the case at hand, however, the proportions of parent to metabolite and their individual toxicities are such that the overall mixture presents less hazard to the worker with time, as is evidenced by the decreasing numbers for each experiment in the last column of Table XI. Finally, it might be argued that the conversion factor, K_d, used here to relate total allowable dose (μg/h) to reentry level (μg/cm2) should reflect Florida data rather than the California data of Popendorf and Leffingwell (1982). However, a repeat of the California study, conducted in Florida by two of us (Nigg et al., 1984) yielded K_d = 5300 cm^2/h, in close agreement with the California K_d of 5100 cm^2/h.

CONCLUSIONS

Application of 4 lb or 1 lb of a.i./acre CS resulted in low surface residues on citrus leaf, fruit, and soil surfaces. The 4-lb application resulted on day 1 of experiment 1 in 0.771 $\mu g/cm^2$ on leaves and fruit, while 1 lb resulted on day 1 of experiment 2 in 0.243 $\mu g/cm^2$ on leaves and fruit (see Tables II and III) or a ratio of 3.2 to 1. CS dissipated rapidly under both hot–wet (experiment 1) and cool–dry (experiment 2) condtiions but more rapidly from fruit, leaf, and soil dripline surfaces in experiment 1 than in experiment 2 (see Table VII). Persistence of CS along the soil dripline exceeded that on fruit or leaves during each experiment. The major observed metabolite of CS was CF. (Only very small levels of 3-hydroxy- and 3-ketocarbofuran were observed in both experiments.) CF dissipated less rapidly from leaves than the parent compound during each experiment.

On the basis of the data presented here, the estimated safe worker reentry interval following CS application was 3 days for experiment 1 and 1–2 days for experiment 2.

ACKNOWLEDGMENT

We thank T. Bailey, R. Queen, and R. Williams for their technical assistance.

Registry No. CS, 55285-14-8; CF, 1563-66-2; 3-hydroxycarbofuran, 16655-82-6; 3-ketocarbofuran, 16709-30-1.

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Synthesis and Biological Activity of Pyrethroids Derived from Halo-4-alkenoic Acids

Hafez M. Ayad and Thomas N. Wheeler*

Sixty-two examples of pyrethroids derived from halo-4-alkenoic acids have been synthesized. The halo-4-alkenoic acids were prepared by a modified malonic ester synthesis or by allylation of O-silylated ketene acetals. The pyrethroids derived from halo-4-alkenoic acids bearing an alkyl group at C_3 are novel, and the crucial effect of the nature and number of alkyl substituents at C_3 on insecticidal activity of the 5,5-dihalo-4-alkenoic esters has not been reported previously. The observed enhancement of insecticidal activity upon substitution of a single methyl group at C_3 would not have been predicted from known structure/activity trends. Several of the novel esters exhibit good broad-spectrum insecticidal and some miticidal activity, but the most active of the halo-4-alkenoic esters is considerably less active, particularly on lepidopterous larvae, than commercial pyrethroids. Experiments with potential synergists failed to demonstrate that susceptibility to degradative enzymes is a probable reason for the reduced activity of the halo-4-alkenoic esters.

An important component of natural pyrethrins is chrysanthemic acid, which contains a *trans*-isobutenyl moiety at C_3 on the cyclopropane ring. This moiety is essential for high pesticidal activity, but it also limits the metabolic and photochemical stability of the pyrethrins. Insects rapidly oxidize the *trans*-methyl group of the isobutenyl moiety to the corresponding alcohols, aldehydes, and carboxylic acids with loss of insecticidal activity (Yamamoto and Casida, 1966; Yamamoto et al., 1969). The isobutenyl group also undergoes rapid photooxidation to epoxides and various hydroxy, keto, and carboxylic acid derivatives (Ueda et al., 1974; Elliott, 1977). These in-

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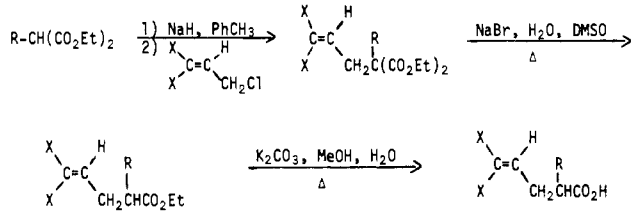
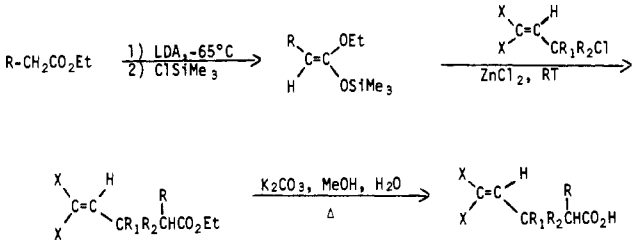
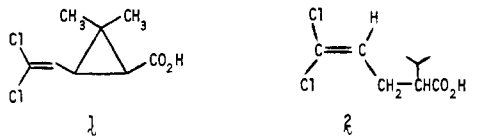
Scheme I



Scheme II



stability problems were solved, in part, by esterifying 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid (1) (Farkas et al., 1958) with newer photostabile alcohols (Holmstead et al., 1971).



Cleavage of the C_2–C_3 bond of **1** would lead to halo-4-alkenoic acids (**2**). The insecticidal activity of pyrethroid esters of 5,5-dihalo-4-pentenoic acids with varying substituents at C_2 has been reported (Drabek et al., 1979; Winternitz, 1978). However, a systematic structure–activity analysis of this series has not appeared in the literature. In particular, the pronounced effect on insecticidal activity of the number and type of alkyl substituents at C_3 in these 5,5-dihalo-4-alkenoic acid esters has not been reported.

