phosphorothio- and -dithioic acid esters (Table IV). Dimethoate contained 6.13% OOSTMPDT and ethion contained 3.45% OOSTEPDT. The spectra of dimethoate and ethion showed numerous unidentified phosphorus contaminants to be present in the technical material. It was not possible to speculate on the nature of all the contaminants detected in the spectra of the technical products nor on their possible source. This was principally due to the lack of standards to effect confirmation, especially for the specific contaminants, and the fact that the history of the technical products was not known.

ACKNOWLEDGMENT

We thank Dr. C. Rodger for helpful discussion.

Registry No. OOOTMPT, 152-18-1; OOSTMPT, 152-20-5; OSSTMPDT, 22608-53-3; OOSTMPDT, 2953-29-9; OOOTEPT, 126-68-1; OOSTEPT, 1186-09-0; OOSTEPDT, 2524-09-6; *O,O,O,O*-tetramethyl pyrophosphate, 690-49-3; SULFOTMPP, 51120-35-5; *O,O,O,O*-tetraethyl pyrophosphate, 107-49-3; *O,O,O,O*-tetraethyl monothiopyrophosphate, 645-78-3; SULFOTEPP, 3689-24-5; ronnel, 299-84-3; fenitrothion, 122-14-5; methyl parathion, 298-00-0; diazinon, 333-41-5; dasanit, 115-90-2; parathion, 56-38-2; dimethoate, 60-51-5; malathion, 121-75-5; methidathion, 950-37-8; ethion, 563-12-2; phosalone, 2310-17-0.

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Received for review December 16, 1982. Accepted March 30, 1983. C.B.R.I. Contribution No. 1371. This work was presented at the Vth IUPAC International Congress of Pesticide Chemistry, Kyoto, Japan, Aug 29–Sept 4, 1982.

2-Acetylpyridine Thiosemicarbazones as Inhibitors of Ecdysis in *Oncopeltus fasciatus*: Structure–Activity Relationship Study

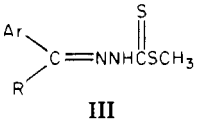
Albert B. DeMilo,* Robert E. Redfern, and Alexej B. Bořkovec

Effects of structural variations of [1-(2-pyridinyl)ethylidene]hydrazide of 1-pyrrolidinecarbothioic acid (**23**) on ecdysis of *Oncopeltus fasciatus* were examined in 50 related compounds. Marked ecdysis-inhibiting effects were elicited by substituted thiosemicarbazones of 2-acetyl-, 2-propionyl-, and 2-butyrylpyridine but 2-formyl, 2-phenylacetyl, and 2-benzoyl derivatives were inactive. Essential for activity was the thiocarbonyl moiety: analogues containing C=O or C=NH groups were inactive. Substitutents on the thiosemicarbazone portion of the molecule had variable effects: the 1-piperidinecarbothioic acid analogue of **23** exceeded the activity of **23**, and five other analogues were as active as **23**. Hydrogenation of the exocyclic C=N in **23** did not reduce its biological activity.

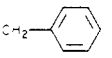
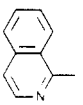
Recently, the broad spectrum of biological activity of thiosemicarbazones was extended to include inhibition of ecdysis in certain insects (Kelly et al., 1982). Although ecdysis and the entire molting process in insects can be disrupted by juvenoids (Sláma et al., 1974), ecdysteroids (Kelly et al., 1981), or chitin synthesis inhibitors (Mitsui et al., 1980), physiological and biochemical effects of thiosemicarbazones suggest that their mechanism of action is different from those proposed for the other groups of compounds (Redfern et al., 1981, 1982). Because Kelly et al. (1982) have shown that various thiosemicarbazones of 2-acetylpyridine differed greatly in their effects on the large milkweed bug, *Oncopeltus fasciatus* (Dallas), we synthesized a series of variously substituted thiosemicarbazones and determined their biological effects in that species. Herein we report results of structure–activity

Insect Reproduction (A.B.D. and A.B.B.) and Livestock Insect (R.E.R.) Laboratories, Agricultural Research Service, U.S. Department of Agriculture, Beltsville, Maryland 20705.

