Synthesis and Larvicidal Properties of Some Cyclopropylcarboxamides Related to *cis*-Permethrin[†]

Wesley G. Taylor,*,[‡] Tse Wai Hall,[‡] and Darrell D. Vedres

Research Centre, Agriculture and Agri-Food Canada, P.O. Box 3000, Lethbridge, Alberta, Canada T1J 4B1

Twenty-seven carboxamide derivatives of (±)-*cis*-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropan-ecarboxylic acid (permethrin acid) have been synthesized and evaluated in the laboratory against mosquito larvae (*Aedes aegypti*). These *cis*-cyclopropylcarboxamides, with *N*-(substituted)phenyl, *N*-(substituted)phenylmethyl, *N*-(substituted)phenylethyl, *N*-phenylpropyl, and *N*-phenylbutyl groups, were synthesized from the acid chloride of permethrin acid and various arylamines in methylene chloride. The samples were characterized by ^{13}C NMR spectroscopy and mass spectrometry. Secondary amides with electron-donating (e.g., methoxy) and electron-withdrawing (e.g., trifluoromethyl) substituents on the phenyl ring as well as nine tertiary amides were investigated. 3-(2,2-Dichloroethenyl)-2,2-dimethyl-*N*-(3-phenoxyphenyl)methylcyclopropanecarboxamide was the most active experimental compound and was 25 times less potent than (±)-*cis*-permethrin. Cyclopropylcarboxamides of the *N*-(substituted)phenyl, *N*-(substituted)phenylethyl, and *N*-phenyl-propyl types were essentially inactive in the larvicidal tests.

Keywords: *Pyrethroid amides; synthesis; purification; spectroscopy; mosquitoes; larvicidal activity*

INTRODUCTION

The majority of synthetic pyrethroid insecticides of commercial interest, illustrated by permethrin (**1**, Figure 1), are esters, like the natural pyrethrin insecticides from which the synthetic derivatives evolved (Davies, 1985). Pyrethroid-like structures lacking the central ester group, including ketone, ether, alcohol, hydrocarbon, amide, and carbamate analogues, have occasionally been described in the literature (Berteau and Casida, 1969; Elliott, 1971; Black, 1977; Brown and Casida, 1984; Lee and Norton, 1990). Although the ester linkage was not always essential for insecticidal activity, compounds without an ester group frequently displayed greatly reduced potencies in insecticidal bioassay screens. Despite the foregoing, interest in the commercial development of several nonester pyrethroids has continued (Naumann, 1990a,b).

Majewski and Snieckus (1984) noted several years ago that amide derivatives of pyrethroid acids (pyrethroid amides) had received relatively little attention and novel cyclopropanecarboxamides were needed to develop structure−activity relationships. New pyrethroid amides might also be valuable in biological studies on insecticide resistance. A few pyrethroid amide structures have been patented for their insecticidal activity (Naumann, 1990b). Pyrethroid amides have also been of chromatographic interest (Jiang and Soderlund, 1982; Taylor et al., 1993).

We report here the synthesis and characterization of a series of pyrethroid amides of general structure **2**

(Figure 1), prepared from (±)-*cis*-permethrin acid and various arylamines. The derivatives **3**−**29** (see Table 1) were evaluated in the laboratory with larvae of *Aedes aegypti*, which are known to be sensitive to pyrethroid insecticides (Mulla et al., 1980; Pap et al., 1996).

EXPERIMENTAL PROCEDURES

General. Column chromatography was performed with Mallinckrodt Inc. (St. Louis, MO) CC-7 silica gel and hexane/ether mixtures. Chemical ionization mass spectra (CI-MS) with isobutane as the reagent gas were obtained on a Hewlett-Packard 5985B mass spectrometer equipped with 30 m capillary columns of DB-5 (J & W Scientific, Folsom, CA) or SPB-1 (Supelco Inc., Bellefonte, PA). ^{1}H (400.1 MHz) and ^{13}C (100.6 MHz) NMR spectra as well as DEPT and XHDEPT experiments were acquired as previously described (Taylor and Schreck, 1989) on a Bruker AM-400 spectrometer. Chemical shifts are reported relative to internal tetramethylsilane (TMS; 0 ppm). Melting points (mp) were taken on a Büchi 530 apparatus. Boiling points (bp) were recorded during bulb-to-bulb vacuum distillations with a Büchi GKR-50 glass tube oven. Elemental analyses were obtained from C. Daessle (Montreal, PQ) or from Guelph Chemical Laboratories Ltd. (Guelph, ON).

