings and on nitrogen but made no mention of any sulfur analogues of TH-6038 and TH-6040. Recently, Oliver et al.[8] and Yu and Kuhr[9], have reported that a number of sulfur analogues of TH-6038 and TH-6040 inhibit the development of a variety of insect species including the tobacco hornworm *Manduca sexta* (L.). Because these sulfur analogues were active against the tobacco hornworm and because TH-6040 has been reported to be active against several other species of moths (Thompson-Hayward Tech. Inf. "TH-6040, Insect growth regulator," Feb. 1974), we felt it worthwhile to examine the biological activity of these sulfur analogues and some related compounds against the fall armyworm, *Spodoptera frugiperda* (J. E. Smith).

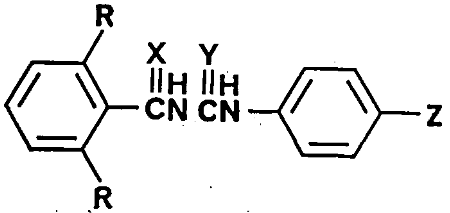
Materials and Methods

Test larvae were laboratory reared from our stock culture on an artificial diet (Redfern and Raulston[10]) and were tested as 36-50mg 3rd-or 4th-instars. TH-6040 was obtained as technical grade (96% pure) from Thompson-Hayward Co., Kansas City, Kansas. The other compounds were synthesized according to procedures of Oliver *et al.*[8] (see Fig. 1). All compounds were prepared as wt:vol acetone solutions and were stored in a freezer until used.

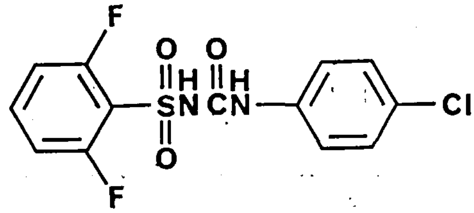
Bioassay.-The test compounds were incorporated into 100 g of standard diet at the rate of 100, 50, 10, 1, 0.1 and 0.01 ppm. Treated diets were poured into 1-oz jelly cups at the rate of 8g/cup and allowed to cool to room temperature. One 3rd-, or 4th-instar was then placed in each cup. (10 cups were set up for each concentration.) The cups were then capped with prepunched lids,

* Lepidoptera : Noctuidae.

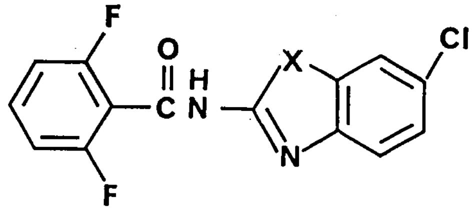
** This paper reports the results of research only. Mention of a pesticide in this paper does not constitute a recommendation for use by the USDA nor does it imply registration under FIFRA as amended.



I, R=F, X=Y=O, Z=Cl (TH-6040)
II, R=Z=Cl, X=Y=O (TH-6038)
III, R=F, X=O, Y=S, Z=Cl
IV, R=Z=F, X=O, Y=S
V, R=Z=Cl, X=O, Y=S
VI, R=F, X=S, Y=O, Z=Cl
VII, R=Z=Cl, X=S, Y=O



VIII



IX, X=O
X, X=S

Fig. 1. Structure of Compounds

Table 1. Growth inhibition of analogues of TH-6038 and TH-6040 obtained by feeding fall armyworm larvae diets containing the compounds (expressed as percentage adult inhibition[a]).

	Concentration in the diet [b), c), d)]		
Compound No.	10 ppm	1 ppm	0.1 ppm
I (TH-6040)	100	100	100
II (TH-6038)	100	100	0
III	100	90	10
IV	100	100	50
V	100	100	60
VI	100	100	10
VII	20		
VIII	100	10	
IX	0		
X	20		

a) Values in table are results from 2 replicates.
b) Complete inhibition was obtained for all compounds at 50 and 100 ppm except for IX which was ineffective at 50 ppm.
c) Acetone check averaged 95% adult emergence.
d) Compound I gave 20% adult inhibition at 0.01 ppm.

placed in a holding room at 27°±1°C with a 50 ±5% RH, and observed daily for dead larvae. The dead larvae were removed and the head capsule measured to determine at what instar death had occurred. Larvae that survived treatment were held and observed for adult emergence.

Results and Discussion

Table 1 summarizes the growth inhibition produced by TH-6038 and TH-6040 analogues in the fall armyworm. Briefly, the structural modifications we investigated were: replacement of the urea oxygen of TH-6038 and TH-6040 by sulfur (benzoyl thioureas III and V, also IV); replacement of the benzoyl oxygen with sulfur (thiobenzoyl ureas, VI and VII); replacement of the benzoyl carbonyl group of I with an SO_2 group (sulfonylurea, VIII); and construction of O-aryl and S-aryl bonds in I and III (benzoxazole and benzothiazole analogs IX and X, respectively).

The most effective growth regulator for the fall armyworm was I (TH-6040). The benzoyl thioureas IV and V were only slightly less effective. The thiobenzoyl ureas VI and VII also had considerable activity (VI was more effective than VII) but as a class were generally less effective than the corresponding benzoyl thioureas. Compound VI (difluorothiobenzoyl) was more active than VII (dichlorothiobenzoyl), as TH-6040 is generally more effective than TH-6038; indeed, difluorobenzoyl derivatives generally seem more active than their dichlorobenzoyl counterparts (Wellinga *et al.*[5], Oliver *et al.*[8], and Yu and Kuhr[9]). However, we did find an exception to this apparent correlation in the activities of the benzoyl thioureas i. e., V>IV> III. This result contrasts with those obtained by Yu and Kuhr with these same thiobenzoyl ureas: they found the relative activities against seedcorn maggots *Hylemya platura* (Meigen), to be III>IV>V.

The sulfonylurea VIII had appreciable activity against fall armyworms, but the benzoxazole IX and benzothiazole X were only marginally effective as growth disruptors. Compound IX gave 100% adult inhibition at 100 ppm but was ineffective at 50 ppm. These results were in good agreement with those reported earlier by Oliver *et al.*[8].

Some of the morphological effects observed in the treated larvae were: old exuvia that could not be shed; retention of the head capsule, which stuck to the mandibles; and formation of a transparent bubble on the anterior notum beneath the cuticle that eventually ruptured and darkened because of air oxidation. In addition to these effects, the physical appearance of the treated immature insects was quite similar to that of viral infected larvae.

All the insects died during transformation from one instar to the next. A few larvae were able to molt from either the 3rd- to the 4th- or from the 4th- to the 5th-instar, but this was probably because late 3rd- or 4th-instars were inadvertently introduced into the media and consequently did not consume enough compound for full effects to be observed.

Summary

Eight sulfur-containing and related analogues of TH-6038 and TH-6040 (Dimilin®), were synthesized and evaluated as insect growth regulating agents for the fall armyworm, *Spodoptera frugiperda* (J. E. Smith). Three compounds were found to be as effective as TH-6038 when they were administered as dietary additives to 3rd-or 4th-instars. Of the sulfur analogues tested the two most effective larvacides were 1-(4-chlorophenyl)-3-(2,6-dichlorobenzoyl) thiourea and 1-(2, 6-difluorobenzoyl)-3-(4-fluorophenyl) thiourea. Both of these compounds were only slightly less effective than TH-6040 (the most active compound) in comparative tests.

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