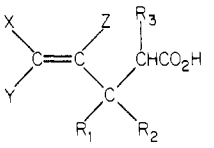
This paper describes the synthesis and biocidal activity of 62 pyrethroids prepared by esterifying halo-4-alkenoic acids with known pyrethroid alcohols. These examples illustrate the structural features required for insecticidal activity among which the most notable is the increase in the biocidal activity of the halo-4-alkenoic esters upon substitution of a methyl group at C_3—an effect that would not have been anticipated by examining the structure/activity features of known pyrethroid esters.

EXPERIMENTAL SECTION

Synthetic Methods. The halo-4-alkenoic acids were synthesized by one of two procedures: (1) a modified malonic ester route (Scheme I); (2) direct allylation of O-silylated ketene acetals (Scheme II). The ketene acetal procedure has been published (Wheeler, 1984). In general, the malonic ester route was used to prepare acids lacking an alkyl substituent at C_3. Table I lists the 22 halo-4-alkenoic acids prepared in this study.

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 197 or Beckman Accu-Lab 2 spectrometer. NMR spectra were obtained with a Varian A-60 or EM 360L spectrometer with Me_4Si as an internal or (in the case of spectra run in CCl_4) external standard. Elemental analyses were obtained by the Union Carbide South Charleston Technical Center Analytical Group. Supplementary material containing spectral, analytical, and biological activity data is available (see paragraph at end of paper regarding supplementary material).

Table I. Halo-4-alkenoic Acids Used To Prepare Pyrethroids



compd no.	X	Y	Z	R_1	R_2	R_3
3	Cl	Cl	H	H	H	*i*-Pr
4	Cl	Cl	H	H	H	*sec*-Bu
5	Cl	Cl	H	H	H	*i*-Bu
6	Cl	Cl	H	H	H	cyclopentyl
7	Cl	Cl	H	H	H	t-Bu
8	Cl	Cl	H	H	H	cyclopropyl
9	H	H	Cl	H	H	*i*-Pr
10[a]	H	Cl	H	H	H	*i*-Pr
11[a]	H	Cl	Cl	H	H	*i*-Pr
12	Cl	Cl	Cl	H	H	*i*-Pr
13	Cl	Cl	Me	H	H	*i*-Pr
14	Br	Br	H	H	H	*i*-Pr
15	Br	Br	H	H	H	Et
16	Cl	Cl	H	Me	H	*i*-Pr
17	Cl	Cl	H	Me	H	cyclopropyl
18	Cl	Cl	H	Et	H	*i*-Pr
19	Cl	Cl	H	Me	Me	*i*-Pr
20	Cl	Cl	H	Me	H	Me
21	Cl	Cl	H	Me	H	Et
22	Cl	Cl	H	Me	Me	Et
23	Cl	Cl	H	Me	H	cyclopentyl
24	Cl	Cl	H	Me	Me	cyclopropyl

[a] Mixture of geometrical isomers.

2-Cyclopropyl-5,5-dichloro-3-methyl-4-pentenoic Acid (17). [This procedure is typical of the modified malonic esters synthesis used to prepare many of the acids in Table I.] A 1-L flask equipped with a mechanical stirrer, thermometer, addition funnel, and reflux condenser with nitrogen inlet was charged with 20.6 g (0.43 mol) of 50% sodium hydride dispersion in mineral oil. The oil was removed by washing the sodium hydride twice with 50-mL portions of toluene. The flask was then charged with 200-mL portions of toluene, the stirred suspension warmed to 45 °C, and 81.1 g (0.43 mol) of diethyl cyclopropyl malonate (Carney and Wojtkunski, 1973) added dropwise over a 2-h period. When all of the malonate had been added, the temperature was raised to 110 °C for 1 h and then the mixture was cooled to 60 °C. The 1,1,3-trichloro-1-butene (68.5 g, 0.43 mol) was added dropwise at such a rate as to maintain the temperature at 60 °C. When the addition was complete, the temperature was raised to 110 °C for 2 h.

The reaction mixture was cooled to room temperature and 10 mL of ice water added, dropwise, to destroy any remaining sodium hydride. The mixture was poured into 200 mL of ice water, the aqueous phase was extracted twice with 250 mL of ether, the ether extracts were combined with the toluene phase, washed with 250 mL of water, and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was vacuum distilled through a vigreux column to give 63.73 g (46%) of the desired malonate as a clear, colorless oil; bp 104–107 °C (0.10 mm); NMR ($CDCl_3$) δ 0.53 (m, 4 H), 1.26 (t, 6 H), 1.20 (d, 3 H), 1.30 (m, 1 H), 3.23 (m, 1 H), 4.20 (q, 4 H), 6.08 (d, 1 H).

A mixture of 107.56 g (0.333 mol) of this malonate, 68.54 g (0.666 mol) of sodium bromide, 350 mL of Me_2SO, and

12 mL of water was heated under nitrogen with stirring to 190 °C until gas evolution had ceased (~5 h). The mixture was cooled to room temperature, diluted with water, and extracted thoroughly with ether. The combined ether extracts were washed with water and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was vacuum distilled to give 67.10 g (80%) of the desired ethyl ester as a clear, colorless oil: bp 79–84 °C (0.15 mm); NMR ($CDCl_3$) δ 0.50–0.82 (m, 5 H), 0.98 and 1.08 (dd, 3 H), 1.23 (t, 3 H), 1.42–1.88 (m, 1 H), 2.71–3.21 (m, 1 H), 4.11 (q, 2 H), 5.73 and 5.96 (dd, 1 H).