Synthesis. Thionyl chloride, oxalyl chloride, and triethyl-amine (99% purity) were purchased from Aldrich Chemical Co. (Milwaukee, WI). *N*-Isopropylaniline was synthesized from aniline (National Aniline and Chemical Co., New York, NY) according to the procedure of Schellenberg (1963). 3-Phenoxy-benzylamine (Itaya and Higo, 1973) was synthesized from 3-phenoxybenzaldehyde (Aldrich) via 3-phenoxybenzaldehyde oxime (Liu et al., 1980) and reduction of this oxime with lithium aluminum hydride. The other arylamines (92−99% purity) were purchased from Aldrich, except for diphenylamine which was obtained from J. T. Baker (Phillipsburg, NJ). (±)-*cis*-Permethrin acid was obtained from Raylo Chemicals Ltd. (Edmonton, AB). A reference sample of (±)-*cis*-permethrin was prepared from the acid chloride of (±)-*cis*-permethrin acid and 3-phenoxybenzyl alcohol according to the procedure of Nakat-suka et al. (1977) and purified by column chromatography followed by recrystallization from hexane.

Carboxamides of Permethrin Acid

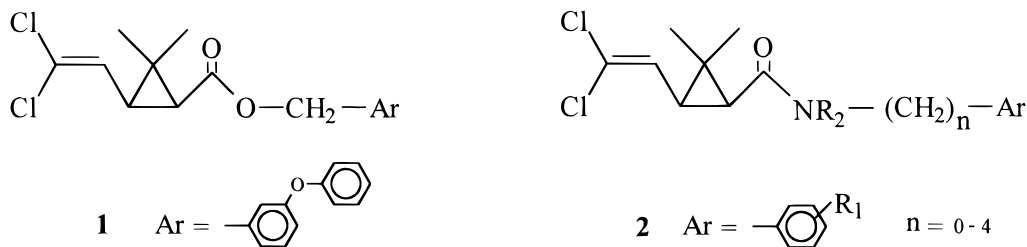*J. Agric. Food Chem.,* Vol. 46, No. 4, 1998 **1573**

Figure 1. Structures of (±)-*cis*-permethrin (**1**) and synthetic cyclopropylcarboxamides (**2**).

Amides **3**−**13** and **15**−**29** were prepared via the acid chloride of (±)-*cis*-permethrin acid, obtained by heating this acid (typically 3.14 g, 15 mmol) under reflux for 4 h with thionyl chloride (4.46 g, 37.5 mmol) in dry methylene chloride (40 mL, distilled from P_2O_5). In the synthesis of **14**, the acid chloride was prepared in sodium-dry hexane using oxalyl chloride. After evaporation of the solvent, sodium-dry toluene (75 mL) was added. The appropriate arylamine (15.57 mmol) in dry toluene (30 mL) and triethylamine (1.52 g, 15 mmol) were added dropwise to the stirred acid chloride solution, initially at 4 °C and then overnight at room temperature (Ar atmosphere). The reaction mixture was filtered, and the filtrate was washed with 2 N HCl, saturated $NaHCO_3$, and water. The organic phase was dried (anhydrous $MgSO_4$), and the solvent was removed on a rotary evaporator. Crude reaction products were purified by recrystallization or by column chromatography.