Table I. Chemical Data for Hydrazinecarbodithioate Intermediates

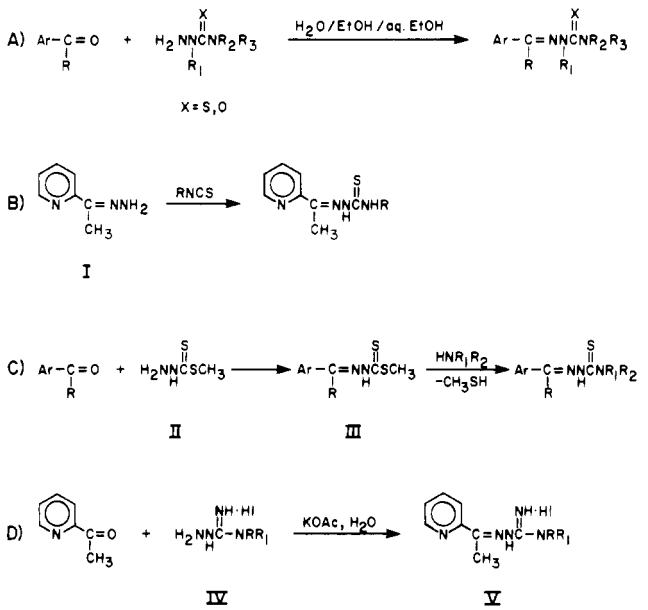


III

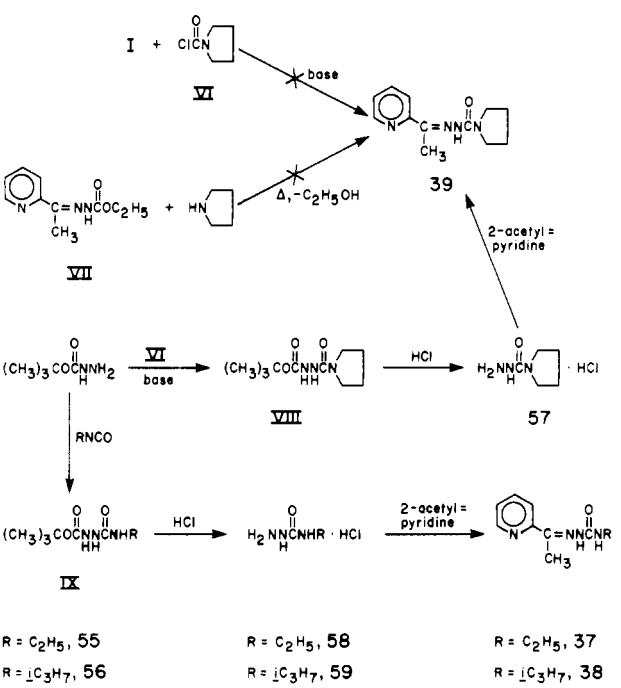
compound no.	Ar	R	yield, %[a]	mp, °C	recrystn solvent
1		C_2H_5	75	111-112	MeOH
2			38	131-132.5	EtOH
3		CH_3	65	200.5-201	EtOAc
4		CH_3	58	111.5-113.5	hexane-EtOAc
5		CH_3	62	146-148	
6		CH_3	85	184.5-187.5 dec	EtOAc

[a] Recrystallized material, except 5.

Scheme I. Synthetic Methods for Thiosemicarbazones and Analogues



Scheme II. Synthetic Methods for Semicarbazones of 2-Acetylpyridine



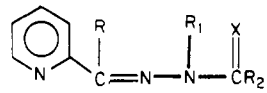
relationship studies of this group of compounds.

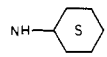
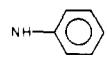
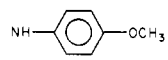
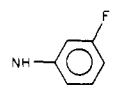
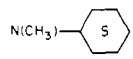
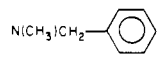
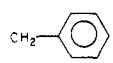
MATERIALS AND METHODS

Chemicals. Tables I–III contain uncorrected melting points for all new compounds and for some known compounds when the literature data differed substantially from ours. Analyses for carbon, hydrogen, and nitrogen in new compounds were satisfactory (±0.4% of theory) and were performed by Galbraith Laboratories, Knoxville, TN.

