Insecticidal and Miticidal Activity of Arylthioformamidines

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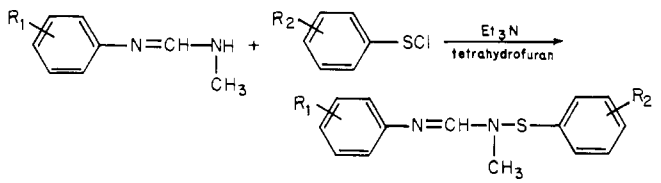
The ovicidal, miticidal, larvicidal, and repellent activities of a series of *N*-methyl-*N*-arylthio-*N'*-arylformamidines were investigated. *N'*-(2,4-Dimethylphenyl)-*N*-methyl-*N*-arylthioformamidines were significantly more effective against adult mites than their corresponding *N'*-(2-methyl-4-chlorophenyl)-*N*-methyl-*N*-arylthioformamidine analogues while the latter compounds proved to be the superior ovicidal and first stage lepidopterous larvicidal chemicals. Of the two mite repellent activities observed, "spinoff" was associated with the nature of the arylthio substituent while "walkoff" was a function of the formamidine portion of the molecules. Though high activities were associated with many of the compounds, *N'*-(2-methyl-4-chlorophenyl)-*N*-methyl-*N*-(thiophenyl)formamidine demonstrated the best spectrum of activity.

Formamidines produce biological responses that are unique among the known classes of insecticides and acaricides. They are represented commercially by only a few compounds, the most notable of which are chlordimeform and amitraz. We have synthesized a series of *N*-methyl-*N*-arylthio-*N'*-arylformamidines, members of which have proved to be highly effective and potentially useful pest control agents. We wish to describe their synthesis and correlate structure with miticidal, ovicidal, lepidopterous larvicidal, and mite repellent activity.

SYNTHESIS OF COMPOUNDS

The *N*-methyl-*N*-arylthio-*N'*-arylformamidines listed in Table I were prepared by the nucleophilic displacement reaction of an *N*-methyl-*N'*-arylformamidine (Harrison et al., 1970) on an arylsulfenyl chloride (Kharasch, 1960) in the presence of a tertiary amine in a suitable solvent, usually tetrahydrofuran, at 0 °C.



The compounds synthesized, with few exceptions, are oils which are obtained in nearly quantitative yield essentially analytically pure.

FORMULATION

Initial two-spotted spider miticidal evaluations were conducted using a 5% v/v wet water (0.132% w/w water solution of Tween 20 emulsifier, Atlas Chemical) solution of acetone. Subsequent studies indicated that some of the compounds were not stable under this condition, especially when concentrations fell below 100 ppm active. Therefore, all additional miticidal and insecticidal tests were conducted by suspending 10–20% w/w emulsifiable concentrate (EC) formulations of each chemical in water; these emulsions were further diluted with water to yield final dilutions of various parts per million. The EC's were prepared using 10–20% active chemical, 5% Sponto AK-3022 emulsifier (Witco Chemical Corp.), 3% epichlorohydrin, and 72–82% xylene; available data indicated a significant stabilizing effect with this formulation.

TEST METHODS

Mites. *Adults.* Seedling lima bean plants were infested with mobile forms, the stems were ringed with lanolin to try to confine the mites, and then both surfaces of the leaves were sprayed to drip. Walkoff (mites walking off the plant and becoming stuck in the lanolin) and spinoff (mites spinning down off the lower surface of the leaf) were recorded 24 and 5 h posttreatment, respectively. Mortality readings were assessed 4 days later.

Ova. Seedling lima bean plants upon which adult mites had been allowed to oviposit for up to 16 h were dipped into the desired concentration of the test chemical following removal of the mobile forms via a directed air stream. Mortality readings were made after 4 days.

Green Peach Aphid. Naturally infested seedling pepper plants were sprayed to drip. The percent reduction in the population was assessed 2 days posttreatment.

Lepidopterous Insects. *First-Instar Larvae.* Young seedling lima bean foliage was dipped into the desired chemical concentration and allowed to dry and a single leaf was placed atop a moistened filter disk in a petri dish. Larvae less than 1 day old were placed atop the leaf, the dish was closed and sealed, and the larvae were held for 2–3 days at which time mortality was recorded.

Ova. Pieces of paper toweling upon which adult cabbage looper, bollworm, or tobacco budworm moths had been allowed to oviposit for up to 12 h were dipped into water emulsions of the test chemical, allowed to dry, and then sealed inside petri dishes. The percent control of egg hatch was recorded 3–5 days later. The procedure used for the southern armyworm ovicidal evaluations was essentially the same as that described for the mite ovicide studies, i.e., lima bean plants upon which newly laid egg masses had been deposited were dipped and held for mortality counts.