Bioassays. Larvicidal activity was assessed with early fourth-instar larvae from a laboratory colony of *A. aegypti* mosquitoes. The technique (Taylor and Shemanchuk, 1984) was similar to the procedure described by the World Health Organization (1963). Chemical solutions were prepared fresh in 95% ethanol so that ≤5 mL of solution was added to each beaker, which contained 25 larvae and 250 mL of distilled water. Mortality of larvae was assessed after 24 h. The experimental compounds were initially tested in triplicate (25 larvae in 3 beakers) at 5 ppm. If ≥10% larval mortality was observed, new test solutions were prepared and the compounds were retested (in triplicate) over an appropriate concentration range (e.g., 7.5, 5, 2.5, 1, and 0.5 ppm final concentrations). On the day of a bioassay, beakers containing control larvae received 5 mL of solvent, giving a range of mortality from 0 to 2%. Each day, (±)-*cis*-permethrin was also tested at final concentrations of 0.001 ppm (100% mortality) and 0.00005 ppm (0−5% mortality) to check the sensitivity of the individual batches of larvae. LC_{50} values (of <5 ppm) were obtained by probit analysis with SAS software (SAS Institute Inc., 1989).

RESULTS AND DISCUSSION

The *cis*-cyclopropylcarboxamides that have been synthesized and characterized (Table 1) fell into two main groups: *N*-(substituted)phenylcarboxamides (**3**−**16**) prepared from aniline or substituted anilines and *N*-(substituted)phenylmethylcarboxamides (**17**−**25**) obtained from benzylamine or substituted benzylamines. The choice of which derivative to prepare was based in part on the commercial availability of the starting arylamine, with emphasis on those amines bearing an electron-donating methoxy or an electron-withdrawing trifluoromethyl substituent (R_1). In tertiary amide structures, the substituent on the nitrogen atom (R_2) was usually an alkyl group. To extend the length of the spacer methylene bridge in **2**, three compounds (**26**, **28**, **29**) were synthesized from phenylethyl-, phenylpropyl-, and phenylbutylamine. Compound **27** was synthesized from 2-methoxyphenylethylamine.

Except for **11**, **12**, **24**, and **29**, the experimental cyclopropylcarboxamides were isolated as solids that were purified by recrystallization, usually with a mix-

ture of ethanol and water. Compounds **13**−**16**, **23**, **25**, and **28** required purification with silica gel before the samples solidified. The yields, based on the weight of purified material from recrystallization or vacuum distillation, ranged from 16 to 79%. Analytically pure samples of these compounds were homogeneous by TLC and capillary GC. Strong quasimolecular ions were observed during CI-MS, which helped to confirm their identities.

The compounds of Table 1 appeared to be novel, except for **3** and **25**. Reference to **3** (isomer unspecified) was made in a patent (Fuchs et al., 1981) and to *trans*-**3** in a publication on the phase-transfer synthesis of amides (Jaszay et al., 1989). (±)-*cis,trans*-**25** has been evaluated as a moth-proofing agent (de Sousa et al., 1982), (±)-*trans*-**25** has been prepared and tested for insecticidal activity (Brown and Casida, 1984), and a cis isomer of **25** has been used as a model compound to aid in predicting the activity of soil-applied insecticides (Simmons et al., 1992).

Partial ^{13}C NMR chemical shift assignments to samples of **3**−**29** in deuteriochloroform solution (Table 2) were made by a combination of one- and two-dimensional experiments and from NMR data on related structures described in the literature. Furthermore, the trifluoromethyl group appeared as a quartet due to ^{13}C−^{19}F scalar coupling (270−275 Hz) in the broadband-decoupled ^{13}C NMR spectra of **7**, **8**, and **20**−**22**.

Signal assignments to the quaternary carbons of the cyclopropyl moiety (C-1, C-3, C-8) were straightforward. Primary carbons of C-4 (15−16 ppm) and C-5 (28−29 ppm) were also readily assigned because of the shielding effect of the amide carbonyl group. In the ^{13}C NMR spectra of related *cis*-pyrethroid esters (Crombie et al., 1975; Janes, 1977; Nakazawa et al., 1980; Bertok et al., 1996), C-2 was upfield compared to C-6. In the ^1H NMR spectra of **3**−**29**, the doublet for the proton at C-2 (near 2 ppm) and the doublet of doublets for the proton at C-6 (1.7 ppm) were easily identified. By conducting ^{13}C−^1H chemical shift correlation experiments (XHDEPT) on representative samples (**3**, **15**, **17**, **26**, and **27**), we demonstrated that the chemical shift of C-2 was downfield relative to C-6.