Except for 1-acetylisoquinoline (a gift from D. Klayman, Walter Reed Army Institute of Research), ketones used in this study were purchased or were synthesized by (a) treatment of 2-pyridinyllithium with the appropriate alkylnitrile followed by acid hydrolysis of the resulting ketimine (Wibaut et al., 1951) or (b) oxidation by active manganese dioxide (Turner, 1954) of pyridinylmethanols derived from 2-pyridinecarboxaldehyde treated with alkyl Grignard reagents. Intermediate thiosemicarbazides were purchased or prepared by standard methods. Syntheses of thiosemicarbazides **51–54** are described in this section. Most compounds listed in Tables I–III were prepared by methods described by Klayman et al. (1979a,b), and the synthetic approaches are outlined in Scheme I. For preparing hydrazinecarbodithioate intermediates III (Table I), we preferred methanol as the solvent: a model preparation is described for **6**. Intermediate **4** was prepared by azeotropic distillation of water from a refluxing benzene solution containing a trace of *p*-toluenesulfonic acid and equimolar amounts of methyl hydrazinecarbodithioate (II; Klayman et al., 1979a) and 2-acetylpyrrole. Hydrazinecarbodithioate intermediates not listed in Table I are known compounds. Guanidinylhydrazones **40** and **41** (Scheme I, V) were prepared by heating (ca. 65 °C, 0.2–0.5 h) an aqueous mixture of the appropriate aminoguanidine

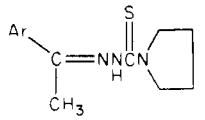
Table II. Chemical and Biological Data for Thiosemicarbazones and Related Compounds

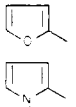
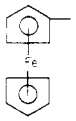


compd no.	X	R	R_1	R_2	method of prepn[a]	yield, %[b]	mp, °C	recrystn solvent	minimal effective dose,[c] μg/nymph
7	S	CH_3	H	NH_2	A	30			I
8	S	CH_3	H	$NHCH_3$	A	77	180-181.5	EtOH	50
9	S	CH_3	H	NHC_2H_5	A, B	54[d]			1.0
10	S	CH_3	H	NH-*n*-C_3H_7	A[e]	56	85-91	2-propanol	0.5
11	S	CH_3	H	NH-*i*-C_3H_7	C	48			1.0
12	S	CH_3	H	NH-*n*-C_4H_9	A, B	42[d]	104.5-106.5	benzene-hexane	5.0
13	S	CH_3	H	NH-*n*-C_7H_{15}	A	57	98-100.5	benzene-hexane	5.0
14	S	CH_3	H		A	35			5.0
15	S	CH_3	H		B	73			I
16	S	CH_3	H		B	43			I
17	S	CH_3	H		B	72			I
18	S	CH_3	H	$N(CH_3)_2$	C	69			0.5
19	S	CH_3	H	$N(CH_3)$-*n*-C_4H_9	C	38			1.0
20	S	CH_3	H		*f*				0.1
21	S	CH_3	H		C	57			5.0
22	S	CH_3	H	$N(C_2H_5)_2$	*f*				0.1
23	S	CH_3	H		C	79	154-155.5 dec[g]	MeOH	0.1
24	S	CH_3	H		*f*				0.5
25	S	CH_3	H		C	34	186-188 dec	MeOH	50
26	S	CH_3	H		C	83	155 dec	EtOH	0.05
27	S	H	H		C	52			I
28	S	C_2H_5	H		C	42	125.5-129	cyclohexane	0.1
29	S	*i*-C_3H_7	H		A	23	161-163	EtOAc	50
30	S	*n*-C_3H_7	H		A	44	115-118	MeOH	0.1
31	S		H		C	33	144-145	MeOH	I
32	S		H		C	49	195-196	acetonitrile	I
33	S	CH_3	CH_3	NH-*i*-C_3H_7	A[e]	57	69-72	hexane	0.5
34	S	CH_3	CH_3	$N(CH_3)_2$	A	43	74.5-77.5	MeOH	50
35	S	CH_3	CH_3		A	66	95.5-96.5	heptane	50
36	O	CH_3	H	NH_2	A	26			50
37	O	CH_3	H	NHC_2H_5	A	24	154.5-156.5	cyclohexane	I
38	O	CH_3	H	NH-*i*-C_3H_7	A	75	146-147	cyclohexane	I
39	O	CH_3	H		A	53	157-158.5	cyclohexane	I
40	NH·HI	CH_3	H	$N(CH_3)_2$	D	72	197-198	acetonitrile	I
41	NH·HI	CH_3	H		D	44	223.5-225 dec	acetonitrile	I

