N-Alkyl-*N*-(5-isothiazolyl)- and *N*-(Alkylisothiazolin-5-ylidene)-phenylacetamides. Synthesis and Biological Activity

Jack G. Samaritoni,* Lena Arndt, Timothy J. Bruce, James E. Dripps, James Gifford, Christopher J. Hatton, William H. Hendrix, Joseph R. Schoonover, George W. Johnson, Vidyadhar B. Hegde, and Scott Thornburgh

Discovery Research, DowElanco, 9330 Zionsville Road, Indianapolis, Indiana 46268-1054

Treatment of 5-amino-4-chloro-3-methylisothiazole (**3**) with the acid chloride of [*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetic acid (**6**) afforded the amide *N*-(4-chloro-3-methyl-5-isothiazolyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide (**1**), which was substituted with various alkyl groups in an effort to alleviate toxicity toward non-target organisms through a proinsecticide approach. Alkylations of **1** under a variety of reaction conditions afforded two major products which were derived from amide-nitrogen substitution, *N*-alkyl-*N*-(4-chloro-3-methyl-5-isothiazolyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamides (**7**), and ring-nitrogen substitution, *N*-(2-alkyl-4-chloro-3-methyl-3-isothiazolin-5-ylidene)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamides (**8**). Derivatives **7** and **8** were found to exhibit lessened toxicity to trout as well as insects, but, in general, efficacy toward insects was retained to a greater degree. In particular methoxymethyl, ethoxymethyl, ethyl, and ethyl-d_5 substituents demonstrated the best combination of insect efficacy and safening toward trout. Significantly different *in vivo* efficacies of the *N*-methyl and *N*-CD_3 analogs suggest that **7** and **8** are proinsecticides requiring activation by dealkylation.

Keywords: *Isothiazolylphenylacetamides; isothiazolinylidenephenylacetamides; insect control; proinsecticide; synthesis*

INTRODUCTION

Agricultural chemists are frequently challenged with the task of safening pesticides toward non-target organisms while simultaneously retaining sufficient efficacy toward pests to be of practical use. This is particularly true with insect control agents, many of which operate by modes of action adversely affecting life-sustaining biochemical pathways common to insects, mammals, and fish.

One approach which has been commonly used in our industry to mitigate this toxicity problem involves chemically modifying the pesticide to produce an intrinsically inactive propesticide requiring *in vivo* activation (Drabek and Neumann, 1985) Usually this approach takes advantage of rate differences of metabolic activation processes that are common to target and non-target organisms and this is what lies behind the success of chlorfenapyr (Pirate). This broad spectrum insecticide and acaricide features an *N*-ethoxymethyl group which is oxidatively removed *in vivo* to afford a potent mitochondrial uncoupler (Black et al., 1994). Wilkes and co-workers have successfully exploited the oxidative *N*-demethylation pathway in their efforts to reduce toxicity to rat and eliminate phytotoxicity in a series of insecticidal thiazolylbenzamides (Wilkes et al., 1991). Evidence for *in vivo* activation (demethylation) was generated by the observation that the *N*-CD_3 analog was considerably less active, a finding explained on the basis of a deuterium isotope effect occurring during oxidative demethylation.

The *N*-(5-isothiazolyl)phenylacetamides (Hackler et al., 1995), inhibitors of mitochondrial electron transport at Complex 1 (Thoreen et al., 1996; Johnson et al., 1996) and represented by **1**, possess excellent broad spectrum insect activity but have been found to be unacceptably toxic to fish and appeared to us to be a suitable series for the application of the propesticide concept via *N*-alkylation. This paper discusses the synthetic aspects of the *N*-alkylation of **1** and the biological activities of the products derived therefrom.

* Author to whom correspondence should be addressed (phone (317) 337-3157; fax (317) 337-3215; e-mail jgsamaritoni@dowelanco.com).

MATERIALS AND METHODS

Synthesis. Melting points were measured in open tubes using a Thomas Hoover capillary melting point apparatus and are uncorrected. All reagents were purchased from Aldrich Chemical Company (Milwaukee, WI) and were used without further purification. Solvents were dried using 3 Å molecular sieves. Thin-layer chromatography was carried out using 5 × 20 cm^2 plates precoated with a 250 μm thick layer of silica gel 60 F_{254} purchased from E. Merck, Darmstadt, Germany. Chromatography was performed using 230−400 mesh ASTM silica gel 60 from EM Science, Darmstadt, Germany. High-performance liquid chromatography (HPLC) was performed on a 25 cm, 4.6 mm inner diameter Dynamax-60A C_{18} reversed-phase column (8 μm mesh size) using a 9/1 acetonitrile/water mobile phase at a flow rate of 1.0 mL/min and a detection wavelengh of 227 nm. Proton NMR spectra were obtained on a Varian Gemini 300 spectrometer using deuterochloroform as solvent, unless otherwise indicated, and are reported in ppm (δ) downfield from tetramethylsilane as internal reference. Infrared spectra were obtained on a Bio-Rad FTS-40 spectrophotometer using potassium bromide pellets or as neat oils and are reported as wavenumbers (ν) in cm^{-1}. Mass spectra were obtained on a Hewlett-Packard model 5989A mass spectrometer using the electron impact (EI, 70 eV) or chemical ionization (CI) techniques and are reported as *m*/*z*. Gas chromatography/mass spectrometry (GC/MS) was run on a Hewlett-Packard model 5890 gas chromatograph coupled to a Hewlett-Packard model 5971 mass spectrometer detector. Microanalyses were performed by Midwest Microlab of Indianapolis, IN.

S0021-8561(96)00679-6 CCC: $14.00

5-Amino-4-chloro-3-methylisothiazole (3). 5-Amino-3-methylisothiazole (18.9 g, 0.166 mol), obtained by neutralization of the hydrochloride (Aldrich Chemical Company, Milwaukee, WI), was slurried in carbon tetrachloride (600 mL) under nitrogen. *N*-Chlorosuccinimide (22.1 g, 0.166 mol) was then added over a 5 min period at 30−44 °C, and the mixture was stirred overnight at room temperature. The mixture was then diluted with ether and was filtered. The filtrate was concentrated to a red oil which was taken up in ethyl acetate and was washed with two portions of water, once with brine, and dried ($MgSO_4$). Concentration gave 22.0 g (79%) of **3** as a brown solid: ^{1}H NMR δ 2.3 (s, 3H), 4.7 (bs, 2H).

[*p*-[(α,α,α-Trifluoro-*p*-tolyl)oxy]phenyl]acetic Acid (6). To a mixture of 21.4 g (0.535 mol) of 60% sodium hydride/mineral oil dispersion in 80 mL of dry dimethyl sulfoxide (DMSO) was added slowly with cooling a solution of 40.2 g (0.264 mol) of (*p*-hydroxyphenyl)acetic acid in 80 mL of dry DMSO. This was followed by the addition of 95.4 g (0.528 mol) of *p*-chloro-α,α,α-trifluorotoluene in 50 mL of dry DMSO. The contents were then heated for 16 h at 160−175 °C. Upon cooling, the contents were poured onto 700 mL of ice water and washed with three portions of tetrachloroethylene. The aqueous volume was then adjusted to pH 1−2 with concentrated hydrochloric acid, and the precipitate was collected and dried *in vacuo* at 40−50 °C to afford 62 g (79%) of **6** as a light brown solid: ^{1}H NMR δ 3.65 (s, 2H), 7.0 (m, 2H), 7.05 (m, 2H), 7.3 (m, 2H), 7.6 (m, 2H).

***N*-(4-Chloro-3-methyl-5-isothiazolyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide (1).** A solution of 26.8 g (0.0904 mol) of the phenylacetic acid **6** in 240 mL of thionyl chloride was heated at reflux for 2 h, cooled, and concentrated *in vacuo* to an oil which was dissolved in 200 mL of xylenes and added dropwise to a mixture of 13.4 g (0.0904 mol) of the amine **3** in 50 mL of xylenes. The contents were heated at reflux for 2 h, cooled, and diluted with toluene. The volume was then washed twice with saturated sodium bicarbonate, once with brine, and dried ($MgSO_4$). Concentration gave a solid which was triturated under heptane to afford 37 g (86%) of **1** as a light brown solid, mp 125−129°C; ^{1}H NMR δ 2.4 (s, 3H), 3.9 (s, 2H), 7.1 (m, 2H), 7.2 (m, 2H), 7.4 (m, 2H), 7.6 (m, 2H), 8.1 (bs, 1H); MS (EI) *m*/*z* 428 ($[M + 2]^+$, 4), 426 (M^+, 11), 251 (100). Anal. Calcd for $C_{19}H_{14}ClF_3N_2O_2S$: C, 53.46; H, 3.30; N, 6.56. Found: C, 53.73; H, 3.40; N, 6.49.

General Procedure for the Preparation of Amide-Nitrogen (7a−l) and Ring-Nitrogen (8a−l) Alkylated Isothiazolylphenylacetamides (Method A). A 0.16 M solution of the amide **1** in 1 part water and 2 parts dichloromethane, potassium carbonate (3.54 equiv), triethylbenzylammonium bromide (TEBAB, 1.07 equiv), 10% aqueous sodium hydroxide (ca. 3.2 equiv), and the alkyl halide (ca. 1.1−20 equiv) was stirred at room temperature. Reaction progress was monitored by thin-layer analysis on silica gel which was developed using dichloromethane/ethyl acetate and heptane/ethyl acetate mixtures and was complete within 48 h. The organic phase was passed through phase-separating paper and was concentrated to a residue which was partitioned between water and ethyl acetate. The organic phase was then washed once with brine and dried over magnesium sulfate. Concentration usually gave an oil which was chromatographed on silica gel. Amide-nitrogen alkylated derivatives **7** were eluted first using relatively nonpolar eluants such as 4:1 heptane:ethyl acetate (see Table 1) and, in general, existed as oils at room temperature. Ring-nitrogen alkylated amides **8** were eluted with increasing polarity of the eluant (such as ethyl acetate, see Table 2) and, without exception, existed as solids at room temperature. Compounds **8d** and **8l** crystallized from their crude reaction mixtures after workup and were recrystallized from heptane/ethyl acetate.