This ester (57.0 g, 0.227 mol), 27.24 g (0.681 mol) of sodium hydroxide, 97 mL of water, and 67 mL of ethanol were refluxed for 4 days with stirring under nitrogen. The mixture was cooled to room temperature, most of the ethanol removed under reduced pressure, and the residue diluted with water and extracted thoroughly with ether. The aqueous layer was acidified with concentrated HCl and extracted with ether. The combined ether extracts were twice washed with water and dried ($MgSO_4$), and the solvent was removed to give 45.82 g (90%) of the desired 17 as a yellow oil: NMR ($CDCl_3$) δ 0.10–0.90 (m, 4 H), 1.18 (dd, 3 H), 0.90–3.50 (m, 3 H), 5.93 (dd, 1 H), 11.65 (br s, 1 H); IR (film) 3500–2400, 3080, 2970, 2930, 1700, 1620, 1465, 1460, 1420, 1380, 1290, 1220, 1180, 1140, 1050, 1025, 985, 935, 905, 860, 825, 795, 765 cm^{-1}.

α-Cyano-*m*-phenoxybenzyl 5,5-Dibromo-2-(1-methylethyl)-4-pentenoate (27). [This procedure is typical of the synthesis and purification of the pyrethroid esters.] A mixture of 6.00 g (0.0201 mol) of 5,5-dibromo-2-(1-methylethyl)-4-pentenoic acid, 4 drops of dry pyridine, and 30 mL of CCl_4 was stirred under N_2 and cooled in an ice bath. Thionyl chloride (4.76 g, 0.0400 mol) was added dropwise. The mixture was heated to reflux for ~1 h. After the mixture was cooled to room temperature, the excess thionyl chloride and CCl_4 were removed under reduced pressure. The residue was taken up in 30 mL of CCl_4 and cooled under N_2 in an ice bath. To this mixture was added dropwise a solution of 5.00 g (0.0222 mol) of α-cyano-*m*-phenoxybenzyl alcohol in 10 mL of CCl_4 containing 1.84 g (0.0230 mol) of pyridine. The reaction mixture was stirred for 1 h at 0 °C and then overnight at room temperature. The mixture was diluted with 150 mL of CH_2Cl_2, 25 mL of water was added, and the layers were separated. The organic layer was washed twice with 50 mL of 5% HCl, twice with 50 mL of 10% Na_2CO_3, and once with 50 mL of water. The solution was dried ($MgSO_4$) and filtered, and the solvent was removed to leave 9.4 g of a yellow oil.

This oil was purified by low-pressure liquid chromatography using a prepacked EM silica gel column and eluting with 500 mL of hexane, 500 mL of 99:1 hexane–ethyl acetate, 500 mL of 97:3 hexane–ethyl acetate, and 1000 mL of 95:5 hexane–ethyl acetate. The eluent was collected in 10-mL volumes by using an automatic fraction collector, and all fractions showing a single spot at R_f 0.45 (70:30 hexane–ethyl acetate) were combined and the solvent was removed to leave 3.5 g of the desired ester as a clear, colorless oil: NMR ($CDCl_3$) δ 0.91 (m, 6 H, isopropyl Me), 1.95 (m, 1 H, isopropyl CH), 2.37 (m, 3 H, allylic CH_2 and C_2–H), 6.27 (m, 1 H, olefinic), 6.40 (d, 1 H, CHCN), 7.20 (m, 9 H, aromatic); IR (film) 2960, 1745, 1585, 1480, 1245, 1205, 1140, 1120, 790, 690 cm^{-1}. Anal. Calcd for $C_{22}H_{21}Br_2NO_3$: C, 52.10; H, 4.17; N, 2.76. Found; C, 51.83; H, 4.22; N, 2.81.

[α-Cyano(6-phenoxy-2-pyridinyl)]methyl 2-Cyclopropyl-5,5-dichloro-4-pentenoate (71). [This procedure is typical of that used to prepare esters containing the cyano-6-phenoxypyridine moiety.] A 100-mL flask equipped with addition funnel, magnetic stirrer, and N_2 inlet tube was dried and charged with 3.00 g (0.0144 mol) of 2-cyclopropyl-5,5-dichloro-4-pentenoic acid, 30 mL of CCl_4, and 4 drops of pyridine. The mixture was cooled in an ice bath and 3.40 g (0.0288 mol) of thionyl chloride added. The mixture was refluxed for 2 h, the solvent and excess thionyl chloride were removed under reduced pressure, and the residue was taken up in 10 mL of CCl_4 and placed in an addition funnel.

A 100-mL round-bottomed flask was equipped with a magnetic stirrer and N_2 inlet. The flask was charged with 2.84 g (0.0142 mol) of 6-phenoxy-2-pyridinecarboxaldehyde, 1.43 mL (0.156 mol) of acetone cyanohydrin, 15 mL of CCl_4, and 5 drops of triethylamine. The reaction mixture was stirred at room temperature and monitored by NMR. When the aldehyde peak at δ 9.89 had disappeared, the mixture was cooled in an ice bath, and the acid chloride was added. To this mixture was added 2.0 mL of pyridine, and the mixture was allowed to come to room temperature and stirred overnight.

