Synthesis and Miticidal and Insecticidal Activities of 4-(2-Fluoroethyl)-5,6-dihydro-4*H*-1,3,4-oxadiazines

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Dihydrooxadiazines, substituted by a fluoroethyl chain, were prepared by reaction of benzhydrazides with 2 molar equiv of bromofluoroethane. Ten compounds with various substitutions on the phenyl ring were compared with clofentezine, a commercial miticide, for miticidal activity against the egg stage of *Tetranychus urticae*; the compounds were also compared with thiodicarb, a commercial tobacco budworm insecticide, for insecticidal activity against the egg stage of *Heliothis virescens*. The mortality data were correlated with the phenyl substitution in the tested compounds. Some halophenyl oxadiazines showed greater miticidal and insecticidal activities than the commercial standards.

INTRODUCTION

The 1,3,4-oxadiazine class of compounds has useful biological activities; dihydrooxadiazines are anticonvulsants (Trepanier et al., 1966) and insecticides (Dekeyser et al., 1993a,b), and oxadiazinones are effective insecticides (Dekeyser et al., 1988, 1991; Dekeyser and Moore, 1991).

As part of a continuing effort to develop new pesticidal agents of high potency, new fluoroethyl oxadiazines (Figure 1) were synthesized to determine the effect of this type of substitution on miticidal and insecticidal activities. The compounds were tested against the twospotted spider mite, *Tetranychus urticae*, and the tobacco budworm, *Heliothis virescens*, which are two serious pests of agricultural crops.

Chemistry. *Synthesis* of the title compounds was achieved according to the method outlined in Scheme I. The new fluoroethyl oxadiazines (**IIa–j**) were prepared from the appropriate substituted benzhydrazides (**Ia–j**) by reaction with 2 molar equiv of bromofluoroethane. Benzhydrazides (**Ia–j**) were synthesized from the corresponding benzoic acids by esterification with methanol followed by reaction with hydrazine. The fluoroethyl oxadiazines (**IIa–j**) were purified by column chromatography and then converted to their hydrochloride salts. The structural determination of the synthesized compounds was based on elemental analyses, IR, and ^{1}H NMR spectra (Tables I and II). The IR spectra of fluoroethyl oxadiazines (**IIa–j**) revealed a strong band around 1630 cm^{-1} ($\nu_{C=N}$). The ^{1}H NMR spectra of fluoroethyl oxadiazines (**IIa–j**) revealed separate signals for each proton in the fluoroethyl chain, with a C*H*F triplet found at about 5.1 ppm and an NC*H* triplet at about 3.5 ppm. These chemical shift assignments are consistent with those reported for other fluoroethyl heterocycles (Baklouti and Hedhli, 1989). Yields of fluoroethyl oxadiazines (**IIa–j**) were 10–40%.

Biology. Data on the miticidal and insecticidal activities of the fluoroethyl oxadiazines are presented in Table III. The activity of fluoroethyl oxadiazines against mite eggs was assessed by placing about 25 adult female mites on a cowpea leaf within a circle of tree tanglefoot. The

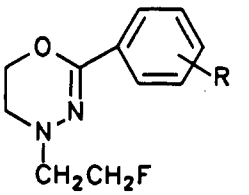
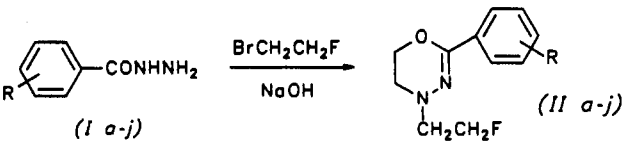


Figure 1. General structure of fluoroethyl oxadiazines.

Scheme I. Synthesis of Fluoroethyl Oxadiazines



Ia,IIa: R = 2-I	If,IIf: R = 4-Br
Ib,IIb: R = 2-NO_2	Ig,IIg: R = 2,5-Br
Ic,IIc: R = 3-Cl	Ih,IIh: R = 3,4-CH_3
Id,IId: R = 3-F	Ii,IIi: R = 3-Br, 4-Cl
Ie,IIe: R = 3-Br	Ij,IIj: R = 3-Cl, 4-Br

females were allowed to oviposit eggs for 24 h until 1 h before treatment, when they were removed. The cowpea plants were sprayed to runoff with fluoroethyl oxadiazines which had been dissolved in a minimum of acetone and then diluted with water containing a wetting agent. Nine days following treatment, the plants were examined for unhatched eggs. Controls were treated identically except for the exclusion of test compound from the spray. The percentage mortality was estimated relative to the number of unhatched eggs on the control plants according to Abbott's formula (Abbott, 1925). One replicate of each compound was tested at a concentration of 1000 ppm. The compounds yielding at least 90% mortality were further tested at 100 and 25 ppm. In these subsequent studies, four replicates of 20–40 eggs each were used at each concentration. A commercial mite ovicide, clofentezine (Figure 2), was tested for comparative purposes at two concentrations using four replicates per concentration.