General Procedure for the Preparation of Amide-Nitrogen (7m,n) and Ring-Nitrogen (8m,n) Alkoxymethylated Isothiazolylphenylacetamides (Method B). To a suspension (ca. 0.8 M) at 0 °C of 60% sodium hydride (1.05 equiv) in tetrahydrofuran was added dropwise a 0.8 M solution of the amide **1** in tetrahydrofuran. The solution was stirred for 1 h, cooled to −50 °C, and treated dropwise with a 4 M solution of the halomethyl alkyl ether (ca. 3−4 equiv) in tetrahydrofuran. **CAUTION!** *Halomethyl alkyl ethers, such as bromomethyl methyl ether, are highly toxic and should always be handled in a hood with gloves.* The mixture was held at −50 °C for 2 h and was then allowed to gradually warm to room temperature and was stirred overnight. The contents were then poured onto ice water and extracted twice with ethyl ether. The combined extracts were then washed once with brine and dried ($MgSO_4$). Concentration gave an oil which was purified by silica gel chromatography. Amide-nitrogen alkylated derivatives **7** were eluted first followed by the ring-nitrogen alkylated isomers **8** as described in the general procedure for Method A.

General Procedure for the Preparation of Amide-Nitrogen (7o,p) and Ring-Nitrogen (8o,p) Alkylated Isothiazolylphenylacetamides (Method C). A 0.5 M mixture of the amide **1** in dry acetone, potassium carbonate (1.0 equiv), and the alkyl bromide (ca. 4−5 equiv) was heated at reflux overnight. The mixture was then concentrated *in vacuo* to a residue which was then partitioned between ethyl ether and water. The organic layer was washed once with brine and then dried ($MgSO_4$). Concentration gave an oil which was purified by silica gel chromatography. Amide-nitrogen alkylated derivatives **7** were eluted first followed by the ring nitrogen-alkylated isomers **8** as described in the general procedure for Method A.

Data for *N*-alkylated amides **7** and **8** are assembled in Tables 1−3.

***N*-[4-Chloro-2-(2-hydroxyethyl)-3-methyl-3-isothiazolin-5-ylidene]-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]-acetamide (8q).** To a mixture cooled in ice of 2.00 g (3.90 mmol) of the ester **8l** in 20 mL of absolute ethanol was added in one portion 0.147 g (3.90 mmol) of sodium borohydride. The mixture was allowed to warm to room temperature and was stirred overnight. Sodium borohydride (68 mg) was added to the reaction mixture and after 4 h was cooled in ice and was treated portionwise with 10 mL of 0.1 N hydrochloric acid followed by dilution with 100 mL of water and 200 mL of ethyl acetate. The acidified mixture was then treated with saturated sodium bicarbonate to facilitate separation. The organic phase was then washed once with brine and was dried ($MgSO_4$). Concentration afforded 1.78 g (97%) of **8q** as a white solid, mp 164−166 °C: ^{1}H NMR δ 1.28 (bs, 1H), 2.48 (s, 3H), 3.92 (t, 2H, J = 4.8 Hz), 4.00 (s, 2H), 4.06 (t, 2H, J = 4.8 Hz), 6.95 (m, 2H), 7.00 (m, 2H), 7.36 (m, 2H), 7.51 (m, 2H); IR (KBr) ν 3398 (m); MS (EI) *m*/*z* 471 ($[M + H]^+$, 2), 351 (100). Anal. Calcd for $C_{21}H_{18}ClF_3N_2O_3S$: C, 53.56; H, 3.85; N, 5.95; S, 6.81. Found: C, 53.78; H, 4.14; N, 5.75; S, 6.99.

4-Chloro-3-methyl-5-[[[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]-phenyl]acetyl]imino]-3-isothiazoline-2-acetic Acid (8r). A solution of 0.40 g (0.78 mmol) of the ester **8l** and 0.78 mL of 1.0 N sodium hydroxide in 15 mL of ethanol was stirred at room temperature for 20 h. Hydrochloric acid (0.78 mL of a 1.0 N solution) was then added, and the solution was concentrated to a residue which was partitioned between ethyl acetate and brine. The organic phase was then dried over magnesium sulfate. Concentration gave 340 mg of **8r** as a pale yellow solid which was shown by ^{1}H NMR and HPLC to be 95% pure. This material was recrystallized from ethyl acetate/tetrahydrofuran to afford 165 mg (44%) which was shown by HPLC to be 99.6% pure, mp 164−167 °C (dec): ^{1}H NMR δ 2.49 (s, 3H), 4.02 (s, 2H), 4.59 (s, 2H), 7.00 (m, 2H), 7.04 (m, 2H), 7.41 (m, 2H), 7.55 (m, 2H); MS (CI) *m*/*z* 296 ($[M + H - C_5H_6ClNO_2]^+$, 69), 193 ($[M + 2H - C_{15}H_{12}F_3NO_2]^+$, 68), 51 (100). Anal. Calcd for $C_{21}H_{16}ClF_3N_2O_4S$: C, 52.02; H, 3.33; N, 5.79. Found: C, 51.16; H, 3.27; N, 5.82.

4-Chloro-3-methyl-5-[[[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]-phenyl]acetyl]imino]-3-isothiazoline-2-acetic Acid, Sodium Salt (8s). A solution of 0.70 g (1.36 mmol) of the ester **8l** and 0.68 mL of 2.0 N aqueous sodium hydroxide in 15 mL of ethanol was stirred at room temperature for 20 h. The mixture was cooled in ice and then filtered and dried *in vacuo* at 80 °C to afford 270 mg (39%) of **8s** as a white solid: ^{1}H NMR (D_2O) δ 2.22 (s, 3H), 3.75 (bs, 2H), 4.37 (bs, 2H), 6.45 (m, 2H), 6.55 (m, 2H), 7.02 (m, 2H), 7.13 (m, 2H). Anal. Calcd for $C_{21}H_{15}ClF_3N_2NaO_4S$: C, 49.76; H, 2.98; N, 5.53; S, 6.33. Found: C, 49.90; H, 2.65; N, 5.57; S, 6.13.

Table 1. Preparative Information and Proton NMR Data of *N*-Alkylated Amides 7

compd	R	reagent (equiv)	method	eluant	yield (%)	mp (°C)	^{1}H NMR δ ($CDCl_3$)
7a	CH_3	CH_3I (20)	A	4/1 heptane/EtOAc	36	84−86	2.5 (s, 3H), 3.3 (bs, 3H), 3.6 (bs, 2H), 6.95 (bm, 2H), 7.0 (m, 2H), 7.1 (bm, 2H), 7.6 (m, 2H)
7b	CD_3	CD_3I (20)	A	4/1 heptane/EtOAc	34	84−89	2.5 (s, 3H), 3.6 (bs, 2H), 6.95 (bm, 2H), 7.0 (m, 2H), 7.1 (bm, 2H), 7.6 (m, 2H)
7c	CH_2CH_3	CH_3CH_2I (18)	A	4/1 heptane/EtOAc	31	oil	1.18 (t, 3H, J = 6.9 Hz), 2.51 (s, 3H), 3.53 (bs, 2H), 3.77 (bq, 2H), 6.96 (bm, 2H), 7.04 (m, 2H), 7.12 (bm, 2H), 7.57 (m, 2H)
7d	CD_2CD_3	CD_3CD_2I (11)	A	85/15 heptane/EtOAc	24	oil	2.47 (s, 3H), 3.51 (bs, 2H), 6.95 (m, 2H), 7.03 (m, 2H), 7.08 (bm, 2H), 7.54 (m, 2H)
7e	*n*-propyl	*n*-PrI (11)	A	9/1 CH_2Cl_2/EtOAc	13	oil	0.90 (t, 3H, J = 9.0 Hz), 1.60 (m, 2H), 2.49 (s, 3H), 3.52 (bs, 2H), 3.67 (bt, 2H), 6.95 (m, 2H), 7.02 (m, 2H), 7.09 (bm, 2H), 7.55 (m, 2H)
7f	isopropyl	iso-PrI (13)	A	CH_2Cl_2	3	oil	1.34 (d, 6H, J = 6.2 Hz), 2.43 (s, 3H), 3.64 (bs, 2H), 5.32 (bm, 1H), 6.95 (m, 2H), 7.02 (m, 2H), 7.14 (m, 2H), 7.58 (m, 2H)
7g	*n*-butyl	*n*-BuI (10)	A	9/1 heptane/EtOAc	13	oil	0.88 (t, 3H, J = 7.5 Hz), 1.26−1.33 (m, 2H, J = 7.5 Hz), 1.49−1.54 (m, 2H), 2.47 (s, 3H), 3.51 (bs, 2H), 3.68 (bt, 2H), 6.93 (m, 2H), 7.00 (m, 2H), 7.07 (bm, 2H), 7.53 (m, 2H)
7h	allyl	allyl bromide (10)	A	85/15 heptane/EtOAc	27	oil	2.51 (s, 3H), 3.59 (bs, 2H), 4.33 (bs, 2H), 5.12−5.22 (m, 2H), 5.77−5.92 (m, 1H), 6.97 (m, 2H), 7.04 (m, 2H), 7.12 (bm, 2H), 7.57 (m, 2H)
7i	CH_2c-C_3H_5	c-$C_3H_5CH_2Br$ (12)	A	85/15 heptane/EtOAc	14	oil	0.18 (m, 2H), 0.48 (m, 2H), 0.95 (m, 1H), 2.49 (s, 3H), 3.53 (s, 2H), 3.58 (d, 2H, J = 7.3 Hz), 6.92 (m, 2H), 7.00 (m, 2H), 7.10 (m, 2H), 7.55 (m, 2H)
7j	benzyl	benzyl bromide (7)	A	CH_2Cl_2	2	oil	2.46 (s, 3H), 3.59 (bs, 2H), 4.88 (bs, 2H), 6.97 (m, 2H), 7.07 (m, 2H), 7.12 (m, 2H), 7.20 (m, 2H), 7.31 (m, 3H), 7.56 (m, 2H)
7k	4-*tert*-butylbenzyl	4-*tert*-butylbenzyl bromide (5.5)	A	3/2 heptane/CH_2Cl_2	15	oil	1.32 (s, 9H), 2.47 (s, 3H), 3.61 (bs, 2H), 4.87 (bs, 2H), 6.98 (m, 2H), 7.04 (m, 2H), 7.12 (bm, 2H), 7.13 (m, 2H), 7.32 (m, 2H), 7.58 (m, 2H)
7l	CH_2CO_2Et	$BrCH_2CO_2Et$ (1.1)	A	4/1 heptane/EtOAc	14	oil	1.29 (t, 3H, J = 7.8 Hz), 2.45 (s, 3H), 3.65 (s, 2H), 4.22 (q, 2H, J = 8.4 Hz), 4.37 (bs, 2H), 6.96 (m, 2H), 7.02 (m, 2H), 7.10 (m, 2H), 7.55 (m, 2H)
7m	CH_2OCH_3	CH_3OCH_2Br (3.1)	B	4/1 heptane/EtOAc	42	oil	2.51 (s, 3H), 3.42 (s, 3H), 3.63 (bs, 2H), 5.06 (bs, 2H), 6.97 (m, 2H), 7.04 (m, 2H), 7.14 (bm, 2H), 7.59 (m, 2H)
7n	CH_2OEt	$EtOCH_2Cl$ (4.0)	B	9/1 heptane/EtOAc	26	oil	1.22 (t, 3H, J = 7.3 Hz), 2.47 (s, 3H), 3.61 (bs and q, 4H, J = 6.9 Hz), 5.10 (bs, 2H), 6.97 (m, 2H), 7.02 (m, 2H), 7.12 (bm, 2H), 7.57 (m, 2H)
7o	propargyl	propargyl bromide (5.0)	C	9/1 heptane/EtOAc	44	oil	2.30 (bs,1H), 2.55 (s, 3H), 3.58 (bs, 2H), 4.55 (bs, 2H), 6.92 (m, 2H), 7.03 (m, 2H), 7.11 (m, 2H), 7.58 (m, 2H)
7p	CH_2CN	$BrCH_2CN$ (4.0)	C	9/1 heptane/EtOAc	10	oil	2.53 (s, 3H), 3.62 (s, 2H), 4.60 (s, 2H), 7.00 (m, 6H), 7.57 (m, 2H)