The mixture was taken up in 100 mL of CCl_4, washed once with 500 mL of water, twice with 75 mL of 2% HCl, and twice with water. The solution was dried ($MgSO_4$), and the solvent was removed to leave 6.58 g of a yellow oil. This oil was purified by LPLC through silica gel eluting with hexane–ethyl acetate to give 3.39 g (56%) of the desired ester as a pale yellow oil: NMR ($CDCl_3$) δ 0.10–1.33 (m, 4 H, cyclopropyl CH_2's), 1.81 (m, 1 H, cyclopropyl CH), 2.55 (m, 2 H, allylic CH_2), 5.88 (t pair, 1 H, olefinic), 6.40 (s, 1 H, CHCN), 6.83–7.90 (m, 8 H, aromatic); IR (film) 3080, 3040, 3000, 2920, 1750, 1620, 1590, 1570, 1485, 1440, 1320, 1270, 1255, 1200, 1140, 1120, 1020, 870, 690 cm^{-1}. Anal. Calcd for $C_{21}H_{18}Cl_2N_2O_3$: C, 60.45; H, 4.35; N, 6.71. Found: C, 60.73; H, 4.24; N, 6.62.

Biological Methods. The biological activity of all compounds was evaluated on insects and mites by using procedures described by Payne et al. (1966) and Weiden et al. (1967). Suspensions of the test compounds were prepared by dissolving 1 g of compound in 50 mL of acetone containing 0.1 g of an alkylphenoxypolyethoxyethanol surfactant. This solution was diluted with 150 mL of water and stirred well to give a 0.5% by weight solution of the test compound. The test concentrations were obtained by appropriate dilutions of this stock suspension with water.

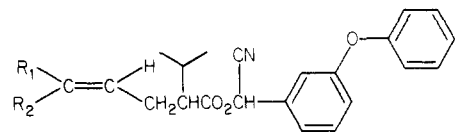
Bioassays with the black bean aphid (*Aphis fabae* Scop.) were conducted by spraying nasturtium plants previously infested with approximately 125 adult and nympha stages of aphids with aqueous formulations of the test compound. After being sprayed, plants were held at 65–70 °F and 50–70% relative humidity, and mortality counts were taken after 24 h.

Tests on the southern armyworm, *Spodoptera eridania* (Cram.), and Mexican bean beetle, *Epilachna varivestis* (Muls.), were conducted by placing third instar larvae in Petri dishes that contain two leaves of tendergreen bean plant previously treated with aqueous formulations of the toxicants. The closed dishes were held at 80 ± 5 °F and 50 ± 5% relative humidity and biological activity was assessed after 3 days.

The pyrethroids were screened against 4–6-day-old adult house flies (*Musca domestica*, L.) by allowing the flies to feed for 24 h on a 10% sugar solution of the test compounds.

Bioassays on the two-spotted spider mite, *Tetranychus urticae* (Kock), were conducted by spraying infested tendergreen bean plants with aqueous formulations of the test compounds. The treated plants were held at 80 ± 5 °F

Table II. Effect of Variations in Double-Bond Terminus on Activity



compd no.	R_1	R_2	LC_{50}, ppm aphid	mite	SAW	MBB	HF[a]
87	H	H	32	500	231	194	225
40[b]	Cl	H	30	330	250	46	74
25	Cl	Cl	8	330	79	24	60
88	CH_3	CH_3	18		316	79	97
41[b]	CH_3	Cl	12	500	222	21	86

[a] SAW = southern armyworm; MBB = Mexican bean beetle; HF = housefly. [b] Mixture of approximately equal amounts of *E* and *Z* isomers.

and 50 ± 5% relative humidity for a period of 7 days, and mortality counts of motile forms (adults and nymphs) were made.

Insectidical and acaridical activity are reported as LC_{50} values (ppm).

RESULTS AND DISCUSSION

Chemistry. The majority of the halo-4-alkenoic acids were synthesized by a modified malonic ester synthesis (Scheme I). Because of the extreme steric hinderance associated with these malonates, conventional saponification required concentrated base and long reaction periods. Under such conditions, the halo vinyl functionality frequently underwent dehydrohalogenation and decomposition. Even when the malonic acids could be obtained, the high temperatures (160–180 °C) required for their decarboxylation often resulted in lactonization of the 4-alkenoic acids.

These difficulties were overcome by modifying the classical malonic ester synthesis to incorporate the decarboethoxylation methods applied by Krapcho (1978) to malonates. It was found that sodium chloride in Me_2SO–water at 185 °C produced a slow decarboethoxylation of the malonates, but the use of 1–2 equiv of sodium bromide in Me_2SO–water resulted in the smooth and rapid decarboethoxylation of even highly hindered malonates.

Halo-4-alkenoic acids that bear one or two alkyl groups at C_3 could not be readily prepared by the malonic ester route due to competing elimination of the allyl halides to 1,3-dienes by the very basic substituted malonate anions. Those halo-4-alkenoic acids with one or two alkyl groups at C_3 were prepared by a route involving allylation of O-silylated ketene acetals (Wheeler, 1984). This method provided convenient access to extremely hindered 4-alkenoic acids.

Biology. The biological objectives of the synthesis program were to determine the insecticidal and acaricidal effects of halogen and alkyl substituents at C_4 and C_5, alkyl substituents at C_2 and C_3, and cycloalkyl groups at C_2 and to identity the preferred alcohol moiety for maximum insecticidal and acaricidal activity.

The five compounds in Table II illustrate the impact of variations in terminal substituents on the biological activity of the 4-alkenoic esters.

