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Insecticidal Effectiveness of Thiourea Derivatives

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As to about forty thiourea derivatives and some thiol compounds, effects on pupation and imago emergence of housefly larvae were examined by feeding and dipping tests. As the result, it was elucidated that N-benzoyl-N′-(*p*-dimethylamino)-phenylthiourea, 3-(*p*-chlorophenyl)-thioureide-propionic acid and N-(3,4-methylenedioxy)-benzoyl-N′-(3′,6′-dichloro-2′-methoxy)-phenylthiourea inhibited markedly the imago emergence, but inhibited the pupation little. Moreover, some of the effective compounds restrained the anterior inhibition, suggesting that the inhibitory activity was concerned with depriving of metals.

Thiourea has been known as an antimetabolite for larvae of housefly, *Musca domestica* L. (Negherbon, 1959). Some derivatives of thiourea exhibited a rodenticidal activity (Tokumitsu, 1973), an antituberculous activity (Fujikawa *et al.*, 1968, 1971, 1972), herbicidal (Everest-Todd, 1969; Pyne *et al.*, 1974), fungicidal (Noguchi *et al.*, 1969), and insect chemosterilantal (Oliver *et al.*, 1971, 1973; Fye and Oliver, 1974). These activities have been presumed to be due to depriving metals by thiourea (Uzumasa and Okura, 1950). However, it seems that there are no detailed studies on thiourea derivatives as insecticide. As an attempt to develop pesticides disturbing metamorphosis of noxious insects, present paper deals with the investigation on insecticidal effect of thiourea derivatives by feeding and dipping tests to housefly.

As the result, it was found that some derivatives inhibited strongly both of pupation and imago emergence, and not a few others inhibited the latter only.

EXPERIMENTALS

1. Feeding and dipping test

Compounds used were purchased or synthetized. The syntheses of the compounds will be reported elsewhere.

Feeding test

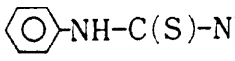
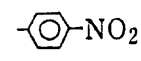
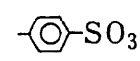
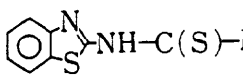
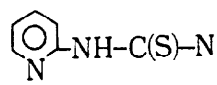
Each compound was added in the artificial diet comprised of powdered yeast and wheat bran (1 : 1) to give the desired final concentration. One hundred larvae on second day after hatching were placed in a beaker (100 ml) containing the diet (25 g), the testing compound (usually 50 mg) and water (25 ml), then reared at 25°C. The number of the pupation and the imago emergence were counted occasionally.

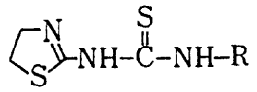
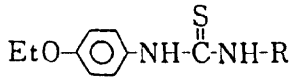
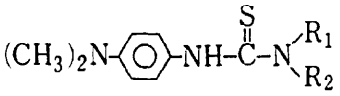
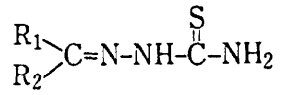
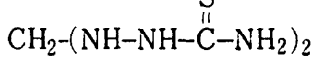
Dipping test

Twenty final instar larvae were dipped in 0.5 % acetone (or methanol) solution of each compound for 10 seconds. After 24 hours the number of pupae was counted, and the imago emergence was also examined afterwards.

The results obtained are presented in Tables 1 and 2. From these experiments, it was inferred that for the revelation of the activity in general one

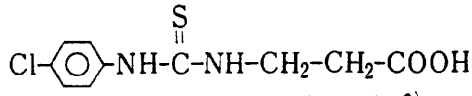
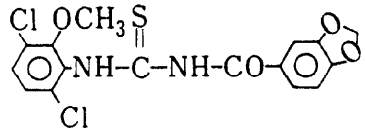
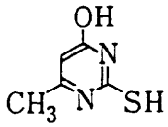
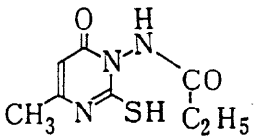
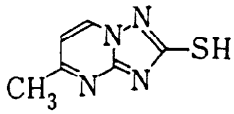
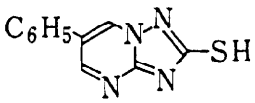
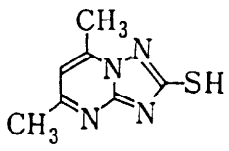
Table 1. Insecticidal effectiveness of thiourea derivatives to housefly (feeding test, 100 ppm otherwise indicated).