***N*-(4-Chloro-3-methyl-5-isothiazolyl)thio-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide (9).** A mixture of 7.00 g (16.4 mmol) of the amide **1** and 9.7 g (25 mmol) of Lawesson's reagent in 200 mL of dry benzene was heated at reflux for 5 days, cooled, and filtered, and the filtrate was concentrated to dryness to give an oil which was chromatographed on silica gel using 1/2 heptane/dichloromethane as eluant to afford 4.64 g (64%) of **9** as a brownish-yellow solid, mp 114−117 °C: ^{1}H NMR δ 2.44 (s, 3H), 4.37 (s, 2H), 7.10 (m, 2H), 7.18 (m, 2H), 7.41 (m, 2H), 7.65 (m, 2H), 9.32 (bs, 1H); MS (CI) m/z 445 ($[M + 2 + H]^+$, 45), 443 ($[M + H]^+$, 100). Anal. Calcd for $C_{19}H_{14}ClF_3N_2OS_2$: C, 51.52; H, 3.18; N, 6.33; S, 14.46. Found: C, 51.68; H, 3.24; N, 6.19; S, 14.33.

Methyl *N*-(4-Chloro-3-methyl-5-isothiazolyl)thio-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetimidate (10). A mixture of 1.00 g (2.26 mmol) of the thioamide **9**, 0.312 g (2.26 mmol) of anhydrous potassium carbonate, and 0.57 g (4.52 mmol) of dimethyl sulfate in 10 mL of dry toluene was heated

Table 2. Preparative Information and Proton NMR Data of *N*-Alkylated Amides 8

compd	R	reagent (equiv)	method	eluant	yield (%)	mp (°C)	^{1}H NMR δ ($CDCl_3$)
8a	CH_3	CH_3I (20)	A	EtOAc	27	145−147	2.48 (s, 3H), 3.61 (s, 3H), 4.06 (s, 2H), 6.95 (m, 2H), 7.00 (m, 2H),7.40 (m, 2H), 7.55 (m, 2H)
8b	CD_3	CD_3I (20)	A	EtOAc	28	165−168	2.48 (s, 3H), 4.06 (s, 2H), 7.00 (m, 2H), 7.03 (m, 2H), 7.40 (m, 2H), 7.56 (m, 2H)
8c	CH_2CH_3	CH_3CH2I (18)	A	EtOAc	31	138−141	1.43 (t, 3H, J = 7.8 Hz), 2.49 (s, 3H), 3.99 (q, 2H, J = 8.0 Hz), 4.08 (s, 2H), 6.99 (m, 2H), 7.03 (m, 2H), 7.40 (m, 2H), 7.53 (m, 2H)
8d	CD_2CD_3	CD_3CD_2I (11)	A	recryst. from heptane/EtOAc	24	140−143	2.48 (s, 3H), 4.02 (s, 2H), 6.94 (m, 2H), 6.98 (m, 2H), 7.36 (m, 2H), 7.50 (m, 2H)
8e	*n*-propyl	*n*-PrI (11)	A	diethyl ether	29	100−101	0.98 (t, 3H, J = 7.7 Hz), 1.82 (m, 2H), 2.50 (s, 3H), 3.90 (t, 2H, J = 7.5 Hz), 4.08 (s, 2H), 7.05 (m, 2H), 7.08 (m, 2H), 7.45 (m, 2H), 7.61 (m, 2H)
8f	isopropyl	iso-PrI (13)	A	1/2 heptane/EtOAc	7	117−119	1.53 (d, 6H, J = 8.8 Hz), 2.49 (s, 3H), 4.07 (s, 2H), 4.53 (m, 1H, J = 9.4 Hz), 7.00 (m, 2H), 7.04 (m, 2H), 7.40 (m, 2H), 7.53 (m, 2H)
8g	*n*-butyl	*n*-BuI (10)	A	1/1 heptane/EtOAc	29	108−111	0.92 (t, 3H, J = 7.5 Hz), 1.30−1.38 (m, 2H, J = 7.4 Hz), 1.69−1.74 (m, 2H, J = 7.3 Hz), 2.44 (s, 3H), 3.88 (t, 2H, J = 7.3 Hz), 4.02 (s, 2H), 6.96 (m, 2H), 7.00 (m, 2H), 7.36 (m, 2H), 7.51 (m, 2H)
8h	allyl	allyl bromide (10)	A	EtOAc	15	92−95	2.46 (s, 3H), 4.06 (s, 2H), 4.52 (m, 2H, J_{vic} = 5.3 Hz, J_{allyl} = 1.6 Hz), 5.08 (m, 1H, J_{trans} = 17.1 Hz, J_{allyl} = 1.6 Hz), 5.31 (m, 1H), 5.82−5.95 (m, 1H), 6.99 (m, 2H), 7.03 (m, 2H), 7.40 (m, 2H), 7.55 (m, 2H)
8i	CH_2c-C_3H_5	c-$C_3H_5CH_2Br$ (12)	A	1/1 heptane/EtOAc	7	121−122	0.41 (m, 2H), 0.70 (m, 2H), 1.16 (m, 1H), 2.48 (s, 3H), 3.74 (bd, 2H, J = 6.7 Hz), 4.05 (bs, 2H), 7.02 (m, 4H), 7.40 (m, 2H), 7.53 (m, 2H)
8j	benzyl	benzyl bromide (7)	A	CH_2Cl_2	18	132−133	2.39 (s, 3H), 4.06 (s, 2H), 5.06 (s, 2H), 6.98 (m, 2H), 7.02 (m, 2H), 7.14 (bm, 2H), 7.37 (m, 3H), 7.43 (m, 2H), 7.55 (m, 2H)
8k	4-*tert*-butylbenzyl	4-*tert*-butylbenzyl bromide (5.5)	A	3/2 heptane/CH_2Cl_2	30	149−154	1.30 (s, 9H), 2.44 (s, 3H), 4.07 (s, 2H), 5.03 (s, 2H), 7.00 (m, 2H), 7.03 (m, 2H), 7.08 (m, 2H), 7.36 (m, 2H), 7.41 (m, 2H), 7.55 (m, 2H)
8l	CH_2CO_2Et	$BrCH_2CO_2Et$ (1.1)	A	recryst. from heptane/EtOAc	39	127−130	1.29 (t, 3H, J = 7.2 Hz), 2.41 (s, 3H), 4.06 (s, 2H), 4.24 (q, 2H, J = 6.6 Hz), 4.59 (s, 2H), 7.00 (m, 2H), 7.04 (m, 2H), 7.41 (m, 2H), 7.55 (m, 2H)
8m	CH_2OCH_3	CH_3OCH_2Br (3.1)	B	2/3 heptane/EtOAc	28	123−128	2.55 (s, 3H), 3.34 (s, 3H), 4.10 (s, 2H), 5.18 (s, 2H), 7.00 (m, 2H), 7.04 (m, 2H), 7.41 (m, 2H), 7.55 (m, 2H)
8n	CH_2OEt	$EtOCH_2Cl$ (4.0)	B	2/3 heptane/EtOAc	27	113−114	1.18 (t, 3H, J = 7.3 Hz), 2.57 (s, 3H), 3.61 (q, 2H, J = 8.0 Hz), 4.08 (s, 2H), 5.20 (s, 2H), 7.00 (m, 2H), 7.02 (m, 2H), 7.40 (m, 2H), 7.55 (m, 2H)
8o	propargyl	propargyl bromide (5.0)	C	2/3 heptane/EtOAc	16	153−155	2.50 (t, 1H, J = 2.4 Hz), 2.60 (s, 3H), 4.08 (s, 2H), 4.62 (d, 2H, J = 2.4 Hz), 7.02 (m, 4H), 7.40 (m, 2H), 7.58 (m, 2H)
8p	CH_2CN	$BrCH_2CN$ (4.0)	C	2/3 heptane/EtOAc	5	130−134	2.62 (s, 3H), 4.10 (s, 2H), 4.75 (s, 2H), 7.05 (m, 4H), 7.39 (m, 2H), 7.57 (m, 2H)