Cross-peaks found in XHDEPT experiments were also useful for chemical shift assignments to C-7 (at 125−127 ppm) since the olefinic proton doublet could be clearly seen at ∼6.5 ppm. Frequently the chemical shift of C-7 was in the same region as the unassigned tertiary carbon atoms of the phenyl group. Signals for other protonated carbons of R_1 and R_2 were found as expected. Methylene carbons of **17**−**29** were readily identified in the DEPT experiments.

The ^{13}C NMR spectra of **16** and **23** were unusual because these compounds gave two signals of nearly equal intensity for most of their carbon atoms (Table 2). We have tentatively attributed the doubling of

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Table 1. Physical Properties of Synthetic Cyclopropylcarboxamides

compd	R_1	R_2	purification[a]	bp, °C (mmHg)	recrystallization solvent	mp, °C	yield, %	formula (MW)[b]	analysis, %, found (theory) C	H	N
					n = 0						
3	H	H	R		ethanol/water	149.5–150.5	63	$C_{14}H_{15}Cl_2NO$ (283)	58.86 (59.17)	5.59 (5.32)	5.07 (4.93)
4	4-OCH$_3$	H	R		ethanol/water	123.5–125	51	$C_{15}H_{17}Cl_2NO_2$ (313)	57.09 (57.33)	5.60 (5.45)	4.64 (4.46)
5	3-OCH$_3$	H	R		ethanol/water	126.5–127.5	48	$C_{15}H_{17}Cl_2NO_2$ (313)	57.63 (57.33)	5.59 (5.45)	4.53 (4.46)
6	2-OCH$_3$	H	R		ethanol	154.5–155.5	41	$C_{15}H_{17}Cl_2NO_2$ (313)	57.53 (57.33)	5.45 (5.45)	4.57 (4.46)
7	4-CF$_3$	H	R		ethanol/water	130–131	22	$C_{15}H_{14}Cl_2F_3NO$ (351)	51.01 (51.15)	4.21 (4.01)	4.03 (3.98)
8	2-CF$_3$	H	R		ethanol/water	126.5–127.5	40	$C_{15}H_{14}Cl_2F_3NO$ (351)	51.28 (51.15)	4.15 (4.01)	3.92 (3.98)
9	3, 5-(CH$_3$)$_2$	H	R		ethanol/water	186–187.5	16	$C_{16}H_{19}Cl_2NO$ (311)	61.26 (61.54)	6.14 (6.13)	4.36 (4.49)
10	H	CH$_3$	R		ethanol/water, hexane	79–80	52	$C_{15}H_{17}Cl_2NO$ (297)	60.67 (60.41)	5.69 (5.75)	4.83 (4.70)
11	H	CH$_2$CH$_3$	C, D	200 (1.7)			60	$C_{16}H_{19}Cl_2NO$ (311)	61.45 (61.54)	6.39 (6.13)	4.34 (4.49)
12	H	CH(CH$_3$)$_2$	C, D	162 (0.02)			53	$C_{17}H_{21}Cl_2NO$ (325)	62.40 (62.58)	6.84 (6.49)	4.46 (4.29)