RESULTS AND DISCUSSION

Biological effectiveness (Tables I and II) is indicated by relative LC_{50} values calculated by probit analysis and corrected to a standard. In some cases where only approximations were possible, the LC_{50} values are shown as ranges or as values greater or less than experimental observations. Despite the use of replicated and repeated experiments, insecticidal and miticidal evaluations using the formamidines are difficult at best due to the fact that, in general, they display repellent effects, kill slowly, show only a gradual dose–reponse slope, and vary markedly in their toxicity to different growth stages of the same species.

The importance of the 2,4 substitution of the *N'*-aryl ring of the formamidines in imparting potent acaricidal and insecticidal activity has been pointed out by previous authors (Knowles et al., 1972; Harrison et al., 1973; Knowles and Roulston, 1973; Atkinson and Knowles, 1974; Stone et al., 1974) and is supported by the data presented in Table I. Clearly, the *N'*-(2,4-dimethylphenyl)-*N*-methyl-*N*-(arylthio)formamidines (VI, IX, XII, XV, XVIII,

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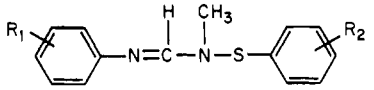
Table I. Chemical Data[a] and Biological Activities of *N*-Methyl-*N*-arylthio-*N'*-arylformamidines



Compd	R_1	R_2	Mp, °C	LC_{50}, ppm 2SSM-A[b]	2SSM-O	CRM-A	SAW-1stL	SAW-O[c]
I	2-CH_3	H	Oil	100-500				
II	3-Cl	H	Oil	>1000				
III	3-CF_3	H	Oil	>1000				
IV	4-*n*-C_4H_9	H	Oil	>1000				
V	3-CF_3, 4-Cl	H	Oil	>1000				
VI	2,4-$(CH_3)_2$	H	Oil	13-A-A	10-30	6	>20	>20
VII	2-CH_3, 4-Cl	H	Oil	42-B-C	<3	14	7	<5
VIII	2-CH_3, 4-Br	H	Oil	70-B-D	7	17	5-20	5-20
IX	2,4-$(CH_3)_2$	3-CH_3	Oil	25-B-A	14	11	>20	>20
X	2-CH_3, 4-Cl	3-CH_3	Oil	61-C-A	<3	10	5	<5
XI	2-CH_3, 4-Br	3-CH_3	Oil	123-C-C	<3	27	>20	5-20
XII	2,4-$(CH_3)_2$	4-Cl	Oil	32-B-B	13	7	>20	>20
XIII	2-CH_3, 4-Cl	4-Cl	Oil	59-C-B	<3	8	15	5-20
XIV	2-CH_3, 4-Br	4-Cl	70-71	223-C-C	<3	20	20	5-20
XV	2,4-$(CH_3)_2$	4-Br	Oil	42-C-A	14	7	>20	5-20
XVI	2-CH_3, 4-Cl	4-Br	49-50	114-D-B	<3	6	15	<5
XVII	2-CH_3, 4-Br	4-Br	71-72	>225-D-C	7	21	<10	5-20
XVIII	2,4-$(CH_3)_2$	4-*t*-C_4H_9	Oil	62-D-A	13	5	<20	~20
XIX	2-CH_3, 4-Cl	4-*t*-C_4H_9	Oil	>225-D-B	<3	28	8	<5
XX	2-CH_3, 4-Br	4-*t*-C_4H_9	Oil	>225-D-B	8	33	9	<5
XXI	2,4-$(CH_3)_2$	4-CH_3	Oil	30-B-A	8	2	>20	>20
XXII	2-CH_3, 4-Cl	4-CH_3	49-50.5	45-C-B	3	8	14	<5
XXIII	2-CH_3, 4-Br	4-CH_3	50-52	114-C-B	<3	21	5-20	5-20
Chlordimeform				>225-D-D	4	57	8	<5

[a] Satisfactory elemental analyses were obtained for all compounds. [b] Compounds I-V tested using the initial insecticide evaluation method, all others were treated using the followup method; first letter following the LC_{50} value indicates the degree of spindown, the second letter the degree of walkdown (A, B, and C = mites spinning or walking down from the plant at 25, 75, or 225 ppm, respectively; D = no mites spinning or walking down at 225 ppm). [c] Scientific names: 2SSM-A = two-spotted spider mite, *Tetranychus urticae*, adults; 2SSM-O = two-spotted spider mite ova; CRM = citrus red mite, *Panonychus citri*, adults; SAW-1stL = southern armyworm, *Spodoptera eridania*, first-instar larvae; SAW-O = southern armyworm ova.