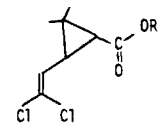
It is apparent that two halogens at the double-bond terminus afford maximum insecticidal activity but do not have a marked impact on the acaricidal activity. One or no halogens or methyl groups at the double-bond terminus results in noticeably lower insecticidal activity.

The examples in Table III illustrate that when C_5 is unsubstituted, placing a chlorine at C_4 does not have a major impact on insecticidal or acaricidal activity (compare **87** and **37**). However, compounds with dichloro substitutents at C_5 (**25**) suffer a substantial decrease in biocidal activity when a chlorine (**44**) or methyl (**45**) is placed at C_4. These results indicate the specific structural requirements needed for the toxicant to achieve the proper fit at the site of action.

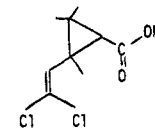
With Mexican bean beetle as the only exception, the geometrical isomerism about the double bond has little effect on the insecticidal and acaricidal activity, e.g., **42** and **43** (Table IV). In addition, the nature of the halogen at C_5, i.e., chlorine (**25**) or bromine (**27**), does not seem to cause major differences in the biocidal activity of these compounds. The latter result is consistent with the observation that the fully resolved isomer of **25** analogous in configuration to **27A** is essentially equivalent in insecticidal activity to that of **27A** (Elliott et al., 1978).

The results presented in Table V demonstrate the effect of alkyl substituents at C_3 on the biocidal activity of a group of halo-4-alkenoic acid esters. An isopropyl moiety at C_2 and a single methyl group at C_3 (**32**) resulted in a 16-fold and an 8-fold increase in toxicity to aphids and Mexican bean beetle, respectively, relative to that of the analogous compound with two hydrogens at C_3 (**25**). Replacing the methyl group at C_3 by an ethyl moiety (**52**) proved (with the exception of Mexican bean beetle) to be detrimental to insecticidal activity but had littel effect on acaricidal activity. Adding two methyl substituents to C_3 (**53**) resulted in a substantial decrease in insecticidal and acaricidal activity. These findings indicate that both the size and number of substituents at C_3 have a major impact on the biological activity of these compounds.

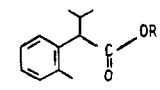
If the substituent at C_2 is an ethyl or cyclopropyl moiety, substitution of a methyl group at C_3 produced a dramatic enhancement of insecticidal and acaricidal activity (compare **26** with **55** and **48** with **51** in Table V). This increase in the biocidal activity of the halo-4-alkenoic esters upon substitution of methyl at C_3 would not have been anticipated by examining the structure–activity features of the alkenyl cyclopropane carboxylates or those of the α-isopropylarylacetates (Elliott, 1977). Pyrethroid esters of **88**



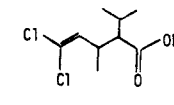
88



89



90

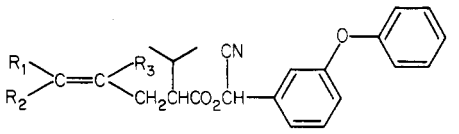


91

show a high level of broad-spectrum insecticidal activity, but methyl substitution at C_3 to give **89** produces a substantial loss of activity. Pyrethroid esters of α-isopropylphenylacetic acid also exhibit intense insecticidal activity, but ortho substitution on the aryl ring, as in **90**, results in a reduction in activity. Structures **88** and **90** are similar to the halo-4-alkenoic acids substituted with methyl at C_3, **91**, and the divergent consequences of a similar structural change in these three series is interesting.

In the cyclopropyl pyrethroids, the geminal dimethyl

Table III. Effect of Substitution at C_4 on Biological Activity

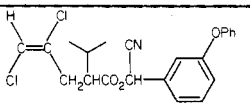
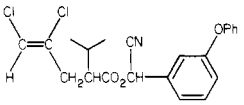
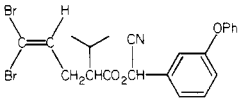
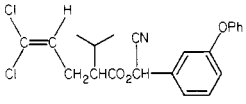
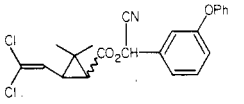
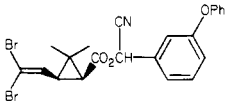


compd no.	R_1	R_2	R_3	LC_{50}, ppm aphid	mite	SAW	MBB	HF[a]
87	H	H	H	32	500	231	194	225
37	H	H	Cl	45	212	305	160	~500
25	Cl	Cl	H	8	330	79	24	60
44	Cl	Cl	Cl	~500	>500	500	70	>500
45	Cl	Cl	CH_3	>500	>500	~500	168	>500

[a] SAW = southern armyworm; MBB = Mexican bean beetle; HF = housefly.

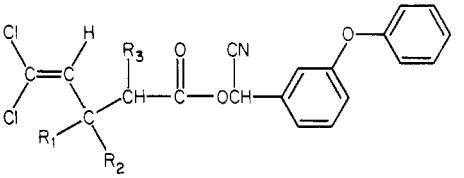
substituents at C_2 of the cyclopropane ring appear to be directly involved in the poisoning mechanism (Elliott, 1970). Opening of the cyclopropane ring to produce the halo-4-alkenoic esters does not appear to invalidate this assumption. Thus, the results presented in Table VI demonstrate that when hydrogen is present at C_3, the isopropyl group at C_2 affords optimum insecticidal activity. The specific need for an isopropyl group at C_2 is further emphasized by the fact that replacing this moiety with the structurally very similar cyclopropyl group results in a dramatic reduction of toxicity to armyworm, Mexican bean beetle, and housefly (compare 25 and 48). Increasing or decreasing the bulk of the C_2 substituent beyond that of the isopropyl group has an adverse effect on the overall insecticidal activity. The minimal acaricidal activity is essentially uneffected by variations in the alkyl substituent at C_2.