The activity of fluoroethyl oxadiazines against tobacco budworm eggs was determined by allowing female tobacco budworms to deposit eggs onto cheesecloth 1 day before treatment. The cheesecloth, containing 40–80 eggs, was

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Table I. Analytical Data of Compounds IIa–j

compd	yield	mp, °C	molecular formula	found (calcd), % C	H	N
IIa	16	128–130	$C_{11}H_{13}ClFIN_2O$	36.03 (35.65)	3.65 3.53	7.48 7.55)
IIb	16	126–128	$C_{11}H_{13}ClFN_3O_3$	45.68 (45.60)	4.63 4.52	14.05 14.50)
IIc	27	153–155	$C_{11}H_{13}Cl_2FN_2O$	47.08 (47.33)	4.68 4.69	9.80 10.03)
IId	30	143–145	$C_{11}H_{13}ClF_2N_2O$	50.69 (50.29)	5.17 4.98	10.87 10.66)
IIe	24	159–160	$C_{11}H_{13}BrClFN_2O$	40.94 (40.82)	4.17 4.05	8.52 8.66)
IIf	16	155–157	$C_{11}H_{13}BrClFN_2O$	40.69 (40.82)	4.14 4.05	8.63 8.65)
IIg	36	125–127	$C_{11}H_{12}Br_2ClFN_2O$	32.58 (32.82)	2.97 3.00	6.80 6.96)
IIh	22	80–83	$C_{13}H_{18}ClFN_2O$	57.62 (57.24)	6.43 6.65	9.98 10.27)
IIi	39	157–161	$C_{11}H_{12}BrCl_2FN_2O$	37.30 (36.90)	3.46 3.37	7.91 7.82)
IIj	29	160–162	$C_{11}H_{12}BrCl_2FN_2O$	37.13 (36.90)	3.60 3.37	7.73 7.82)

Table II. Spectral Data of Compounds IIa–j

compd	IR (KBr), $\nu_{C=N}$, cm^{-1}	^1H NMR (DMSO-d_6), ppm
IIa	1625	7.1–7.9 (m, 4H), 5.1 (t, 1H), 4.2–4.5 (m, 3H), 3.4 (t, 1H), 2.9–3.2 (m, 3H)
IIb	1630	7.7–8.0 (m, 4H), 5.1 (t, 1H), 4.2–4.6 (m, 3H), 3.4 (t, 1H), 2.9–3.2 (m, 3H)
IIc	1630	7.4–7.7 (m, 4H), 5.2 (t, 1H), 4.3–4.6 (m, 3H) 3.5 (t, 1H), 2.9–3.3 (m, 3H)
IId	1620	7.2–7.5 (m, 4H), 5.1 (t, 1H), 4.2–4.5 (m, 3H), 3.5 (t, 1H), 2.9–3.2 (m, 3H)
IIe	1625	7.2–7.8 (m, 4H), 5.1 (t, 1H), 4.2–4.6 (m, 3H) 3.4 (t, 1H), 2.9–3.2 (m, 3H)
IIf	1630	7.4–7.9 (m, 4H), 5.3 (t, 1H), 4.5–5.0 (m, 3H) 3.8 (t, 1H), 3.3–3.6 (m, 3H)
IIg	1625	7.5–7.7 (m, 3H), 5.1 (t, 1H), 4.2–4.6 (m, 3H) 3.4 (t, 1H), 2.9–3.2 (m, 3H)
IIh	1625	7.2–7.7 (m, 3H), 5.1 (t, 1H), 4.2–4.6 (m, 3H), 3.5 (t, 1H), 3.0–3.3 (m, 3H), 2.3 (s, 6H)
IIi	1625	7.6–8.0 (m, 3H), 5.1 (t, 1H), 4.3–4.6 (m, 3H), 3.5 (t, 1H), 2.9–3.2 (m, 3H)
IIj	1620	7.5–7.9 (m, 3H), 5.2 (t, 1H), 4.3–4.6 (m, 3H), 3.5 (t, 1H), 3.0–3.3 (m, 3H)

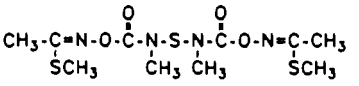
Table III. Miticidal and Insecticidal Screening Results of Compounds IIa–j

	av % mortality in vivo at 9 and 5 days, respectively, against					
	T. urticae			*H. virescens*		
compd	1000 ppm	100 ppm	25 ppm	1000 ppm	100 ppm	25 ppm
IIa	100	58	33	100	3	nd[a]
IIb	100	47	16	93	0	nd
IIc	100	83	9	100	96	0
IId	100	64	18	100	100	0
IIe	100	60	40	100	89	0
IIf	100	99	93	100	94	60
IIg	100	30	8	97	0	nd
IIh	70	nd	nd	87	0	nd
IIi	95	32	2	100	100	2
IIj	100	95	18	100	100	1
clofentezine	nd	94[b]	76	nd	nd	nd
thiodicarb	nd	nd	nd	97	71	6