No	Compound	Substituent (R)	Pupa emergence (%)	Imago emergence (%)
	Thiourea			14[2]
	Thiosemicarbazide		0	0
1			92	58
2	〃		82	67
3	〃		38	23
4	〃		98	90
5	〃		79	95
6	〃		85	85
7	〃	$-CH_3$	83	84
8	〃	$-CH_2-CH=CH_2$	73	84
9	〃	$-C_2H_4OH$	91	67
10			97	89
11	〃	$-CH_2-CH=CH_2$	94	83
12			79	95
13	〃	$-CH_2-CH=CH_2$	98	81

14		- 	95	90
15	〃	$-CH_2CH=CH_2$	93	82
16		- 	93	100
17	〃	$-CH_2CH=CH_2$	96	77
		(R_1) (R_2)		
18		H H	97	72
19	〃	H OH	86	78
20	〃	H CH_3	97	75
21	〃	H C_2H_5	96	68
22	〃	C_2H_5 C_2H_5	68	73
23	〃	CH_3 CH_3	58	76
24	〃	H $CH_2CH_2CH_3$	64	51
25	〃	H - 	100	64
26	〃	H -  -Cl	82	82
27	〃	H -CO-	67	0
	〃	$+Zn(OAc)_2$[3]	*98*	*76*
28		H H	77	64
29	〃	CH_3 H	91	55
30	〃	C_2H_5 H	58	43
31	〃	CH_3 CH_3	57	30
32	〃	CH_3 CN	69	39
33			21	19

amino-group of thiourea-derivatives was requisite to be free (compounds 30, 31, 32, and 33). Compounds 27, 34, and 35 did not inhibit so much the pupation, while they inhibited strongly the imago emergence. As these compounds possess another functional group besides $>C=S$, it is supposed that this functional group contributes to the revelation of the activity.

On the other hand, compounds 3 and 45 which have NO_2 or CN group inhibited pupation in parallel with imago emergence. Thus, it was inferred that they acted non-specifically as a poison. Furthermore, the obvious delay of pupal and imago emerged stages was observed in comparison with control in some of these active compounds (Fig. 1).

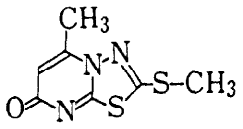
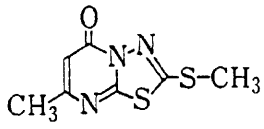
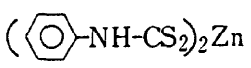
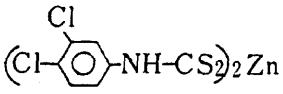
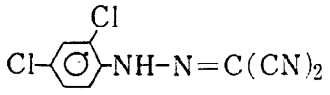
34		93	2
	$+Zn(OAc)_2$ [3]	*92*	*86*
	$+Cu(OAc)_2$ [4]	*96*	*71*
35		61	1
	$+Zn(OAc)_2$ [3]	*98*	*81*
	$+Cu(OAc)_2$ [4]	*100*	*81*
36		100	95
37		100	95
38		100	85
39		99	81
40		99	85

2. Morphological changes in the pupal stage

Morphological changes in the pupal stage of housefly larvae treated with these compounds are summarized in Table 3. Larvae fed with thiourea (in concentration of 100, 500 ppm) fell in the shape of pupa-larva intermediate. They pupated, retaining a form of larval stage, and a great many of them was a rod like shape, but some of them had curved form. By feeding phenobarbital, one of urea derivatives, larvae were restrained almost from the growth, and resulted in small pupae (in conc. of 500 ppm) which were one half or one third in comparison with normal pupae. These abnormal or small pupae could not emerge by half.

3. Effect on anterior inhibition

Housefly larvae are generally ligated at position I as shown in Fig. 2. This

41		95	75
42		80	85
43		100	69
44		0	
45		71	32
46	Phenobarbital	28	14[1]
	Control	97	90

[1] at 500ppm, [2] at 100ppm, [3] 5 equiv. mole, [4] 1 equiv. mole

Table 2. Dipping test of mature larvae.

Compound[1]	Pupation in 24 hrs. (%)	Imago emergence (%)
Thiourea	90	90
Phenylthiourea	30	70
1	80	90
3	100	80
27	45	90
30	65	80
31	50	85
32	75	85
33	60	80
34	45	80
35	50	100
44	60	60
45	0	5
Control (CH_3OH)	90	100
〃 (acetone)	95	100

[1] conc. 0.5 %

technique aims at placing prothoracic glands which secrete ecdysone in the anterior position, or destroying prothoracic glands (Chino *et al.*, 1974). However, ligated larvae showed sometimes abnormal pupation in which only posterior position pupated, or failed completely to pupate. This situation varies very much,