[a] See Scheme I. [b] Values represent recrystallized yields from the last reaction of the sequence. [c] See Bioassay; I = inactive at 50 μg/nymph. [d] By method A. [e] Azeotropic distillation of water from a benzene solution of precursors plus a trace of acid catalyst (PTSA). [f] Provided by D. Klayman, Walter Reed Army Institute of Research. [g] Sinters at 144.5 °C and then melts briskly at 154-155.5 °C with decomposition.

Table III. Chemical and Biological Data for 1-Pyrrolidinylthiosemicarbazones



compound no.	Ar	yield, %[a]	mp, °C	minimal effective dose,[b] μg/nymph
23				0.1
42		73	149.5-150	I
43		75	185-185.5 dec	I
44		74	137.5-138.5	10
45		73	150-151	I
46		33	166.5-169	10
47		85	141.5-143[c]	50
48		72	181.5-183	0.1
49		82	186.5-188	0.5
50		67	135-136	50

[a] Prepared by method C. All compounds recrystallized from methanol except 46 (EtOH). [b] See Bioassay; I = inactive at 50 μg/nymph. [c] After drying under high vacuum (80 °C).

salt IV (Jensen and Pedersen, 1961), 2-acetylpyridine, and potassium acetate. Hydriodide salts of the products were obtained in both cases.

Synthetic methods for semicarbazones **37–39** are outlined in Scheme II. Because treatment of 2-acetylpyridine hydrazone (I) with 1-pyrrolidinecarbonyl chloride (VI) in the presence of an acid acceptor or heating carbazate VII with pyrrolidine did not yield **39**, the semicarbazones **37–39** were prepared by treating the appropriate semicarbazide hydrochloride (**57–59**, obtained by acid hydrolysis of the corresponding *tert*-butyl hydrazinecarboxylate VIII or IX) with 2-acetylpyridine in a NaOAc-buffered aqueous medium. Treatment of thiosemicarbazones **18** and **23** with sodium borohydride in methanol gave reduction products **60** and **61**, respectively (details are given in this section). After this work was submitted for publication, a similar synthetic method was published for **60**, **61**, and related reduction products (Klayman et al., 1983). Our melting points for **60** and **61** are in good agreement with those reported by Klayman et al.

1-Pyrrolidinecarbothioic Acid Hydrazide (**51**). A mixture of methyl hydrazinecarbodithioate (II, 12.2 g, 0.1 mol; Klayman et al., 1979a), pyrrolidine (7.1 g, 0.1 mol), and ethanol (100 mL) was boiled under reflux for 7 h. The hot mixture was filtered and cooled to allow crystallization of **51** (6.3 g, 43%; mp 173.5–174.5 °C dec). Recrystallization from ethanol gave the analytical sample: mp 178–180 °C dec. Nardi et al. (1967) reported mp 177–178 °C.

1-Pyrrolidinecarbothioic Acid 1-Methylhydrazide (**52**). A solution of 1-pyrrolidinethiocarbonyl chloride (6.9 g, 46 mmol; Ried et al., 1954) in methylene chloride (30 mL) was added dropwise over a 0.5-h period to a solution of methylhydrazine (4.2 g, 92 mmol) in methylene chloride (15 mL). After being stirred at room temperature for 2 h, the mixture was washed with water (2 × 30 mL) and brine (30 mL). The organic layer was separated and dried ($MgSO_4$) and the solvent evaporated to give a solid product. Recrystallization from 2-propanol gave 4.0 g (55%) of **52**: mp 72.5–74 °C. Anal. Calcd for $C_6H_{13}N_3S$: C, 45.25; H, 8.23; N, 26.39. Found: C, 45.35; H, 8.34; N, 26.43.