13	H	Ph	C, R		ethanol/water	98–99.5	58	$C_{20}H_{19}Cl_2NO$ (359)	66.52 (66.67)	5.18 (5.32)	4.02 (3.89)
14	3, 4-OCH$_2$O	CH$_2$CH$_3$	C, D[c]			58.5–61	79	$C_{17}H_{19}Cl_2NO_3$ (355)	56.97 (57.31)	5.28 (5.38)	3.63 (3.93)
15	3-CH$_3$	CH$_2$CH$_3$	C, D, R	157 (0.02)	ethanol/water	67–68.5	53	$C_{17}H_{21}Cl_2NO$ (325)	62.86 (62.58)	6.57 (6.49)	4.31 (4.29)
16	2, 3-(CH$_3$)$_2$	CH$_2$CH$_3$	C, R		ethanol/water	69.5–71	41	$C_{18}H_{23}Cl_2NO$ (339)	63.57 (63.53)	6.87 (6.81)	4.08 (4.12)
					n = 1						
17	H	H	R		ethanol/water	93–94	37	$C_{15}H_{17}Cl_2NO$ (297)	60.26 (60.41)	5.77 (5.75)	4.55 (4.70)
18	2-CH$_3$	H	R		ethanol/water	112–112.5	41	$C_{16}H_{19}Cl_2NO$ (311)	61.59 (61.54)	6.29 (6.13)	4.29 (4.49)
19	2-OCH$_3$	H	R		ethanol/water	117–117.5	60	$C_{16}H_{19}Cl_2NO_2$ (327)	58.77 (58.54)	5.76 (5.83)	4.18 (4.27)
20	4-CF$_3$	H	R		ethanol/water	119.5–120.5	45	$C_{16}H_{16}Cl_2F_3NO$ (365)	52.63 (52.47)	4.50 (4.40)	3.97 (3.83)
21	3-CF$_3$	H	R		hexane, methanol/water	92–93.5	64	$C_{16}H_{16}Cl_2F_3NO$ (365)	52.21 (52.47)	4.48 (4.40)	3.68 (3.83)
22	2-CF$_3$	H	R		ethanol/water	114.5–116	40	$C_{16}H_{16}Cl_2F_3NO$ (365)	52.70 (52.47)	4.58 (4.40)	4.07 (3.83)
23	H	CH$_2$CH$_3$	C, D	170 (0.015)		47–49[d]	61	$C_{17}H_{21}Cl_2NO$ (325)	62.49 (62.58)	6.68 (6.49)	4.36 (4.29)
24	H	CH$_2$Ph	C, D	215 (0.02)			72	$C_{22}H_{23}Cl_2NO$ (387)	68.00 (68.04)	6.22 (5.97)	3.73 (3.61)
25	3-OPh	H	C, R		hexane	93–95.5	27	$C_{21}H_{21}Cl_2NO_2$[e] (389)	64.47 (64.62)	5.53 (5.42)	3.51 (3.59)
					n = 2						
26	H	H	R		ethanol/water	106–107	75	$C_{16}H_{19}Cl_2NO$ (311)	61.72 (61.54)	6.33 (6.13)	4.64 (4.49)
27	2-OCH$_3$	H	R		methanol/water	101.5–104	37	$C_{17}H_{21}Cl_2NO_2$ (341)	59.47 (59.65)	6.04 (6.19)	4.22 (4.09)
					n = 3						
28	H	H	C, R		hexane	63.5–64.5[f]	59	$C_{17}H_{21}Cl_2NO$ (325)	62.40 (62.58)	6.30 (6.49)	4.38 (4.29)
					n = 4						
29	H	H	C, D	225 (0.03)			73	$C_{18}H_{23}Cl_2NO$ (339)	63.35 (63.53)	7.05 (6.81)	4.22 (4.12)