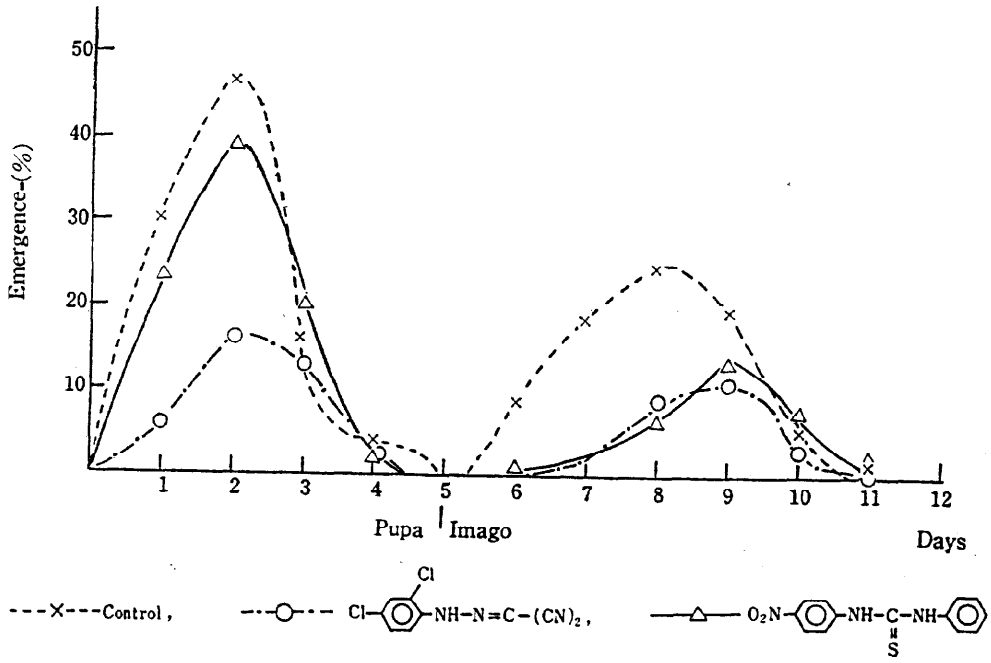


Fig. 1. Effect of thiourea derivatives on pupation and imago emergence of housefly larvae.

Table 3. Morphological change on puparium stage.

Compound	Treatment	Feature
Thiourea	oral (0.01% in diet)	pupa-larva intermediate
CH_2-(NH-NH-C(S)-NH_2)$_2$	〃	〃
4-Methyl-2-thiouracil	〃	small pupa
Piperonylbutoxide	dipping (0.1%)	pupa-larva intermediate
Phenobarbital	oral (0.05% in diet)	non ecdysis, small pupa

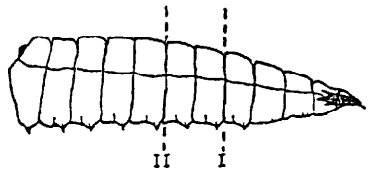


Fig. 2. Ligating position of larva.

if the ligating position is moved to the position II (Price, 1970). These abnormal pupations of ligated larvae have been named as an anterior inhibition. As the course of this inhibition, it was supposed recently by Ratnasiri and Fraenkel (1974) that oxygen-deficiency in the tissue by damage of trachea caused by the ligation was principal reason. They suggested also that supply of insufficient ecdysone, an excess of juvenile hormone and hormonal unbalance might participate in this phenomenon. Thereupon, the investigation on the effect of thiourea

Table 4. Effect of thiourea derivatives on anterior inhibition.

Compound	Pupa appeared at 48 hrs. after the treatment			
				
Thiourea	3	1	6	0
Phenylthiourea	0	7	2	1
+ Cu^{2+}	*1*	*3*	*5*	*1*[1]
+ Zn^{2+}	*1*	*0*	*8*	*1*[1]
1	3	1	5	1
27	2	1	5	2
+ Cu^{2+}	*1*	*0*	*3*	*6*[1]
+ Zn^{2+}	*0*	*0*	*8*	*2*[1]
34	1	5	4	0
+ Cu^{2+}	*2*	*1*	*5*	*2*[1]
+ Zn^{2+}	*0*	*1*	*6*	*3*[1]
44	5	2	1	2
45	0	5	2	3
Ecdysterone	1.3	1.7	5	2
Control	2	1.7	5	1.3

 →colored
→white

[1] Larvae were immersed beforehand for 20 sec. in 5% aqueous solution of copper or zinc acetate, then treated similarly as the other examples.

derivatives on the anterior inhibition was undertaken.

The testing method is as following: 10-30 final instar larvae were dipped in acetone containing each compound at a concentration of 0.5% for 10 sec. at 25°C, then ligated immediately at the position II. After 48 hours, the pupation of the ligated larvae was observed. Larvae were immersed beforehand for 20 sec. in 5% aqueous solution of copper or zinc acetate, then treated similarly with the sample solutions. The results obtained are illustrated in Table 4.

From these results, it was concluded that ecdysterone did not have any effect on the anterior inhibition, however, some of thiourea derivatives restrained markedly that phenomenon. Especially, bifunctional compounds such as phenylthiourea and 34, 45, namely the group which did not inhibit so much the pupation, but restrained the imago emergence, showed clearly this effect. This fact might be ascribed to that these compounds functioned essentially as metal-deprival. Furthermore, considering from the effect of compound 44, and 34 or 35 and zinc-acetate, zinc probably took a great part in this phenomenon.

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