N,N,1-Trimethylhydrazinecarbothioamide (**53**). **53** was prepared in a 61% yield from dimethylthiocarbamoyl chloride and methylhydrazine in the manner described for **52**. Recrystallization from 2-propanol gave the analytical sample: mp 61–62 °C. Anal. Calcd for $C_4H_{11}N_3S$: C, 36.07; H, 8.32; N, 31.54. Found: C, 36.18; H, 8.21; N, 31.48.

1-Methyl-N-(1-methylethyl)hydrazinecarbothioamide (**54**). **54** was prepared from methylhydrazine and isopropyl isothiocyanate by the method of Jensen et al. (1968): mp 118–119.5 °C (benzene-cyclohexane); reported mp 108–109 °C.

[1-(1-Isoquinolinyl)ethylidene]hydrazinecarbodithioic Acid Methyl Ester (**6**). To a warmed (ca. 40–45 °C) solution of methyl hydrazinecarbodithioate (II, 2.65 g, 21.7 mmol) in methanol (15 mL) was added 1-acetylisoquinoline (3.72 g, 21.7 mmol). Within 0.25 h the product precipitated from solution. After being allowed to stand at room temperature for 16 h the mixture was cooled and the product collected by filtration. Recrystallization from ethyl acetate gave 5.11 g (85%) of **6**: mp 184.5–187.5 °C dec. Anal. Calcd for $C_{13}H_{13}N_3S$: C, 56.70; H, 4.76; N, 15.26. Found: C, 56.78; H, 4.81; N, 15.28.

[1-(2-Pyridinyl)ethylidene]hydrazinecarboxylic Acid Ethyl Ester (*VII*). A mixture of 2-acetylpyridine (12.1 g, 0.1, mol), ethyl hydrazinecarboxylate (10.4 g, 0.1 mol), and ethanol (100 mL) was boiled under reflux for 3 h. Removal of the solvent and recrystallization of the residue from 2-propanol gave 13.5 g (65%) of VII: mp 111–113.5 °C. A second recrystallization from 2-propanol gave pure VII: mp 114–114.5 °C. Anal. Calcd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.86; H, 6.35; N, 20.20.

1-Pyrrolidinecarboxylic Acid 2-[(1,1-Dimethylethoxy)carbonyl]hydrazide (*VIII*). To a mixture of *tert*-butyl hydrazinecarboxylate (6.6 g, 0.05 mol), pyridine (5 mL), and benzene (50 mL) was added 1-pyrrolidinecarbonyl chloride (VI, 6.7 g, 0.05 mol). The mixture was heated under reflux for 1.5 h, cooled, and filtered. The solvent was removed and the residue was combined with the filter cake (benzene insolubles). The combined solids were triturated with water and filtered to give 5.2 g (52%) of crude VIII: mp 192–193 °C. The analytical sample was recrystallized from 2-propanol: mp 192.5–193.5 °C. Anal. Calcd for $C_{10}H_{19}N_3O_3$: C, 52.39; H, 8.35; N, 18.33. Found: C, 52.34; H, 8.13; N, 18.35.

2-[(Ethylamino)carbonyl]hydrazinecarboxylic Acid 1,1-Dimethylethyl Ester (**55**). Ethyl isocyanate (7.1 g, 0.1 mol) was added to benzene (50 mL) containing *tert*-butyl hydrazinecarboxylate (13.2 g, 0.1 mol). The mixture was cooled and the product collected by filtration (18 g, 89%; mp 136–136.5 °C). Crude **55** was used without further purification. Anal. Calcd for $C_8H_{17}N_3O_3$: C, 47.28; H, 8.43; N, 20.67. Found: C, 47.34; H, 8.46; N, 20.69.

1,1-Dimethylethyl 2-[[(1-Methylethyl)amino]carbonyl]hydrazinecarboxylate (**56**). **56** was prepared in the same manner as **55** from isopropyl isocyanate and

tert-butyl hydrazinecarboxylate. Crude **56** (yield, 97%) was used without further purification. Recrystallization from water gave the analytical sample: mp 109–110 °C. Anal. Calcd for $C_9H_{19}N_3O_3$: C, 49.75; H, 8.81; N, 19.34. Found: C, 49.74; H, 8.85; N, 19.36.