[a] C, column chromatography; D, distillation; R, recrystallization. [b] Based on Cl = 35. M + 1 ions (100% relative abundance) were observed for each compound during CI-MS analysis. [c] This sample solidified on attempted distillation. [d] This sample solidified after distillation. [e] This compound has been described (de Sousa et al., 1982). [f] This sample solidified after column chromatography.

signals to the existence of syn and anti rotational isomers, interconversion of which was apparently slow on the NMR time scale to allow the detection of both isomers. Although rotational isomerism has been commonly observed in the ^{13}C NMR spectra of tertiary amides (Fritz et al., 1977; Taylor et al., 1992), it was interesting that these isomers were detected only when R_1 was 2,3-dimethyl and R_2 was ethyl with the *N*-(substituted)phenylcarboxamides and in the *N*-(substituted)phenylmethylcarboxamides, when R_1 was hydro-

gen and R_2 was an ethyl group. This indicated that steric bulk probably influenced the rate of interconversion (and hence the ability to detect the rotational isomers) in the former series but other factors seemed to be important with the latter series of compounds. Coalescence of signals did not occur when the ^{13}C NMR spectra of **16** and **23** in deuteriochloroform were acquired at an elevated temperature (55 °C).

Compounds **3**–**29** were found to be less active than *cis*-permethrin (**1**) when evaluated in a mosquito larvi-

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Table 2. ^{13}C NMR Chemical Shifts of Cyclopropylcarboxamides in Deuteriochloroform Solution[a]
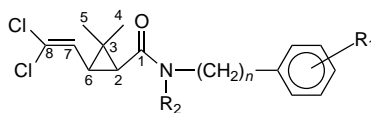
compd	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	−(CH$_2$)$_n$−	R$_1$	R$_2$	quaternary carbons (phenyl group)[b]
									n = 0			
3[c]	167.92	34.62	27.27	14.97	28.74	32.50	125.25	120.20				137.81
4	167.80	34.44	27.09	14.99	28.76	32.37	125.39	120.02		55.51		130.92, 156.40
5	167.88	34.69	27.30	14.98	28.73	32.51	125.22	120.22		55.34		139.07, 160.18
6	167.68	35.00	27.13	15.05	28.76	32.40	125.40	120.09		55.67		127.72, 147.58
7	168.20	34.63	27.74	14.86	28.70	32.84	124.81	120.66		124.05 (272 Hz)[d]		125.96 (33 Hz), 140.84
8[e]	168.14	34.61	27.40	15.00	28.61	32.73	124.91	121.01		124.10 (272 Hz)		135.46[f]
9	167.76	34.72	27.19	15.02	28.79	32.46	125.28	120.19		21.37		137.69, 138.78
10	169.88	33.03	26.83	15.55	27.71	32.45	126.43	119.14			37.20	144.18
11	169.25	33.42	26.56	15.51	27.61	32.21	126.59	118.98			13.26, 44.06	142.45
12	169.33	34.24	26.33	15.58	27.57	32.05	126.78	118.82			21.10, 21.18, 45.90	138.73
13[e]	170.04	34.05	27.57	15.49	27.81	33.17	126.18	119.86			126.82−129.29	143.14
14	169.50	33.23	26.61	15.49	27.82	32.29	126.56	119.04		101.81	13.21, 44.07	136.27, 147.06, 148.40
15[c]	169.28	33.46	26.56	15.55	27.60	32.20	126.65	118.90		21.32	13.28, 44.01	139.51, 142.37
16[c,g]	169.74	31.90	27.02	15.17	27.66	32.70	126.70	118.82		14.29, 20.50	12.96, 43.16	134.73, 138.59, 140.88
	169.58	33.00	26.36	15.46	28.54	32.15	126.38	119.06		14.18, 20.50	13.02, 43.49	134.47, 138.91, 141.20
									n = 1			
17[c]	169.46	33.79	26.52	15.13	28.68	31.95	125.72	119.72	43.68			138.30
18	169.20	33.74	26.48	15.10	28.66	31.92	125.67	119.75	41.76	18.93		135.84, 136.48
19	169.08	33.97	26.32	15.16	28.71	31.77	125.90	119.48	39.43	55.34		126.32, 157.61
20	169.72	33.69	26.69	15.08	28.65	32.07	125.49	120.01	43.08	124.08 (272 Hz)		129.75 (32 Hz), 142.49
21	169.72	33.75	26.72	15.06	28.70	32.10	125.49	120.03	43.15	124.03 (272 Hz)		131.07 (32 Hz), 139.48
22	169.48	33.72	26.60	15.06	28.65	31.98	125.54	119.92	40.04	124.45 (275 Hz)		128.12 (30 Hz), 136.84
23[c,g]	169.94	31.65	26.00	16.01	28.32	31.36	126.53	119.43	47.70		12.90, 41.58	137.90
	169.59	31.94	26.00	15.71	27.95	31.36	126.53	119.29	50.80		13.77, 41.23	137.32
24	170.56	31.74	26.40	15.97	28.02	31.63	*h*	119.67	50.10		48.42, 126.32−129.01[i]	136.68, 137.41
25	169.44	33.78	26.58	15.08	28.68	31.99	125.60	119.81	43.35	119.09, 123.50, 129.82[j]		140.35, 156.89, 157.72
									n = 2			
26[c]	169.55	33.81	26.37	15.08	28.70	31.82	125.77	119.57	35.74, 40.59			138.86
27[c]	169.45	33.89	26.23	15.08	28.73	31.75	125.90	119.40	30.26, 39.72	55.31		127.39, 157.53
									n = 3			
28	169.50	33.83	26.28	15.11	28.70	31.77	125.82	119.56	31.33, 33.39, 39.32			141.45
									n = 4			
29	169.47	33.87	26.28	15.11	28.67	31.77	125.82	119.56	28.70, 29.31, 35.46, 39.38			142.10