[a] nd, not determined. [b] Tested at 50 ppm.

immersed for 1 min in a solution of each fluoroethyl oxadiazine, prepared as in the mite egg study, and kept on moist filter paper for 5 days. The numbers of hatched and unhatched eggs were counted, and an adjusted percentage mortality was determined by Abbott's formula (Abbott, 1925). One replicate of each compound was screened at concentrations of 1000 and 100 ppm, and four replicates were screened at 25 ppm. A commercial tobacco budworm ovicide, thiodicarb (Figure 2), was tested for comparative purposes under the same conditions as the fluoroethyl oxadiazines.

Thiodicarb



Clofentezine

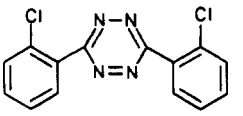


Figure 2. Structures of the commercial standards.

EXPERIMENTAL PROCEDURES

Melting points were determined in open glass capillaries and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 283B spectrophotometer. Elemental analyses were recorded on a Perkin-Elmer 240C elemental analyzer. ^1H NMR spectra were recorded on a Varian EM-360L (60-MHz) NMR spectrometer in DMSO-d_6 using TMS as internal reference; chemical shifts are expressed in parts per million.

Benzhydrazides (Ia–j). These were prepared by the usual esterification of appropriate benzoic acids (0.1 mol) with methanol (200 mL) and concentrated sulfuric acid (10 drops) followed by condensation of the resulting methyl benzoates (0.1 mol) with hydrazine hydrate (0.5 mol) and recrystallization from ethanol.

4-(2-Fluoroethyl)-5,6-dihydro-4*H*-1,3,4-oxadiazines (IIa–j). A solution of sodium hydroxide (0.03 mol) in water (10 mL) was added dropwise to a stirring mixture of I (0.01 mol) and 1-bromo-2-fluoroethane (0.02 mol) in ethanol (50 mL). The reaction mixture was refluxed for 2 h on an oil bath; the solution thus obtained was allowed to cool and then poured into water (100 mL) and extracted with diethyl ether (300 mL). The ether extract was dried over sodium sulfate and then evaporated, leaving an oil. The oil was purified, when deemed necessary, by column chromatography on silica gel by eluting with dichloromethane. The purified oil was dissolved in diethyl ether (100 mL) and treated with hydrogen chloride gas until no further precipitate formed. The precipitated solid was collected, washed with diethyl ether, and air-dried to furnish II as the hydrochloride salt.

Analytical data of compounds IIa–j, as their hydrochloride salts, are given in Table I, and spectral data are recorded in Table II.

RESULTS AND DISCUSSION

The synthesis of fluoroethyl oxadiazines (IIa–j) is likely to involve a cyclization reaction between benzhydrazides (Ia–j) and bromofluoroethane to form the oxadiazine ring followed by reaction with a second equivalent of bromofluoroethane at the oxadiazine nitrogen giving rise to a fluoroethyl substitution. Detection of de(fluoroethyl) oxadiazines in the reaction mixture supports the proposed reaction pathway. Alternately, the reaction may involve the intermediacy of the bis(fluoroethyl)benzhydrazides through the initial reaction of 2 equiv of bromofluoroethane with the benzhydrazides followed by cyclization to the oxadiazine; however, the bis(fluoroethyl)benzhydrazides have not been detected in the reaction mixture.

The mortality data in Table III indicate that most of the fluoroethyl oxadiazines show significant ovicidal

activity at 1000 ppm against twospotted spider mites and tobacco budworms, but in many cases, the activity decreased sharply at lower concentrations. In general, halophenyl substitution augmented ovicidal activity against twospotted spider mites and tobacco budworms. Halophenyl compounds **IIa,c–f,j** gave more than 50% mortality of twospotted spider mite eggs at 100 ppm. Compound **IIf** displayed greater mite ovicidal activity than the commercial miticide, clofentezine, at 25 ppm, the lowest concentration tested.

Halophenyl compounds **IIc–f,i,j** showed greater tobacco budworm ovicidal activity than the commercial insecticide, thiodicarb, at 100 ppm. Compound **IIf** displayed the greatest tobacco budworm ovicidal activity at 25 ppm, the lowest concentration tested.

The presence of one or more halogen atoms in the phenyl moiety of these compounds tends to increase the miticidal and insecticidal activities. However, when a methyl or nitro group is present in the phenyl moiety of these compounds, activities are substantially reduced, as in **IIb,h**. Overall, halophenyl compounds **IId–f,j** showed the greatest ovicidal activities against both twospotted spider mites and tobacco budworms, with halophenyl compound **IIf** showing greater activity than either commercial standard.

Biochemical studies on fluoroethyl oxadiazines are under investigation and will be reported in future publications.

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