Table 3. Microanalytical, Infrared, and Mass Spectral Data of *N*-Alkylated Amides 7 and 8

compd	R	%C (theory)	%H (theory)	%N (theory)	%S (theory)	IR (ν)	MS (m/z)
7a	CH_3	54.53 (54.48)	3.64 (3.66)	6.46 (6.35)		(KBr) 1682 (s)	(EI) 442 ($[M + 2]^+$, 1.8), 440 ($[M]^+$, 4.3), 251 (100)
7b	CD_3	54.03 (54.11)	3.76 (3.63)	6.25 (6.31)		(KBr) 1650 (s)	(EI) 445 ($[M + 2]^+$, 3), 443 ($[M]^+$, 8), 251 (100)
7c	CH_2CH_3	55.39 (55.44)	3.93 (3.99)	6.09 (6.16)		(film) 1681 (s)	(CI) 457 ($[M + H + 2]^+$, 0.06), 455 ($[M + H]^+$, 0.15), 251 (100)
7d	CD_2CD_3	54.94 (54.83)	4.01 (3.99)	6.07 (6.09)			(CI) 459 ($[M]^+$, 26), 251 (100)
7e	*n*-propyl	56.57 (56.34)	4.40 (4.30)	6.10 (5.97)		(film) 1685 (s)	(CI) 470 ($[M + 2]^+$, 0.02), 468 ($[M]^+$, 0.05), 251 (100)
7f	isopropyl	55.60 (56.35)	4.33 (4.30)	5.94 (5.97)		(film) 1647 (s)	(CI) 471 ($[M + H + 2]^+$, 38), 469 ($[M + H]^+$, 100)
7g	*n*-butyl	57.29 (57.19)	4.96 (4.59)	5.72 (5.80)		(film) 1683 (s)	(EI) 482 ($[M]^+$, 2), 251 (100)
7h	allyl	56.62 (56.59)	3.84 (3.89)	5.98 (6.00)		(film) 1683 (s)	(CI) 469 ($[M + H + 2]^+$, 24), 467 ($[M + H]^+$, 61), 189 (100)
7i	CH_2c-C_3H_5	57.53 (57.44)	4.32 (4.19)	5.85 (5.83)	6.31 (6.67)		(EI) 251 (100), 278 (23), 480 ($[M]^+$, 7)
7j	benzyl	60.49 (60.40)	3.89 (3.90)	5.30 (5.42)		(film) 1681 (s)	(CI) 519 ($[M + H + 2]^+$, 29), 517 ($[M + H]^+$, 71), 91 (100)
7k	4-*tert*-butylbenzyl	62.94 (62.87)	4.92 (4.92)	4.80 (4.89)		(film) 1684 (s)	(EI) 574 ($[M + 2]^+$, 0.3), 572 ($[M]^+$, 0.7), 147 (100)
7l	CH_2CO_2Et	54.00 (53.86)	3.92 (3.93)	5.36 (5.46)		(film) 1744 (s), 1659 (s)	(CI) 513 ($[M + H]^+$, 1), 235 (100)
7m	CH_2OCH_3	53.39 (53.56)	3.85 (3.85)	5.80 (5.95)		(film) 1696 (s)	(CI) 471 ($[M + H]^+$, 11), 278 (100)
7n	CH_2OEt	54.58 (54.49)	4.30 (4.16)	5.80 (5.78)	6.33 (6.61)	(film) 1694 (s)	(CI) 487 ($[M + H + 2]^+$, 21), 485 ($[M + H]^+$, 50), 161 (100)
7o	propargyl	56.74 (56.83)	3.32 (3.47)	6.16 (6.03)	6.84 (6.90)		(EI) 464 ($[M]^+$), 278, 251
7p	CH_2CN	54.04 (54.14)	3.13 (3.25)	8.96 (9.20)	6.61 (6.88)		(EI) 465 ($[M]^+$, 7), 214 (100)
8a	CH_3	54.63 (54.48)	3.57 (3.66)	6.29 (6.35)	8.22 (8.04)		(EI) 442 ($[M + 2]^+$, 0.57), 440 ($[M]^+$, 1.45), 189 (100)
8b	CD_3	54.03 (54.11)	3.61 (3.63)	6.47 (6.31)			(EI) 445 ($[M + 2]^+$, 0.21), 443 ($[M]^+$, 0.57), 192 (100)
8c	CH_2CH_3	55.58 (55.44)	4.29 (3.99)	6.10 (6.16)	7.34 (7.05)		(EI) 456 ($[M + 2]^+$, 0.02), 454 ($[M]^+$, 0.04), 203 (100)
8d	CD_2CD_3	54.75 (54.83)	4.01 (3.99)	6.08 (6.09)			(CI) 459 ($[M]^+$, 14), 208 (100)
8e	*n*-propyl	56.33 (56.34)	4.43 (4.30)	5.81 (5.97)			(EI) 470 ($[M + 2]^+$, 0.004), 468 ($[M]^+$, 0.012), 217 (100)
8f	isopropyl	56.72 (56.35)	4.68 (4.30)	5.98 (5.97)	6.89 (6.84)		(EI) 471 ($[M + H + 2]^+$, 26), 469 ($[M+H]^+$, 68), 205 (100)
8g	*n*-butyl	57.35 (57.19)	4.43 (4.59)	5.87 (5.80)	6.43 (6.64)		(EI) 482 ($[M]^+$, 2), 231 (100)
8h	allyl	56.59 (56.59)	3.83 (3.89)	5.95 (6.00)	7.06 (6.87)		(EI) 466 ($[M]^+$, 4), 215 (100)
8i	CH_2c-C_3H_5	57.66 (57.44)	4.35 (4.19)	6.01 (5.83)	6.32 (6.67)		(EI) 480 ($[M]^+$, 2), 251 (31), 229 (100)
8j	benzyl	60.21 (60.40)	4.19 (3.90)	5.40 (5.42)	6.32 (6.20)		(EI) 519 ($[M + H + 2]^+$, 4), 517 ($[M+H]^+$, 18), 173 (100)
8k	4-*tert*-butylbenzyl	63.11 (62.87)	4.98 (4.92)	4.69 (4.89)			(EI) 572 ($[M]^+$, 0.4), 147 (100)
8l	CH_2CO_2Et	53.95 (53.86)	4.20 (3.93)	5.42 (5.46)	6.49 (6.25)	(KBr) 1736 (s)	(CI) 513 ($[M + H]^+$, 1), 157 (100)
8m	CH_2OCH_3	53.31 (53.56)	3.92 (3.85)	5.94 (5.95)	6.86 (6.81)		(CI) 473 ($[M + H + 2]^+$, 4), 471 ($[M + H]^+$, 10), 219 (100)
8n	CH_2OEt	54.94 (54.49)	4.30 (4.16)	5.80 (5.78)	6.39 (6.61)		(CI) 485 ($[M + H]^+$, 62), 233 (100)
8o	propargyl	56.98 (56.83)	3.52 (3.47)	5.95 (6.03)	7.00 (6.90)		(EI) 464 ($[M]^+$), 251, 213
8p	CH_2CN	54.53 (54.14)	3.57 (3.25)	9.03 (9.20)			(EI) 465 ($[M]^+$, 10), 251 (100)

for 18 h at 40−50 °C. The mixture was cooled, diluted with 15 mL of heptane, and washed once with water and once with brine, and dried ($MgSO_4$). Concentration gave a red oil which was chromatographed on silica gel using 9/1 heptane/ethyl acetate as the eluant to give 760 mg (74%) of **10** as a yellow solid, mp 72−73 °C: ^{1}H NMR δ 2.41 (s, 3H), 2.47 (s, 3H), 3.84 (br s, 2H), 6.97 (m, 2H), 7.04 (m, 2H), 7.17 (bm, 2H), 7.57 (m, 2H); MS (CI) m/z 459 ($[M + 2 + H]^+$, 12), 457 ($[M + H]^+$, 30), 55 (100). Anal. Calcd for $C_{20}H_{16}ClF_3N_2OS_2$: C, 52.57; H, 3.53; N, 6.13: S, 14.03. Found: C, 52.65; H, 3.58; N, 6.13; S, 13.82.

A small quantity of *N*-(4-chloro-2,3-dimethyl-3-isothiazolin-5-ylidene)thio-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide (**11**) was formed in the reaction (1 part **11** to 14 parts **10** as indicated by proton NMR analysis) and was also purified by silica gel chromatography using 4/1 dichloromethane/heptane as eluant, mp 165−166 °C: ^{1}H NMR δ 2.48 (s, 3H), 3.56 (s, 3H), 4.36 (s, 2H), 6.98 (m, 2H), 7.02 (m, 2H), 7.42 (m, 2H), 7.54 (m, 2H); MS (EI) m/z 458 ($[M + 2]^+$, 14), 456 (M^+, 33), 205 (100). Anal. Calcd for $C_{20}H_{16}ClF_3N_2OS_2$: C, 52.57; H, 3.53; N, 6.13: S, 14.03. Found: C, 52.86; H, 3.53; N, 6.16; S, 14.09.

Methyl *N*-(4-Chloro-3-methyl-5-isothiazolyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetimidate (12). To a solution of 90 mg (0.20 mmol) of the thioimidate **10** in 3 mL of absolute methanol was added a solution of 10.5 mg (0.194 mmol) of sodium methylate in 3 mL of methanol. After 1.5 h the solution was concentrated to a residue which was partitioned between ethyl ether and brine. The organic phase was then dried ($MgSO_4$) and concentrated to an oil which was chromatographed on silica gel using 85/15 heptane/ethyl acetate as eluant to afford 70 mg (81%) of **12** as a pale yellow oil: ^{1}H NMR δ 2.42 (s, 3H), 3.63 (br s, 2H), 3.90 (s, 3H), 6.96 (m, 2H), 7.03 (m, 2H), 7.15 (m, 2H), 7.57 (m, 2H); MS (EI) m/z 442 ($[M + 2]^+$, 29), 440 (M^+, 77), 251 (100). Anal. Calcd for

$C_{20}H_{16}ClF_3N_2O_2S$: C, 54.48; H, 3.66; N, 6.35. Found: C, 54.32; H, 3.61; N, 6.28.