Table II. Biological Activities of Two Thiophenylformamidines Compared with Chlordimeform

Compound	LD_{50} (95% confidence interval) CSM-A	CSM-O	CL-O	CL-1stL	BW-O	TB-O	GPA[a]
VI	23 (17-31)	>30	>80	40 (21-74)	<4[b]	4 (0.7-21.9)	<20[c]
VII	36 (32-39)	3.3 (2.3-4.9)	<5	2.3 (0.6-8.8)	<1	<1	<20
Chlordimeform	138 (27-703)	4.2 (2.9-6.0)	50-100	4.9 (2.5-9.2)	<1	<1	20-50

[a] Scientific names: CSM-A = Carmine spider mite, *Tetranychus cinnabarinus*, adults; CSM-O = Carmine spider mite ova; CL-O = cabbage looper, *Trichoplusia ni*, ova; CL-1stL = cabbage looper 1st-instar larvae; BW-O = bollworm, *Heliothis zea*, ova; TB-O = Tobacco budworm, *H. virescens*, ova; GPA = green peach aphid, *Myzus persicae*. [b,c] Significantly less[b] (more[c]) effective than VII and chlordimeform (based on Duncan's multiple range test at a 0.05 level of significance).

and XXI) are more effective against the adult two-spotted spider mite than their corresponding *N'*-(2-methyl-4-chloro- or bromophenyl)-*N*-methyl-*N*-(arylthio)formamidine analogues (VII and VIII, X and XI, XIII and XIV, XVI and XVII, XIX and XX, and XXII and XXIII). The same order of activity holds for the adult citrus red mite but this species is considerably more susceptible to all of the compounds. On the other hand, the formamidines having a 4-chloro or 4-bromo substituent in the *N'*-aryl ring are significantly more effective against eggs of the two-spotted spider mite, southern armyworm, and first-stage larvae of this latter species. The marked difference in susceptibility of the two developmental stages of the two-spotted spider mite implies a difference in the nature of the active site(s) and/or a differential metabolism between the developmental stages. The parallel activities demonstrated by analogous *N'*-aryl-substituted formamidines regardless of the nature of the *N*-arylthio substituent lead to one possible conclusion that some of the observed activities may be derived from a common metabolite, perhaps the parent *N'*-aryl-*N*-methylformamidine. This has been suggested by Knowles and Roulston (1973) following their investigations involving several formamidines on southern cattle ticks and work by some (Aziz and Knowles, 1973; Stone et al., 1974) but not all (Harrison et al., 1973; Beeman and Matsumura, 1974) researchers supports this hypothesis.

The two behavioral phenomena, i.e., walkoff and spinoff, are fast reactions. Within 1 h following treatment, mites can be observed either spinning down and/or walking down the plant. In the case of the arylthioformamidines, the former behavioral response is associated with the nature and probable reactivity of the arylthio moiety; however, with other compounds this is not always true (Kaugars et al., 1973). The walkdown pattern is associated with the nature of the formamidine portion of the molecule (2,4-dimethylphenyl types being more effective than the 2-methyl-4-chloro analogues) and this behavioral response

is believed to be analogous to tick detachment behavior (Stone and Knowles, 1973; Stone et al., 1974). Despite these fast reactions, mortality is generally slow in developing, frequently requiring 2–3 days or more to achieve maximum kill.

Two of the most active arylthioformamidines, VI against adult mites and VII against eggs and first-instar larvae, were examined for toxicity to other insects and mites compared with chlordimeform (Table II). The susceptibilities of the adult and egg of the carmine spider mite were essentially the same as that displayed by the closely related species, the two-spotted spider mite. The order of susceptibility of the green peach aphid to the three compounds parallels that of the adult mite susceptibility and not that of the ovicidal or first-stage larvicidal activities.

The ovicidal effectiveness of the compounds against the two species of *Heliothis*, the bollworm and tobacco budworm, proved to be very high: even compound VI was effective, though less so than VII and chlordimeform. Compared to the ova of the southern armyworm (Table I) and the cabbage looper, ova of these species are much more susceptible to the action of formamidines.

A most interesting observation from this study was that ova of the cabbage looper were very tolerant to the action of chlordimeform whereas first-instar larvae were susceptible. Curiously, compound VII, unlike chlordimeform, was effective against both the egg and larva. As chlordimeform is reportedly effective as an ovicide against many lepidopterous insects, including the cabbage looper (Harris and Svec, 1970), these experiments were repeated several times, always with the same results.

It should be noted that all of the formamidines examined permit the lepidopterous embryo to develop to the black head stage before death ensues. Under magnification, the young larvae frequently can be observed manipulating their mandibles within the egg chorion. At this time, they appear normal; however, whereas the control insects chew through the egg shell and eclose within a matter of hours, affected larvae within the eggs fail to eclose though, at times, they are successful in chewing a hole in the chorion. It would appear from our data that, although several formamidines are considered to be lepidopterous ovicides, they might better be classed as early instar larvicides.

The synthesis of the arylthioformamidines has proved to be a significant contribution to the field of insect toxicology, as several members of this class, most notably compound VII, *N'*-(2-methyl-4-chlorophenyl)-*N*-methyl-*N*-(phenylthio)formamidine, have demonstrated greater activity against certain insect and mite species, as well as an increased spectrum of high level toxicity over the prior art compound, chlordimeform.

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