1-Pyrrolidinecarboxylic Acid Hydrazide Monohydrochloride (**57**). To a mixture of VIII (3.1 g, 13.5 mmol) and 95% ethanol (13 mL) was added concentrated hydrochloric acid (2.25 mL, 27 mmol). The mixture was heated under reflux for 0.5 h and then concentrated to dryness. Recrystallization of the residue from ethanol gave 1.6 g (72%) of **57**: mp 182–184 °C; analytical sample, mp 190–192 °C. Nardi et al. (1967) reported mp 192 °C. Anal. Calcd for $C_5H_{12}ClN_3O$: C, 36.26; H, 7.30; N, 25.37; Cl, 21.41. Found: C, 36.28; H, 7.08; N, 25.35; Cl, 21.65.

N-Ethylhydrazinecarboxamide Monohydrochloride (**58**). **58** was prepared similarly to **57** from **55** (yield, 76%): mp 140.5–142 °C (EtOH). Ohme and Preuschhof (1971) reported mp 134–136 °C. Anal. Calcd for $C_3H_{10}ClN_3O$: C, 25.81; H, 7.22; N, 30.10. Found: C, 25.87; H, 7.38; N, 30.10.

N-(1-Methylethyl)hydrazinecarboxamide Monohydrochloride (**59**). **59** was prepared similarly to **57** from **56** (yield, 76%): mp 168–171 °C (EtOH). Ohme and Preuschhof (1971) reported mp 165–169 °C.

N,N-Dimethyl-2-[1-(2-pyridinyl)ethyl]hydrazinecarbothioamide (**60**). To a stirred mixture of **18** (16.5 g, 74.2 mmol) and methanol (1.4 L) was added, portionwise, sodium borohydride (3.3 g, 87 mmol). After the addition, the mixture was stirred for 0.5 h and the solvent removed in vacuo. Water (200 mL) was added to the residue, and the product was extracted into three successive portions (100 mL) of methylene chloride. The extracts were combined, washed with saturated brine, and dried ($MgSO_4$). Removal of the solvent gave a solid product that was recrystallized from ethyl acetate: 13.3 g (80%), mp 140–140.5 °C. Anal. Calcd for $C_{10}H_{16}N_4S$: C, 53.54; H, 7.19; N, 24.98. Found: C, 53.59; H, 7.38; N, 24.94.

1-Pyrrolidinecarbothioic Acid 2-[1-(2-Pyridinyl)ethyl]hydrazide (**61**). To a stirred solution of **23** (2.48 g, 0.01 mol) in methanol (200 mL) was added, portionwise, sodium borohydride (0.9 g, 0.024 mol) over a 1-h period. The solution was concentrated by rotary evaporator to one-fourth of its original volume and poured into cold water, and the precipitated product was collected by filtration. Recrystallization from ethyl acetate gave 1.56 g (62%) of pure **61**: mp 172–173 °C. Anal. Calcd for $C_{12}H_{18}N_4S$: C, 57.57; H, 7.25; N, 22.38; S, 12.80. Found: C, 57.69; H, 7.27; N, 22.39; S, 13.09.

Bioassay. The insects, *O. fasciatus*, from our laboratory colony, were reared at 27 ± 1 °C and 50 ± 5% relative humidity under a 14 h light–10 h dark photoperiod. Field-collected milkweed seed and water in cotton-stoppered vials were supplied ad libitum. Newly ecdysed fifth stage nymphs were collected over a 4–6-h period beginning at 7 a.m. on the day they were to be used and kept in flasks without food or water until treatment. Test compounds were dissolved in a 1:1 (v/v) mixture of acetone and dimethyl sulfoxide (Me_2SO) because the solubility of some of them in acetone was marginal. Solutions (1 μL/nymph) containing 0.001–50 μg of the compound were applied with a calibrated glass micropipet to the dorsal side of the last three abdominal segments. Treated insects, five per test, were held in 0.24-L ice-cream cartons capped with 9-cm clear plastic Petri dishes and supplied with milkweed seed and water. Control insects were handled in exactly the same way except that they were treated with solvent only. The insects were inspected daily until they died, they molted, or the test was terminated. With doses higher than 1 μg/nymph, three replicates were made; with lower doses, five replicates were performed. Because dose–response relationships were unsatisfactory, we considered a compound active if doses of 50 μg/nymph or less prevented normal ecdysis in at least 2 out of 15 or 3 out of 25 treated insects (12–13%); doses with lower effects were considered inactive. Average mortality in controls was 5% and did not exceed 20% for doses mentioned in Tables II and III. Since only minimally active doses were utilized in the present study, the majority of test data was omitted here but can be obtained by request from the authors.