5-(Benzylideneamino)-4-chloro-3-methylisothiazole (13j). A solution of 1.00 g (6.73 mmol) of the amine **3**, 0.785 g (7.40 mmol) of benzaldehyde, and 2 drops of trifluoroacetic acid in 10 mL of toluene was heated at 60 °C overnight. Thin-layer analysis indicated incomplete reaction. Trifluoroacetic acid (5 drops) was added, and the temperature was increased to 75 °C. After 7 h the solution was cooled to room temperature and was treated with 100 mg of benzaldehyde. Heating at 75 °C was then continued for 16 h. Upon cooling, the solution was diluted with ether, washed with three 20 mL portions of 0.1 N sodium hydroxide and once with brine, and dried ($MgSO_4$). Concentration gave an oil which was chromatographed on silica gel using dichloromethane as eluant to give 1.39 g (87%) of **13j** as a solid, mp 63−65 °C: ^{1}H NMR δ 2.50 (s, 3H), 7.52−7.58 (m, 3H), 7.98 (m, 2H), 8.54 (s, 1H); MS (EI) m/z 238 ([M + 2]$^+$, 35), 236 (M$^+$, 100). Anal. Calcd for $C_{11}H_9ClN_2S$: C, 55.81; H, 3.83; N, 11.84. Found: C, 55.93; H, 3.94; N, 12.01.

4-Chloro-5-(ethylamino)-3-methylisothiazole (14c). A mixture of 1.3 g (8.7 mmol) of **3** and 5 drops of trifluoroacetic acid in 15 mL of triethyl orthoacetate was heated at reflux for 9 h under a nitrogen atmosphere. After cooling, the reaction mixture was concentrated to afford **13c** as a thick oil; MS (EI) m/z 218 (M$^+$), 148 (100), 91. The crude **13c** was dissolved in 20 mL of absolute ethanol and cooled to 5 °C. Sodium borohydride (0.33 g, 8.7 mmol) was added to the solution which was then allowed to warm to room temperature and stir overnight. The contents were added to ice water, and the precipitate was collected and dried to afford 1.33 g (87%) of **14c** as a white solid, mp 98−99 °C; ^{1}H NMR δ 1.33 (t, 3H, J = 6.7 Hz), 2.32 (s, 3H), 3.22 (q, 2H, J = 5.7 Hz), 4.52 (bs, 1H); MS (EI) m/z 176 (M$^+$), 141 (100). Anal. Calcd for $C_6H_9ClN_2S$: C, 40.79; H, 5.13; N, 15.86. Found: C, 40.88; H, 5.56; N, 15.84.

4-Chloro-3-methyl-5-(propylamino)isothiazole (**14e**) was prepared according to the procedure described for **14c** using triethyl orthopropionate in place of triethyl orthoacetate. Yield: 1.25 g (76%), mp 68−69 °C; ^{1}H NMR δ 1.01 (t, 3H, J = 7.4 Hz), 1.67 (m, 2H), 2.32 (s, 3H), 3.13 (q, 2H, J = 5.9 Hz), 4.57 (bs, 1H); MS (EI) m/z 190 (M$^+$), 161 (100). Anal. Calcd for $C_7H_{11}ClN_2S$: C, 44.09; H, 5.81; N, 14.69. Found: C, 43.72; H, 6.30; N, 14.56.

5-(Benzylamino)-4-chloro-3-methylisothiazole (14j). To a solution at 0−5 °C of 840 mg (3.55 mmol) of the imine **13j** in 6 mL of tetrahydrofuran was added in one portion 134 mg (3.55 mmol) of sodium borohydride. After 1 h at 0−5 °C, the mixture was allowed to warm to room temperature and was stirred for an additional 6 h. The contents were poured onto ice water, and the pH was then adjusted to 2−3 with 2.0 N hydrochloric acid. The solution was extracted once with ether, and the extract was washed once with brine and dried ($MgSO_4$). Concentration gave 800 mg (94%) of **14j** as a light yellow solid, mp 92.0−98.5 °C: ^{1}H NMR δ 2.34 (s, 3H), 4.38 (d, 2H, J = 5.6 Hz), 4.95 (bs, 1H),7.37−7.40 (m, 5H); IR (KBr) ν 3279 (w); MS (EI) m/z 240 ([M + 2]$^+$), 238 (M$^+$), 91 (100). Anal. Calcd for $C_{11}H_{11}ClN_2S$: C, 55.33; H, 4.64; N, 11.74. Found: C, 55.15; H, 4.89; N, 11.47.

***N*-(4-Chloro-3-methyl-5-isothiazolyl)-*N*-ethyl-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide (7c).** A solution of 0.50 g (2.8 mmol) of the amine **14c** and 0.89 g (2.8 mmol) of the acid chloride of **6** (prepared as described for **1**) in 20 mL of toluene was heated at 100 °C for 6 h under nitrogen. After cooling, the reaction mixture was concentrated under vacuum. The crude residue was dissolved in 150 mL of dichloromethane, washed once with saturated sodium bicarbonate and once with water, and dried over sodium sulfate. Concentration gave an oil which was chromatographed on silica gel using 1/1 ethyl acetate/hexanes to afford 0.95 g (75%) of **7c** as a pale yellow oil. The proton NMR spectrum of **7c** obtained by this method was identical to that of **7c** obtained using Method A. Anal. Calcd for $C_{21}H_{18}ClF_3N_2O_2S$: C, 55.44; H, 3.99; N, 6.16. Found: C, 55.46; H, 4.06; N, 6.87.

***N*-(4-Chloro-3-methyl-5-isothiazolyl)-*N*-propyl-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide (7e).** Compound **7e** was obtained as a thick yellow oil following the procedure described for the preparation of **7c.** Yield: 0.76 g (71%) The proton NMR spectrum of **7e** obtained by this method was identical to that of **7e** obtained by Method A. Anal. Calcd for $C_{22}H_{20}ClF_3N_2O_2S$: C, 56.34; H, 4.30; N, 5.97; S, 6.84. Found: C, 56.23; H, 4.27; N, 6.03; S, 6.89.

***N*-Benzyl-*N*-(4-chloro-3-methyl-5-isothiazolyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide (7j).** A solution of 5.09 g (17.2 mmol) of the phenylacetic acid **6** and 4 mL of thionyl chloride in 30 mL of dichloromethane was heated at reflux for 4.5 h and was concentrated to an oil *in vacuo*. A portion (264 mg, 0.838 mmol) was then taken up in 3 mL of dry toluene and was added dropwise to a solution of 200 mg (0.838 mmol) of the aminoisothiazole **14j** in 5 mL of toluene. The contents were then heated at reflux for 3 h and were allowed to cool. The contents were diluted with ether and saturated sodium bicarbonate. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated to give 400 mg of an oil consisting of the desired amide **7j** (75% yield) and unreacted amine **14j** in a 2:1 ratio as evidenced by GC/MS and proton NMR. A portion of this material (100 mg) was chromatographed on silica gel using 9/1 dichloromethane/ethyl acetate as eluant to give 60 mg of **7j** (mp 102−105 °C) and whose proton NMR spectrum was identical to that of **7j** obtained by Method A.

Determination of Two-Spotted Spider Mite (TSSM, *Tetranychus urticae)* Activity. Summer crookneck squash seedlings (*Cucurbita pepo*), at the expanded cotyledon stage, were pruned to a single cotyledon. All motile stages of two-spotted spider mite were transferred to the seedlings by placing infested leaf sections on seedlings 16−24 h prior to the application of the test material. The infested leaf sections were removed immediately prior to application of experimental compounds.

Experimental compounds were dissolved in a solvent system containing acetone, *N*-methyl pyrrolidone, and Exxon 200. These solutions were diluted in water to yield a series of five rates: 16×, 4×, 1×, 1/4×, 1/16×, with × the approximate LC_{50} of the test compounds.

Application was made with a hand-held 2 cc syringe, using a Teejet TN-3 nozzle adapted to fit the syringe. The solutions were sprayed to run-off on both the upper and lower sides of the cotyledon. Four squash seedlings were treated at each rate, and eight seedlings were treated with a formulation-blank as controls.

Tests were held for 72 h in an environmental chamber at 27 °C and 75% RH, 14 h photoperiod.

Live mites were counted at 72 h. Percent control was determined by comparison of treated plants with the formulation-blank-treated checks according to the following formula: [(mean number untreated − mean number treated)/(mean number untreated)] × 100

Determination of Cotton Aphid (CA, *Aphis gossypii*) Activity. Summer crookneck squash seedlings (*C. pepo*), at the expanded cotyledon stage, were pruned to a single cotyledon. All stages of cotton aphid were transferred to the seedlings by placing infested leaf sections on seedlings 16−24 h prior to the application of the test material. The infested leaf sections were removed immediately prior to application of experimental compounds.

The experimental compounds were dissolved in 2 mL of 90:10 acetone:alcohol and then diluted in water containing 0.05% Tween 20. Serial dilutions were made to yield solutions of 50, 12.5, 3.13, 0.78, 0.195, and 0.049 ppm.

Application was made with a hand-held 2 cc syringe, using a Teejet TN-3 nozzle adapted to fit the syringe. The solutions were sprayed to run-off on both the upper and lower sides of the cotyledon.

Tests were held for 72 h in an environmental chamber at 27 °C and 75% RH, 14 h photoperiod. The tests were then graded using a binocular microscope. Percent control was estimated by visual comparison of the treated plants with the untreated controls.