Table IV. Effect of Halogen-Type and Geometrical Isomerism on Biological Activity

compd no.	structure	LC_{50}, ppm aphid	mite	SAW	MBB	HF[a]
42		88	252	>500	~250	>500
43		94	370	>400	~71	>500
27		5	~500	130	~20	~72
25		8	330	79	24	60
25A		0.2	74	~3	0.4	~5
27A		0.10	~16	0.31	2	0.3

[a] SAW = southern armyworm; MBB = Mexican bean beetle; HF = housefly.

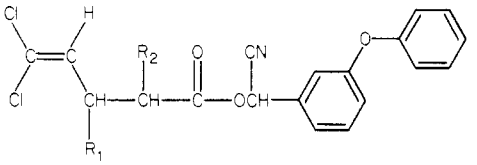
Table V. Effect of Alkyl Substitution at C_3 on Biological Activity



compd no.	R_1	R_2	R_3	LC_{50}, ppm aphid	mite	SAW	MBB	HF[a]
25	H	H	*i*-Pr	8	330	79	24	60
32	Me	H	*i*-Pr	0.5	200	96	3	39
53	Me	Me	*i*-Pr	>500	>500	>500	~500	>500
52	Et	H	*i*-Pr	4	250	~500	19	500
26	H	H	Et	15	>500	>500	>500	>500
55	Me	H	Et	4	~120	62	9	66
56	Me	Me	Et	~500	>500	>500	>100	>500
48	H	H	cyclopropyl	11	>500	>500	>500	>500
51	Me	H	cyclopropyl	0.7	250	31	3	39

[a] SAW = southern armyworm; MBB = Mexican bean beetle; HF = housefly.

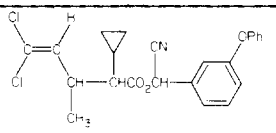
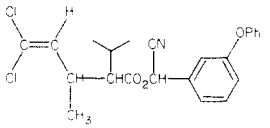
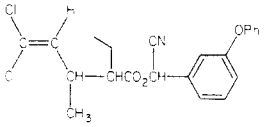
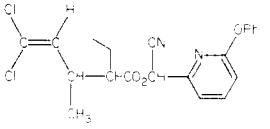
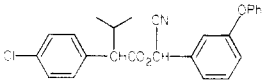
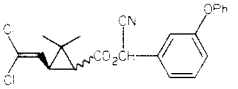
Table VI. Effect of Substituent at C_2 on Biological Activity



compd no.	R_1	R_2	LC_{50}, ppm aphid	mite	SAW	MBB	HF[a]
26	H	ethyl	15	>500	>500	>500	>500
25	H	isopropyl	8	330	79	24	60
48	H	cyclopropyl	11	>500	>500	>500	>500
30	H	*sec*-butyl	130	>500	356	82	>500
31	H	isobutyl	71	>500	~500	287	>500
49	H	*tert*-butyl	213	>500	333	176	500
29	H	isopentyl	140	~500	~500	66	>500
54	Me	methyl	20	>500	>400	147	140
55	Me	ethyl	4	~120	62	9	66
32	Me	isopropyl	0.5	200	96	3	39
51	Me	cyclopropyl	0.7	250	31	3	39
57	Me	cyclopentyl	15	~500	>500	>500	>500

[a] SAW = southern armyworm; MBB = Mexican bean beetle; HF = housefly.

Table VII. Insecticidal Activity of Halo-4-alkenoic Esters vs. Commercial Synthetic Pyrethroids

compd no.	structure	LC_{50}, ppm aphid	mite	SAW	MBB	HF[a]
51		0.7	250	31	3	39
32		0.5	200	96	3	39
55		4	~120	62	9	66
81		8	~100	24	12	78
fenvalerate		0.5	140	5	0.7	8
cypermethrin		0.2	74	~3	0.4	~5

[a] SAW = southern armyworm; MBB = Mexican bean beetle; HF = housefly.

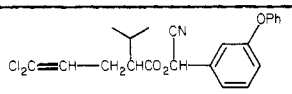
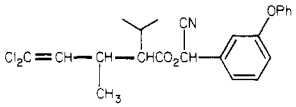
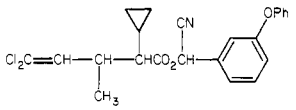
The 4-alkenoic esters bearing a methyl substituent at C_3 show markedly higher insecticidal activity than those that are unsubstituted at C_3. However, in this series, the cyclopropyl substituent at C_2 is essentially equitoxic to insects and mites and somewhat more toxic to southern armyworms than the isopropyl analogue. In general, the acaricidal activity of C_3 methylated compounds is slightly better than their C_3 demethyl analogues.

The results summarized in Tables V and VI emphasize the strict structural requirements at C_2 and C_3 that are necessary to achieve optimum insecticidal activity.

The novel halo-4-alkenoic acids were esterified with a variety of alcohols selected from the pyrethroid art. Included in the selection was 5-benzyl-3-furanmethanol, 3-[(2,2-dichlorovinyl)oxy]-α-cyanobenzyl alcohol, α-cyano-3-phenoxypyridinemethanol, α-cyano-3-(4-fluorophenoxy)pyridinemethanol, α-cyano-3-(4-fluorophenoxy)benzyl alcohol and α-cyano-3-phenoxy-4-fluorobenzyl alcohol. None of these esters afforded superior insecticidal activity to the α-cyano-3-phenoxybenzyl esters.