[a] In ppm from internal TMS. Precision ± 0.02 ppm, temperature 25 °C. The numbering system of the permethrin acid moiety is from Janes (1977). [b] The CH carbons were not assigned. [c] Assignments were checked by ^{13}C−^{1}H chemical shift correlation experiments (XHDEPT). [d] Values in parentheses are ^{13}C−^{19}F coupling constants. [e] These spectra were obtained at 55 °C. [f] The quaternary carbon bearing the CF$_3$ group could not be assigned. [g] The chemical shift of the more intense signal of the pair is reported first. [h] Unassigned. [i] Including the signal for C-7. [j] Assignments for the phenoxybenzyl group are from Janes (1977).

Table 3. Toxicities of Cyclopropylcarboxamides to Mosquito Larvae (*A. aegypti*)

compd	LC$_{50}$, ppm	compd	LC$_{50}$, ppm
3−6	>5	**21**	2.2
7	3.4	**22**	0.5
8−13	>5	**23**	>5
14	4.8	**24**	0.9
15, 16	>5	**25**	0.01
17	1.7	**26−28**	>5
18	0.5	**29**	2.2
19	2.0	*cis*-permethrin	0.0004
20	1.4		

cidal screen (Table 3). Among the *N*-(substituted)-phenylcarboxamides (**3−16**), only the 4-trifluoromethylamide **7** and the 3,4-methylenedioxy-*N*-ethylamide **14** were active at <5 ppm. Their LC$_{50}$ values were 3.4 and 4.8 ppm, respectively, compared to 0.0004 ppm for **1**.

With the *N*-(substituted)phenylmethylcarboxamides (**17−25**), all of the compounds displayed some larvicidal activity, except for *N*-benzyl-*N*-ethylamide **23**. The LC$_{50}$ value for the *N,N*-dibenzylamide **24** was 0.9 ppm. This compound was slightly more active than amides **17**, **20**, and **21**, derived, respectively, from benzylamine, 4-(trifluoromethyl)benzylamine, and 3-(trifluoromethyl)benzylamine. Among the ortho-substituted amides, the 2-methyl (**18**) and 2-trifluoromethyl (**22**) compounds were equipotent (LC$_{50}$ of 0.5 ppm) and 4 times as active as 2-methoxybenzylamide **19**. 3-Phenoxybenzylamide **25**, the nitrogen isostere of **1**, exhibited an LC$_{50}$ of 0.01 ppm and was the most active experimental compound. Although **25** was 50 times more active than the closest competitors, **18** and **22**, it was 25 times less active than **1**.

With the long-chain homologues, phenylethylamides **26** and **27** and phenylpropylamide **28** were inactive at 5 ppm, whereas phenylbutylamide **29** displayed weak activity with an LC$_{50}$ value equal to that of **21** (2.2 ppm).

In summary, selected examples of (±)-*cis*-cyclopropylcarboxamides of general structure **2** were synthesized and characterized. Within the series of *N*-(substituted)-phenylmethylcarboxamides, larvicidal activity could be modulated by the nature of the substituents on the phenyl ring. Although a *m*-phenoxy substituent resulted in the best activity, activity was enhanced over

the unsubstitued amide by *o*-methyl or *o*-trifluoromethyl substituents. Further studies on permethrin amides seem to be worthwhile, using these structure–activity relationships as a guide.

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