Determination of Tobacco Budworm (TBW, *Heliothis virescens*) Activity. Test unit preparation included five diet units and ten leaf units. Diet units consisted of 4-cm diameter

Table 4. Biological Activities of 7

compd	R	TSSM[a]	CA[a]	TBW[a]	ALH[a]	trout[b]	trout LC_{50}[c]
1	H	1.00	1.00	1.00	1.00	87	<0.1
7a	CH_3	0.10	0.07	0.11	0.02	37	1−10
7b	CD_3	0.02	0.01	0.09	0.01	28	10−100
7c	CH_2CH_3	0.10	0.18	0.24	0.17	31	1−10
7d	CD_2CD_3	0.12	0.18	0.04[g]	0.03	22	10−100
7e	n-C_3H_7	0.70[d]	0.07	0.02	0.23	28	1−10
7f	iso-C_3H_7	2.70	0.15	0.53	0.39	70	0.1−1
7g	n-C_4H_9	I	0.02	0.01[g]	0.01	45	1−10
7h	$CH_2CH{=}CH_2$	0.48[e]	0.07	0.08	0.05	42	1−10
7i	CH_2c-C_3H_5	*h*	0.17	0.04[g]	NA	45	1−10
7j	benzyl	NA	0.04[g]	0.08	0.07[f]	43	1−10
7k	4-t-C_4H_9benzyl	0.09	0.01	<0.01	I	0	>100
7l	$CH_2CO_2CH_2CH_3$	0.01	<0.01	I	<<0.01	0	NA
7m	CH_2OCH_3	0.71	0.35	0.18	0.20	43	1−10
7n	$CH_2OCH_2CH_3$	0.67	1.03	0.74	<0.14	42	1−10
7o	CH_2CCH	*i*	0.68	0.67	0.15	60	0.1−1
7p	CH_2CN	0.04	0.25	0.72[g]	0.08	43	1−10

[a] Activity relative to **1** and defined as LC_{50}(**1**)/LC_{50}(**7**). Average LC_{50} for **1**: 0.27 ppm (TSSM), 0.31 ppm (CA), 0.28 ppm (TBW), 0.24 ppm (ALH); NA, not available; I, inactive at 50 ppm. [b] See Materials and Methods. [c] The LC_{50} range in ppb. [d] Activity relative to **1** and defined as % mortality (**7e**)/% mortality (**1**) at 0.20 ppm. [e] Activity relative to **1** and defined as % mortality (**7h**)/% mortality (**1**) at 5.0 ppm. [f] Corn planthopper. [g] Activity relative to **1** and defined as average LC_{50}(**1**)/LC_{50}(**7**). [h] 30% mortality at 50 ppm. [i] 90% mortality at 50 ppm.

(1 oz.) plastic cups containing ca. 7.5 g of insect diet (Southland Products, Stoneville, MS). Leaf units consisted of similar cups, each containing one 1 5/16 in. cotton leaf disc.

Experimental compounds were dissolved in acetone to yield a 2000 ppm stock solution. This was diluted in a 90/10 mixture of distilled water/acetone, with 0.025% Triton X-100 to yield solutions of 200, 50, 12.5, 3.125, 0.78, and 0.2 ppm. Technical grade cypermethrin was formulated and applied in each test as a reference standard.

Application was made using a Rainin multiple-dose pipetter to apply 0.25 mL of formulation of the five lower rates (50, 12.5, 3.125, 0.78, and 0.2 ppm) to each diet cup. The ten cotton leaf discs were treated by immersion in the four high rates of the formulated test solutions (200, 50, 12.5, and 3.125 ppm). After drying, each diet cup was infested with ca. ten *H. virescens* eggs in the "red-ring" development stage (24−48 h old). The ten treated leaf discs were placed in individual cups, and each cup was infested with a single *H. virescens* second-instar larva.

Diet cups were capped and stored (unbagged), and leaf cups were stored in plastic bags with moistened sponges. Both were held at 25 °C and 50% RH for 4−6 days. Percent mortality in diet cups and leaf cups was determined at 4−6 days after treatment. Percent control in each diet cup was estimated based on the total number of live and dead larvae/eggs and on the size and vigor of the live larvae. Total percent control for a treatment was the average of the five treated cups. Larval mortality in the leaf cups was determined by counting live and dead larvae, and percent control results were adjusted using Abbott's correction formula to account for mortality in the control treatment. LC_{50} values and 95% confidence intervals were calculated using the Spearman−Karber statistical program.

Determination of Aster Leafhopper (ALH, *Macrosteles fascifrons*) Activity. Experimental compounds were dissolved in acetone to yield solutions of 100, 25, 6.25, 1.56, and 0.39 ppm. Carbofuran was included in all tests as a reference standard and was prepared in a similar manner.

Aliquots of 0.5 mL of each solution were pipetted into 25 mL scintillation vials. Five vials were treated at each rate. The vials were placed on a hot dog roller to coat the interior of the vial and to allow the solvent to evaporate.

After the acetone evaporated, as indicated by a slight iridescence on the inner vial surface, the vial was infested with approximately seven adult aster leafhoppers. The vial was then capped with a specialized end joint made from polyethylene Caplugs from which the end had been removed. Parafilm M was stretched across the bottom of the cap to act as a reservoir, and 1.0 mL of 10% aqueous sucrose solution was pipetted into this reservoir for the insects to feed upon. The top of the cap was then covered with a 3/4-in. self-sticking paper label to prevent rapid evaporation of the sucrose solution.

Treated vials with infested insects were held in an environmental chamber set at 28 °C, 70% RH, and a 16 h photoperiod. Mortality was assessed at 24 h. Percent mortality was corrected using Abbott's formula. LC_{50} values were determined using the Spearman−Karber statistical program.

Determination of Rainbow Trout (*Oncorhynchus mykiss* Walbaum) Toxicity. Experimental compounds were dissolved in acetone to yield 1000 ppm solutions. The solutions were dissolved serially to yield additional solutions of 100, 10, and 1 ppm. Aliquots of 0.35 mL were transferred to 1 dram vials, and the acetone was allowed to evaporate, yielding vials containing 350, 35, 3.5, or 0.35 μg of compound.

The vials were shipped to the Dow Chemical Environmental Toxicity and Chemistry Research Lab in Midland, MI, by express courier. Acetone (875 μL) was added to each vial, and the contents were added directly to 4 L vessels containing 3.5 L of water, yielding aqueous concentrations of 100, 10, 1, and 0.1 ppb. The water in these vessels was aerated with at least 100 bubbles/min for 4 h prior to addition of the fish. The water in each vessel was stirred, and five rainbow trout, 4−6 months old, were impartially distributed to each test vessel. The vessels were held in a water bath to maintain a temperature of 12 °C and subjected to a 16 h photoperiod.

Observations of mortality and sublethal effects were recorded for each compound at 6, 24, 48, 72, and 96 h of exposure.

In addition to the LC_{50} ranges obtained by this method ("trout LC_{50}" columns in Tables 4 and 5), the mortality figures were also used to assist in differentiating compounds having the same LC_{50} ranges. This was done according to the following method. For each compound the sum of the mortalities at all four concentrations for each of the five time periods was obtained. Since five fish were used at each concentration, a total of one hundred mortalities was possible. This sum is reported in Tables 4 and 5 under the "trout" column. The differentiation that this method provides is actually a reflection of speed of action.

RESULTS AND DISCUSSION

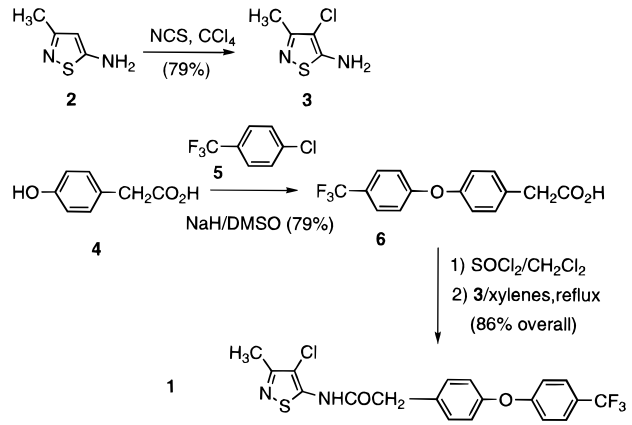
Synthesis. Amide **1** was prepared as outlined in Scheme 1. Ring chlorination of commercially available 5-amino-3-methylisothiazole (**2**) was achieved with *N*-chlorosuccinimide (Ohkata et al., 1994) to afford 5-amino-4-chloro-3-methylisothiazole (**3**). The required acid **6** was obtained through nucleophilic displacement of chloride in **5** with the phenoxide dianion of (*p*-hydroxy-

Table 5. Biological Activities of 8

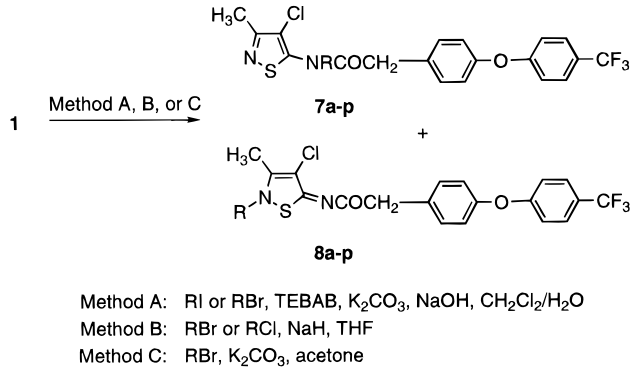
compd	R	TSSM[a]	CA[a]	TBW[a]	ALH[a]	trout[b]	trout LC_{50}[c]
1	H	1.00	1.00	1.00	1.00	87	<0.1
8a	CH_3	0.27	0.01	0.21	0.40	35	1−10
8b	CD_3	0.26	0.01	0.09	0.16	20	10−100
8c	CH_2CH_3	0.32	0.05	0.41	0.91	45	1−10
8d	CD_2CD_3	1.09[d]	0.01	0.06[e]	0.05	36	10−100
8e	n-C_3H_7	0.19	0.04	0.24	0.12	46	1−10
8f	iso-C_3H_7	0.67	I	0.23	0.09	44	1−10
8g	n-C_4H_9	I	I	0.55	I	50	0.1−1
8h	$CH_2CH{=}CH_2$	1.03[d]	0.07	0.56	0.11	55	0.1−1
8i	CH_2c-C_3H_5	I	I	0.37	0.04	54	0.1−1
8j	benzyl	I	I	0.10	<<0.01	38	1−10
8k	4-t-C_4H_9benzyl	<0.01	0.02	0.02	I	3	>100
8l	$CH_2CO_2CH_2CH_3$	0.05	<<0.04	0.01[e]	<<0.01	2	NA
8m	CH_2OCH_3	0.71	0.05	0.13	0.25	60	0.1−1
8n	$CH_2OCH_2CH_3$	0.15	0.22	0.22	<0.04	51	0.1−1
8o	CH_2CCH	I	0.09	1.75	I	50	0.1−1
8p	CH_2CN	[f]	0.04	[g]	0.07	55	0.1−1
8q	CH_2CH_2OH	I	<<0.03	<0.02	<<0.01	26	10−100
8r	CH_2CO_2H	I	I	I	<<0.01	6	10−100
8s	CH_2CO_2Na	I	<<0.03	<0.02	<<0.01	6	>100

[a] Activity relative to **1** and defined as LC_{50}(**1**)/LC_{50}(**8**). Average LC_{50} for **1**: 0.27 ppm (TSSM), 0.31 ppm (CA), 0.28 ppm (TBW), 0.24 ppm (ALH); NA, not available; I, inactive at highest rate. [b] See Materials and Methods. [c] The LC_{50} range in ppb. [d] Activity relative to **1** and defined as % mortality (**8d** or **8h**)/% mortality (**1**) at 0.20 ppm. [e] Activity relative to **1** and defined as average LC_{50}(**1**)/LC_{50}(**8**). [f] 20% mortality at 50 ppm. [g] 100% mortality at 50 ppm.