RESULTS AND DISCUSSION

The main objective of our study was to determine how the ecdysis-inhibiting activity of 2-acetylpyridine thiosemicarbazones was affected by structural modification. Since Kelly et al. (1982) showed that a pyrrolidinyl analogue, **23**, was one of the most effective ecdysis inhibitors, we chose **23** as a key compound to guide syntheses of related materials for the elucidation of structure–activity relationships within this class of compounds.

Previously, Kelly et al. (1982) showed that the expected hydrolysis products of **23**, 2-acetylpyridine and 1-pyrrolidinecarbothioic acid hydrazide (**51**), were inactive. Similar test results were obtained for other ketones and thiosemicarbazides (Scheme I, A) used in this study. We also tested the hydrazinecarbodithioate intermediates listed in Table I and found them inactive except **1**, which reduced ecdysis by 80% at the highest dose of 50 μg/nymph but was ineffective at lower doses.

The general structure in Table II shows substituents R, R_1, R_2, and X that had profound influence on ecdysis-inhibiting properties of the compounds. Considerable structural differences can be seen in the type of amino group (R_2) that provided highly effective compounds. With X, R, and R_1 remaining constant (**7–26**), highest activity was exhibited with compounds bearing dialkylamino groups (**18**, **20**, and **22**) or cyclic amino groups (**23**, **24**, and **26**). Surprisingly, the morpholino analogue **25** was inactive at the highest dose tested. Thiosemicarbazones bearing monoalkylamino (**9–13**) or cyclohexylamino (**14**) substituents were also effective but generally to a lesser extent than those bearing dialkylamino or cyclic amino groups. Clearly, a phenyl substituent on the amino nitrogen was detrimental to activity (**15–17**).

Klayman et al. (1979a) indicated that antimalarial activity was reduced but not eliminated when 2-propionylpyridine thiosemicarbazones were used instead of analogous 2-acetyl derivatives. In our study, the acetyl (**23**), propionyl (**28**), and butyryl (**30**) derivatives were equally active. However, activity was substantially reduced for the isobutyryl derivative **29** and was absent in the formyl (**27**), phenylacetyl (**31**), and benzoyl (**32**) derivatives.

Methylation of the hydrazine nitrogen ($R_1 = CH_3$, **33–35**) did not affect the activity of **11** but drastically reduced activities of **18** and **23**. The thiocarbonyl moiety (X = S), however, appears essential for high activity: the oxygen analogues (X = O, **37–39**) of **9**, **11**, and **23** and the nitrogen analogues (X = NH, **40**, **41**) of **18** and **23** were inactive. To clarify whether the loss of activity of **40** and **41** was caused by decreased penetration of the hydriodide salts through the insect's cuticle, the corresponding free bases of **40** and **41** were prepared and tested: both were inactive.

The effect of the 2-pyridinyl moiety is not as unique for ecdysis-inhibiting properties as it appears to be for antimalarial effects (Klayman et al., 1979a). Other aromatic systems shown in Table III (**42–50**) yield active compounds, most conspicuously the pyrazinyl analogue **48**.

Also apparently not essential to activity is the unsaturation of the exocyclic carbon–nitrogen double bond, i.e., reduced thiosemicarbazone **18**, *N,N*-dimethyl-2-[1-(2-pyridinyl)-ethyl]hydrazinecarbothioamide (**60**), and reduced **23**, 2-[1-(2-pyridinyl)ethyl]hydrazide of 1-pyrrolidinecarbothioic acid (**61**), were both active at the minimal dose of 0.1 μg/nymph.

In summary, we have identified several critical features of thiosemicarbazone derivatives that influence biological activity. Also, we report six additional analogues that elicit appreciable ecdysis-inhibiting effects in *O. fasciatus* when topically applied in doses as low as 0.05–1.0 μg/nymph. This work may serve as a useful guide for the synthesis of additional candidate thiosemicarbazone insect growth regulators.