The most active of the pyrethroids derived from halo-4-alkenoic acids are compared in Table VII to the commercial pyrethroids fenvalerate and cypermethrin. The halo-4-alkenoic esters **32** and **51** exhibit similar aphicidal activity to fenvalerate, but they are less toxic to aphids than cypermethrin. Fenvelerate and cypermethrin are considerably more effective against the other insects listed in Table VII. The acaricidal activity of the esters **55** and

Table VIII. Effect of Synergists on Toxicity of Four Pyrethroids to Selected Insect Species

compd no.	structure	LC_{50}, ppm aphid	SR[a]	SAW	SR	MBB	SR
25							
	alone	8		79		24	
	+pb[b]	0.8	10	24	3.3	18	1.3
	+TPP[b]	9.0	0.9	62	1.3	11	1.2
32							
	alone	0.5		96		3	
	+pb	0.2	2.5	41	2.3	0.2	15
	+TPP	1.5	0.3	58	1.7	0.7	4.3
51							
	alone	0.7		31		3	
	+pb	0.1	7.0	3	10.3	0.7	4.3
	+TPP			32	1.0	1.0	3.0
fenvalerate	alone	0.5		5		0.7	
	+pb	0.05	10	1.2	4.2	0.09	7.8
	+TPP	0.6	0.8	9.0	0.6	0.05	14

[a] Synergistic ratio (SR) = LC_{50} of toxicant alone/LC_{50} of the mixture. [b] For aphid tests 100 and 250 ppm of pb and TPP, respectively, are mixed with the pyrethroid. For SAW and MBB, 500 ppm of the synergists is used.

81 is comparable to that observed for the commercial pyrethroids.

The significance of the apparently beneficial effect of the C_3 methyl in the compositions of Table VI was examined through studies with synergists that may interfere with mfo (piperonyl butoxide) (Pimprikar and Georghiou, 1979) or esteratic (triphenyl phosphate) metabolism (Plapp et al., 1963) (Table VIII). In general, esteratic metabolism seems relatively negligible with these open-chained esters with or without the C_3 methyl. The results with piperonyl butoxide are somewhat different in that **25** (C_3 unsubstituted) is significantly synergized against the aphid but not the armyworm and bean beetle, while the activity of **32** (C_3 methyl) is markedly increased on the bean beetle but not the aphid or armyworm. The cyclopropyl material (**51**) is significantly synergized against both the aphid and the armyworm and, perhaps, the bean beetle. These results suggest that **51** is inherently more toxic than is the isopropyl compound (**32**) to the southern armyworm while being probably (inherently) equitoxic with **32** against the aphid and the bean beetle. It is also clear from Table VIII that although fenvalerate is a generally more toxic material than either **32** or **51**, the activity levels realized through synergism are surprisingly close (except for the bean beetle) for fenvalerate and **51**. Finally, the comparison in Table VIII suggests that the open-chain materials are less active than cypermethrin as well as fenvalerate.

In summary, the structure–activity features of pyrethroids derived from 4-alkenoic acids have been characterized. A considerable enhancement upon substitution of a single methyl group at C_3 has been observed. This enhancement of activity would not have been anticipated from analysis of structure–activity trends in known pyrethroids. Several of the novel esters derived from the halo-4-alkenoic acids exhibit good broad-spectrum insecticidal and some miticidal activity, but the most active of the halo-4-alkenoic esters is considerably less active (particularly on lepidopterous larvae) than the commercial standards fenvalerate and cypermethrin. This reduction in toxicity does not appear to be caused by increased susceptibility to degradative enzymes.

Registry No. **3**, 67829-41-8; **4**, 87953-12-6; **5**, 87953-13-7; **6**, 87953-14-8; **7**, 67829-43-0; **8**, 83190-47-0; **9**, 87953-15-9; (*E*)-**10**, 87953-16-0; (*Z*)-**10**, 87953-38-6; (*E*)-**11**, 87953-17-1; (*Z*)-**11**, 87953-39-7; **12**, 87953-18-2; **13**, 87953-19-3; **14**, 67829-45-2; **15**, 87953-20-6; **16**, 79994-88-0; **18**, 87953-21-7; **19**, 87953-22-8; **20**, 87953-23-9; **21**, 87953-24-0; **22**, 87953-25-1; **23**, 87953-26-2; **24**, 87953-27-3; **25**, 67436-07-1; **26**, 87953-28-4; **27**, 67436-09-3; **28**, 87953-29-5; **29**, 87953-30-8; **30**, 87953-31-9; **31**, 87953-32-0; **32**, 79994-87-9; **33**, 80010-76-0; **34**, 79994-93-7; **35**, 79994-94-8; **36**, 79994-95-9; **37**, 79994-96-0; **38**, 87953-33-1; **39**, 79994-98-2; **40**, 87953-34-2; **41**, 67436-01-5; **42**, 87953-35-3; **44**, 79995-02-1; **45**, 79995-03-2; **46**, 67829-34-9; **47**, 67829-40-7; **48**, 79995-04-3; **49**, 87953-36-4; **50**, 79994-97-1; **51**, 79994-90-4; **52**, 79995-05-4; **53**, 79995-06-5; **54**, 79995-07-6; **55**, 79995-08-7; **56**, 79995-09-8; **57**, 79995-10-1; **58**, 79995-11-2; **59**, 79995-12-3; **60**, 79995-13-4; **61**, 79995-14-5; **62**, 79995-15-6; **63**, 79995-16-7; **64**, 79995-17-8; **65**, 79995-18-9; **66**, 79995-21-4; **67**, 83204-72-2; **68**, 83190-48-1; **69**, 83190-49-2; **70**, 83190-50-5; **71**, 83190-46-9; **72**, 83190-51-6; **73**, 83190-52-7; **74**, 83190-54-9; **75**, 83190-53-8; **76**, 83190-55-0; **77**, 83204-73-3; **78**, 83190-56-1; **79**, 83190-57-2; **80**, 83190-58-3; **81**, 87953-37-5; **82**, 83190-59-4; **83**, 83190-60-7; **84**, 83190-61-8; **85**, 83190-62-9; **86**, 79995-19-0; diethyl cyclopropylmalonate, 42392-68-7; 1,1,3-trichloro-1-butene, 13279-86-2; 5,5-dibromo-2-(1-methylethyl)-4-pentenoic acid, 67829-45-2; α-cyano-*m*-phenoxybenzyl alcohol, 39515-47-4; 2-cyclopropyl-5,5-dichloro-4-pentenoic acid, 83190-47-0; 6-phenoxy-2-pyridinecarboxylate, 68523-22-8.