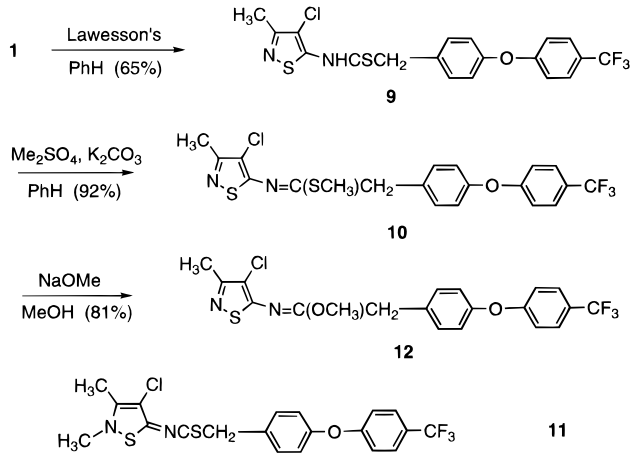
Scheme 1



Scheme 2



Scheme 3

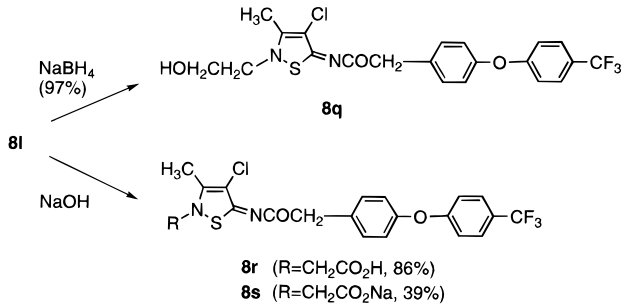


phenyl)acetic acid (**4**). This reaction, although requiring high temperatures (160−170 °C), proceeded cleanly and in excellent yield. The acid **6** was then condensed via its acid chloride with the amine **3** under refluxing xylenes.

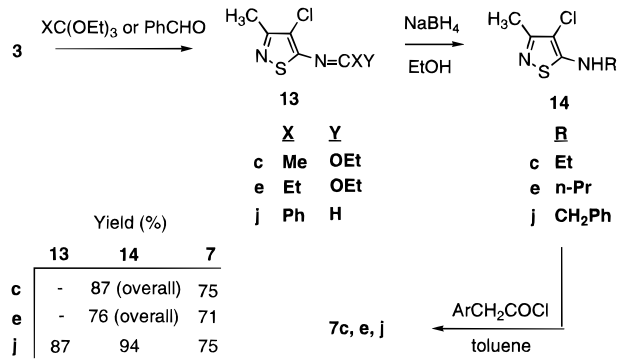
Treatment of the amide **1** with excess methyl iodide under phase transfer conditions (Method A; Wilkes et al., 1991) afforded a 63% combined yield of **7a** and **8a** in nearly a 1:1 ratio (Scheme 2). The amide-nitrogen methylated structure **7a** was proposed to account for signal broadening (proton NMR) of the *N*-methyl, methylene, and phenyl protons ortho to the methylene group, a phenomenon associated with hindered rotation about the carbon−nitrogen bond of amides (Dyer, 1965). This was verified by variable-temperature proton NMR in which the cited proton signals appear sharp and well resolved at 360 K. A carbonyl stretching frequency of 1682 cm^{-1} also corroborated the amide-alkylated structure. Nuclear Overhauser enhancement (NOE) studies carried out on **8a** established the vicinal arrangement of the methyl groups, thereby eliminating the methyl imidate **12** (via *O*-methylation) from consideration. Nearly identical results were obtained upon alkylation of **1** with dimethyl sulfate in the presence of potassium carbonate.

That the structure of **8a** was not the methyl imidate was conclusively shown by an independent synthesis of **12** which is outlined in Scheme 3. The amide **1** was converted to the thioamide **9** using Lawesson's reagent in moderate yield, a conversion which proceeded very slowly but cleanly. Attempts to prepare **9** using phosphorus pentasulfide in pyridine or Brillon's modification (Brillon, 1990) of Scheeren's method (Scheeren et al., 1973), to generate the more reactive phosphorus decasulfide/sodium carbonate reagent, failed. Treatment of **9** using dimethyl sulfate and potassium carbonate afforded the desired *S*-methylated compound **10** along with a small amount of the ring-nitrogen methylated

Scheme 4



Scheme 5



compound **11** in a 14:1 ratio. Reaction of the thioimidate **10** with sodium methoxide then gave **12** whose proton NMR spectrum did not match that of **8a**. Attempts to approach **12** via the imidoyl chloride of **1** were unsuccessful.

Alkylations of **1** using Method A (**7a**−**l**, **8a**−**l**, Tables 1 and 2) were performed with several alkyl iodides and bromides including ethyl bromoacetate, allyl bromide, and benzyl bromide. Reaction with *tert*-butyl iodide failed. Introduction of alkoxymethyl groups (**7m,n**, **8m,n**) through the use of the hydrolytically unstable haloalkyl alkyl ether reagents was accomplished under nonaqueous conditions using sodium hydride as base (Method B). The propargyl and cyanomethyl groups (**7o,p**, **8o,p**) were incorporated by reaction of the amide **1** with the alkyl bromide in the presence of potassium carbonate in acetone (Method C). Each method resulted in the formation of both *N*-substituted product isomers which were easily separable by chromatography or fractional crystallization. Also prepared were the alcohol **8q** and the carboxylic acid derivatives **8r** and **8s** as outlined in Scheme 4.

Certain amide-nitrogen alkylated structures **7** can be prepared exclusively by introduction of the alkyl group at the amine stage using reductive alkylation methodology as shown in Scheme 5. As illustrated for the preparation of **7c**, **7e**, and **7j**, aldehydes and orthoesters can be utilized in the formation of imines **13** which can then be reduced to the amines **14** with sodium borohydride. Condensation of the amines **14** with the acid chloride of **6** under refluxing toluene gave *N*-alkylated amides which were found to be identical to those obtained using Method A.

Insecticidal Activity. *In vivo* activities of the alkylated amides **7** and **8** were characterized on two-spotted spider mite (TSSM), cotton aphid (CA), tobacco budworm (TBW), and aster leafhopper (ALH). The results are reported in Tables 4 and 5. Evidence that *N*-alkylation converts **1** to proinsecticides is seen in a comparison of *N*-methyl and *N*-CD_3 analogs. Efficacy of the deuterated amide **7b** against all four pests was found to be less than that of the unlabeled analog **7a**, consistent with the observations on the *N*-methylated thiazolylbenzamides made by Wilkes and co-workers (1991). Their conclusion that a deuterium isotope effect occurring in rate-limiting hydrogen atom abstraction or deprotonation of the *N*-methyl group can be applied in the present case. The differences in efficacies between **7a** and **7b**, however, were found to vary among the pests spanning a range from 1.2- to 7-fold. This may be a reflection of differences in the actual mechanism of demethylation, that is, whether C−H bond cleavage is heterolytic or homolytic (Karki et al., 1995; Miwa et al., 1983), or it may reflect a profile of oxidative enzymes present in one organism but not another. Efficacy differences between **8a** and **8b** followed the same trend with TBW and ALH (Table 5), although they were found to be nonexistent on TSSM and CA, for which essentially identical LC_{50} values were observed.

No single alkyl group of **7** or **8** could be associated with the greatest retention of activity throughout the entire pest spectrum although isopropyl and ethoxymethyl were more successful than the others, particularly with isomers **7**. The isopropyl analog **7f** performed quite well against TSSM and TBW, retaining greater than 50% of the efficacy of **1**, while the ethoxymethyl amide **7n** retained greater than 65% of the parent activity on TSSM, TBW, and CA.

Almost without exception the amide-nitrogen alkylated structures **7** were found to be more active than their isomers **8** on CA, whereas the ring-nitrogen alkylated compounds **8** were superior to **7** on TBW. No such generalizations can be made for TSSM and ALH.

Although efficacy was found to be retained in high percentages with several of these alkylated analogs (**7f**,**n** and **8c**,**d**,**h**,**o**), it was also required that safety to aquatic organisms be enhanced at least to the same degree. It was hoped that dealkylation in fish would occur at a slow enough rate that expression of toxicity would be suppressed or that detoxification processes would predominate. Each of the alkylated derivatives **7** and **8** along with the parent amide **1** were evaluated in LC_{50} range-finding studies on rainbow trout, and the results are also presented in Tables 4 and 5. The efficacy advantages assumed by the isopropyl analog **7f**, the allyl analog **8h,** and the propargyl derivative **8o** are essentially offset by trout toxicities which represent only a mild alleviation of the toxicity associated with the parent **1**. However, several do offer a combination of 10-fold or better trout safety enhancement with a less than 10-fold efficacy reduction, and this is particularly evident with **7m**,**n** and **8c**,**d**. Although no firm generalization can be made with regard to the relative toxicity to fish of ring-nitrogen versus amide-nitrogen alkylation products, it is the amide-nitrogen alkylated isomer which has achieved greater fish safety enhancement most frequently and this has not always been at the expense of efficacy loss toward pests. This is nicely illustrated by comparing isomers **m** as well as isomers **n** on TSSM, CA, and TBW and isomers **i** as well as isomers **p** on CA. In each case the amide-alkylated isomer **7** was found to retain more of the efficacy associated with the parent **1** while exhibiting less toxicity to trout than **8**.