Registry No. **1**, 81742-04-3; **2**, 85748-35-2; **3**, 85748-36-3; **4**, 85748-37-4; **5**, 60273-81-6; **6**, 85748-38-5; **7**, 6839-90-3; **8**, 75013-64-8; **9**, 32646-35-8; **10**, 75013-65-9; **11**, 32646-25-6; **12**, 75013-66-0; **13**, 75013-69-3; **14**, 70618-53-0; **15**, 63698-06-6; **16**, 70618-31-4; **17**, 70618-03-0; **18**, 71555-14-1; **19**, 71555-17-4; **20**, 71555-19-6; **21**, 71555-21-0; **22**, 71592-42-2; **23**, 71555-26-5; **24**, 71555-29-8; **25**, 71555-39-0; **26**, 71555-28-7; **27**, 16552-99-1; **28**, 85748-39-6; **29**, 85748-40-9; **30**, 85748-41-0; **31**, 85748-42-1; **32**, 85748-43-2; **33**, 85748-44-3; **34**, 75013-88-6; **35**, 85748-45-4; **36**, 14534-93-1; **37**, 85748-46-5; **38**, 85748-47-6; **39**, 85748-48-7; **40**, 85748-49-8; **41**, 85762-03-4; **42**, 85748-50-1; **43**, 85748-51-2; **44**, 85748-52-3; **45**, 85748-53-4; **46**, 85748-54-5; **47**, 85748-55-6; **48**, 85748-56-7; **49**, 85748-57-8; **50**, 85748-34-1; **51**, 6499-14-5; **52**, 85748-58-9; **53**, 2652-62-2; **54**, 21198-45-8; **55**, 85748-59-0; **56**, 85748-60-3; **57**, 85748-61-4; **58**, 35578-80-4; **59**, 35578-82-6; **60**, 83476-77-1; **61**, 83476-78-2; II, 5397-03-5; VI, 1192-63-8; VII, 85748-62-5; VIII, 85748-63-6; pyrrolidine, 123-75-1; 1-pyrrolidinethiocarbonyl chloride, 19009-42-8; dimethylthiocarbamoyl chloride, 16420-13-6; 1-acetylisoquinoline, 58022-21-2; 2-acetylpyridine, 1122-62-9; ethyl hydrazinecarboxylate, 4114-31-2; *tert*-butyl hydrazinecarboxylate, 870-46-2; isopropyl isocyanate, 1795-48-8; methylhydrazine, 60-34-4.

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Received for review December 3, 1982. Accepted March 28, 1983. Mention of proprietary products does not constitute an endorsement by the U.S. Department of Agriculture.

Pyrethroid Insecticides Derived from [1,1′-Biphenyl]-3-methanol. 2. Heteroaromatic Analogues

Ernest L. Plummer

The *cis*-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylic acid (DVA) esters of seven heterocyclic analogues of [1,1′-biphenyl]-3-methanol have been prepared. Activities for topical application against three insect species, southern armyworm, Mexican bean beetle, and milkweed bug, have been determined. The results of quantitative structure–activity studies confirm our earlier findings that for meta-monosubstituted benzyl esters of DVA the variance in southern armyworm response is correlated with the substituent lipophilicity. This provides further evidence that good activity can be obtained without a bridging atom for aromatic substituents of meta-substituted benzyl alcohols.

A common feature in most active pyrethroid esters is an alcohol portion that contains two centers of unsaturation separated by a bridging atom. Qualitative discussions of structure–activity relationships of pyrethroids have generally pointed to this feature as a requirement for good insecticidal activity (Elliott, 1969; Elliott et al., 1974). Recently a series of pyrethroid esters have been prepared from [1,1′-biphenyl]-3-methanol (Plummer and Pincus, 1981). These esters were used to demonstrate that good insecticidal activity can be obtained when the alcohol has two centers of unsaturation even if it lacks an atom bridging these centers.

We now wish to report an extention of this study in which the second center of unsaturation in a series of meta-monosubstituted benzyl esters is a heteroaromatic ring. In addition, we present quantitative structure–activity relationship (QSAR) data relating to our earlier contention that the variance in southern armyworm re-

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0021-8561/83/1431-0718$01.50/0