Supplementary Material Available: Table IX, elemental analyses, Table X, NMR parameters, Table XI, principal infrared bands of pyrethroid esters, and Table XII, insecticidal activity of pyrethroid esters of halo-4-alkenoic acids (19 pages). Ordering information is given on any current masthead page.

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Volatile Constituents of *Amaranthus retroflexus* L.

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The volatile organic compound mixture released by aqueous *Amaranthus retroflexus* L. plant tissue suspensions was examined by combined headspace trapping/gas chromatography/mass spectrometry. The headspace profile was found to change significantly with time; large quantities of hexanal were released immediately after preparation of the blended suspension, along with lesser amouts of other five- and six-carbon oxygenated compounds. With time, the hexanal content dropped considerably, leaving *trans*-2-hexenal as the major released volatile. Headspace examination of a vacuum steam distillate prepared from a freshly prepared tissue suspension revealed no significant composition changes with time, but major quantitative differences were noted on comparison with the tissue suspension headspace profile. The common alcohols *cis*-3-hexen-1-ol, 1-hexanol, and *trans*-2-hexen-1-ol predominated in the steam distillate profile.

Parasitoids of certain crop pests often find a diverse plant environment preferable to the more typical monocultures in commercial agriculture. Presumably, complex crop mixtures are more chemically diverse than monocultures, and therefore they offer a more complex mosaic of local search areas, arousing parasitic wasps (Altieri et al., 1981). Structural plant diversity in crop fields can be increased by intercropping or by permitting selected weed growth in a monoculture. Chemical diversity, however, can be enhanced by applying blended aqueous suspensions of plants that are directly attractive to parasitoids (Monteith, 1960; Read et al., 1970) to the growing crop (Altieri et al., 1981). For example, spray application of *Amaranthus* suspensions to soybean plots resulted in increased parasitization of *Heliothis zea* (Boddie) eggs by the parasitic wasp *Trichogramma* spp. (Altieri et al., 1982). Similar parasitic enhancements have been observed by utilizing tomato extracts (Nordlund, 1983). Since the effectiveness of treatment with these suspensions is thought to be due to certain of their volatile constituents, the evolved volatiles mixtures from the most effective weed tested (*Amaranthus retroflexus* L., pigweed) was examined in some detail.

EXPERIMENTAL SECTION

Materials. Fresh *Amaranthus retroflexus* L. plants were collected from the grounds of the University of California's Gill Tract (Albany, CA) as needed. Tenax-GC (60–80 mesh) was obtained from Applied Science Laboratories, Inc. (State College, PA).

Equipment. Tenax sampling traps were constructed from 7.6-cm lengths of 0.635 cm o.d. Type 304 stainless steel tubing. Fine stainless steel mesh screens held the granular polymer in place (approximately 120 mg; 2.5-cm bed length). Sampling chambers consisted of 2-L glass canning jars fitted with machined aluminum top plates. An inlet tube for charcoal-filtered air and a Swagelok outlet fitting for attachment of the Tenax traps were mounted on the top plates.

A small battery-powered sampling pump was used to draw air from the sample chamber through the polymer trap at a constant rate (20, 50, or 100 cm^3/min) determined by an in-line flow restrictor. Details of the trap, sample chamber, and sampling procedure have been reported previously (Flath and Ohinata, 1982).

Fresh *A. retroflexus* Sample Examination. *A. retroflexus* L. volatiles were first collected from the headspace above intact fresh leaves and stems. Fresh leaves and stems were then blended with distilled water and the resulting headspace volatiles were collected in a second Tenax trap.

Vacuum Steam Distillation. In a typical preparation, *A. retroflexus* (3.9 kg of leaves, stems, and immature seed heads) was blended with distilled water (7 L), and the mixture was distilled at 30 mm. Because of excessive foaming, a quantity of silicone antifoam agent (preboiled with distilled water) was added. The distillate receiver was suspended in a solid carbon dioxide–2-propanol bath. After 5 h, 1.1 kg of distillate had collected. The pot contents were held at room temperature under vacuum overnight, and then two additional fractions were collected

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