CONCLUSIONS

It has been possible through the alkylation of **1** to alleviate fish toxicity 10−100-fold while simultaneously

retaining, in many cases, 20% or more of the efficacy of the parent against various pests. The selectivity achieved is most likely due to differential metabolic rates between the species in which fish bring about dealkylation at a slower rate. Preferred alkyl substituents are methoxymethyl, ethoxymethyl, ethyl, and ethyl-d_5, and, in most cases, it is the amide-nitrogen alkylated isomer **7** which is the preferred isomer. However, based upon available data, an observed trout LC_{50} range of 1−10 ppb in this series still appears to pose unacceptable risk to aquatic species. Whether or not further safening will compromise insect efficacy to the point of impracticality remains unanswered at this time.

Based upon the general observation that the *N*-CD_3 analogs are less active than their unlabeled counterparts, the alkylated isothiazoleamides **7** and **8** are probably functioning as proinsectides requiring activation via dealkylation to give the highly active **1**. Definitive metabolic studies designed to establish the *in vivo* fate of **7** and **8** are underway.

ABBREVIATIONS USED

1, *N*-(4-Chloro-3-methyl-5-isothiazolyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide; **2**, 5-amino-3-methylisothiazole; **3**, 5-amino-4-chloro-3-methylisothiazole; **4**, (*p*-hydroxyphenyl)acetic acid; **5**, *p*-chloro-α,α,α-trifluorotoluene; **6**, [*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetic acid; **7a**, *N*-(4-chloro-3-methyl-5-isothiazolyl)-*N*-methyl-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]-phenyl]acetamide; **7b**, *N*-(4-chloro-3-methyl-5-isothiazolyl)-*N*-([$^2H_3$]methyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]-phenyl]acetamide; **7c**, *N*-(4-chloro-3-methyl-5-isothiazolyl)-*N*-ethyl-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]-phenyl]acetamide; **7d**, *N*-(4-chloro-3-methyl-5-isothiazolyl)-*N*-([$^2H_5$]ethyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]-phenyl]acetamide; **7e**, *N*-(4-chloro-3-methyl-5-isothiazolyl)-*N*-propyl-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]-phenyl]acetamide; **7f**, *N*-(4-chloro-3-methyl-5-isothiazolyl)-*N*-isopropyl-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]-phenyl]acetamide; **7g**, *N*-butyl-*N*-(4-chloro-3-methyl-5-isothiazolyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]-acetamide; **7h**, *N*-allyl-*N*-(4-chloro-3-methyl-5-isothiazolyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide; **7i**, *N*-(4-chloro-3-methyl-5-isothiazolyl)-*N*-(cyclopropylmethyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]-phenyl]acetamide; **7j**, *N*-benzyl-*N*-(4-chloro-3-methyl-5-isothiazolyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]-acetamide; **7k**, *N*-(*p*-*tert*-butylbenzyl)-*N*-(4-chloro-3-methyl-5-isothiazolyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)-oxy]phenyl]acetamide; **7l**, *N*-(4-chloro-3-methyl-5-isothiazolyl)-*N*-[[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetyl]-glycine, ethyl ester; **7m**, *N*-(4-chloro-3-methyl-5-isothiazolyl)-*N*-(methoxymethyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide; **7n**, *N*-(4-chloro-3-methyl-5-isothiazolyl)-*N*-(ethoxymethyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide; **7o**, *N*-(4-chloro-3-methyl-5-isothiazolyl)-*N*-2-propynyl-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide; **7p**, *N*-(4-chloro-3-methyl-5-isothiazolyl)-*N*-(cyanomethyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide; **8a**, *N*-(4-chloro-2,3-dimethyl-3-isothiazolin-5-ylidene)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide; **8b**, *N*-[4-chloro-3-methyl-2-([$^2H_3$]methyl)-3-isothiazolin-5-ylidene]-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide; **8c**, *N*-(4-chloro-2-ethyl-3-methyl-3-isothiazolin-5-ylidene)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide; **8d**, *N*-[4-chloro-2-([$^2H_5$]ethyl)-3-methyl-3-isothiazolin-5-ylidene]-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide; **8e**, *N*-(4-chloro-3-methyl-2-propyl-3-isothiazolin-5-ylidene)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide; **8f**, *N*-(4-chloro-2-isopropyl-3-methyl-3-isothiazolin-5-ylidene)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide; **8g**, *N*-(2-butyl-4-chloro-3-methyl-3-isothiazolin-5-ylidene)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide; **8h**, *N*-(2-allyl-4-chloro-3-methyl-3-isothiazolin-5-ylidene)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide; **8i**, *N*-[4-chloro-2-(cyclopropylmethyl)-3-methyl-3-isothiazolin-5-ylidene]-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide; **8j**, *N*-(2-benzyl-4-chloro-3-methyl-3-isothiazolin-5-ylidene)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]-acetamide; **8k**, *N*-[[2-(*p*-*tert*-butylbenzyl)]-4-chloro-3-methyl-3-isothiazolin-5-ylidene]-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide; **8l**, ethyl 4-chloro-3-methyl-5-[[[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetyl]imino]-3-isothiazoline-2-acetate; **8m**, *N*-[4-chloro-2-(methoxymethyl)-3-methyl-3-isothiazolin-5-ylidene]-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide; **8n**, *N*-[4-chloro-2-(ethoxymethyl)-3-methyl-3-isothiazolin-5-ylidene]-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)-oxy]phenyl]acetamide; **8o**, *N*-[4-chloro-3-methyl-2-(2-propynyl)-3-isothiazolin-5-ylidene]-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide; **8p**, *N*-[4-chloro-2-(cyanomethyl)-3-methyl-3-isothiazolin-5-ylidene]-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]-phenyl]acetamide.

ACKNOWLEDGMENT

We thank Hal Kirk, Jeanne Miller, and Anne Landre of Environmental Toxicology of The Dow Chemical Co. for performing the trout toxicity studies.

LITERATURE CITED

Black, B. C.; Hollingworth, R. M.; Ahammadsahib, K. I.; Kukel, C. D.; Donovan, S. Insecticidal Action and Mitochondrial Uncoupling Activity of AC-303,630 and Related Halogenated Pyrroles. *Pestic. Biochem. Physiol.* **1994**, *50*, 115−128.

Brillon, D. *In Situ* Reagents for Thionation of Amides, Peptides, and Lactams. *Synth. Commun.* **1990**, *20*, 3085−3095.

Drabek, J.; Neumann, R. Proinsectides. In *Progress in Pesticide Biochemistry and Toxicology, Vol. 5. Insecticides;* Hutson, D. H., Roberts, T. R., Eds.; John Wiley and Sons Ltd.: Chichester, England, 1985; Chapter 2.

Dyer, J. R. Applications of Absorption Spectroscopy of Organic Compounds. In *Foundations of Modern Organic Chemistry Series;* Prentice-Hall, Inc.: Englewood Cliffs, NJ, 1965; pp 113−114.

Hackler, R. E.; Johnson, G. W.; Samaritoni, J. G. *N*-(5-Isothiazolyl)amide Pesticides. WO 95/31448, 1995.

Johnson, P. L.; Hackler, R. E.; Sheets, J. J.; Worden, T.; Gifford, J. Synthesis and Insecticidal Activity of *N*-(4-Pyridyl and 4-Pyrimidinyl)phenylacetamides. *Abstracts of Papers*, 212th National Meeting of the American Chemical Society, Orlando, FL, August 1996; American Chemical Society: Washington, DC, 1996; AGRO 075.

Karki, S. B.; Dinnocenzo, J. P.; Jones, J. P.; Korzekwa, K. R. Mechanism of Oxidative Amine Dealkylation of Substituted *N,N*-Dimethylanilines by Cytochrome-P-450: Application of Isotope Effect Profiles. *J. Am. Chem. Soc.* **1995**, *117*, 3657−3664.

Miwa, G. T.; Walsh, J. S.; Kedderis, G. L.; Hollenberg, P. F. The Use of Intramolecular Isotope Effects to Distinguish between Deprotonation and Hydrogen Atom Abstraction Mechanisms in Cytochrome P-450- and Peroxidase-Catalyzed *N*-Demethylation Reactions. *J. Biol. Chem.* **1983**, *258*, 14445−14449.

Ohkata, K.; Ohyama, Y.; Akiba, K. Chlorination of 5-[2-(*N*-Silylamino)vinyl]isothiazole and Related Derivatives with *N*-Chlorosuccinimide. Inhibition of Ring-Transformation

(Bond Switch) by Steric Hindrance. *Heterocycles* **1994**, *37*, 859−867.

Scheeren, J. W.; Ohms, P. H. J.; Nivard, R. J. F. A General Procedure for the Conversion of a Carbonyl Group into a Thione Group with Tetraphosphorus Decasulfide. *Synthesis* **1973**, 149−151.

Thoreen, B. R.; Samaritoni, J. G.; Johnson, G. W.; Davis, L. N.; Gifford, J. M.; Sheets, J. J. Synthesis and Insecticidal Activity of *N*-(4-Quinolinyl)phenylacetamides. *Abstracts of Papers*, 212th National Meeting of the American Chemical Society, Orlando, FL, August 1996; American Chemical Society: Washington, DC, 1996; AGRO 074.

Wilkes, M. C.: Lavrik, P. B.; Greenplate, J. Synthesis of *N*-Benzoyl-*N*-alkyl-2-aminothiazole *Heliothis virescens* Proinsecticides. *J. Agric. Food Chem*. **1991**, *39*, 1652−1657.

Received for review September 9, 1996. Revised manuscript received January 22, 1997. Accepted January 30, 1997.[⊗]

JF960679J

[⊗] Abstract published in *Advance ACS Abstracts,* April 15, 1997.