3-(3,3-Dihalo-2-propenyl) Analogues of Allethrin and Related Pyrethroids: Synthesis, Biological Activity, and Photostability

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Allethrin analogues with 3-(3,3-dihalo-2-propenyl) substituents are prepared by Wittig reaction of a formylmethyl intermediate, from ozonolysis of allethronyl acetate, with appropriate dihalomethylene ylides and then hydrolysis and reesterification to obtain the (1*R*)-*trans*-chrysanthemates, (1*R*)-*cis*-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylates, and 2,2,3,3-tetramethylcyclopropanecarboxylates. Compared with the propenyl compounds, the difluoropropenyl counterparts in each series are generally more insecticidal whereas the dibromo- and dichloropropenyl analogues of allethrin are less toxic to houseflies. There is surprisingly little difference in the toxicity of the above pyrethroids and of cinerin I, jasmolin I, and the 3-(3-methyl-2-butenyl) analogue to piperonyl butoxide treated flies, but they are all less potent than synergized pyrethrin I. The photoreaction rate as thin films is influenced by the 3-substituent of the rethronyl moiety, i.e., (*Z*)-2,4-pentadienyl > (*Z*)-2-butenyl or -pentenyl or -3-methyl-2-butenyl > 2-propenyl or 3,3-difluoro-2-propenyl > 3,3-dichloro- or 3,3-dibromo-2-propenyl. The propenyl substituent of [*propenyl*-3-^{13}C]-*S*-bioallethrin is photoconverted (^{13}C NMR) to cyclopropyl and 2,3-epoxypropyl groups.

Identification of the insecticidal natural pyrethrins prompted synthesis programs resulting in commercialization of the synthetic 3-(2-propenyl) analogues allethrin (Schechter et al., 1949) and terallethrin (Matsui and Kitahara, 1967). Other effective 3-substituents of the rethrins include the cyclopentenyl, phenyl, benzyl, and furfuryl groups (Barthel, 1961). The biological activity and persistence of pyrethrin I and allethrin are limited by metabolic and photochemical reactions at the 3-[(*Z*)-2,4-pentadienyl] and 3-(2-propenyl) substituents of the alcohol moieties and at the (*E*)-methyl group of the 3-(2-methyl-1-propenyl) substituent of the acid moiety (Chen and Casida, 1969; Elliott et al., 1972; Yamamoto, 1973). Limitations in the insecticidal activity due to the instability of the 3-(2-methyl-1-propenyl) substituent in the acid moiety can sometimes be overcome by adding a synergist (e.g., piperonyl butoxide or PB) acting as an oxidase inhibitor (Casida, 1970) or by replacing this substituent with a 3-(2,2-dihalovinyl) group resistant to metabolic attack and photochemical reaction (Elliott and Janes, 1978). It is of interest to apply principles developed with pyrethroid acid moiety substituents to the rethrin alcohol moieties. This report considers the synthesis of 3-(3,3-dihalo-2-propenyl) analogues of allethrin and related compounds and the influence of structure on their insecticidal activity and stability.

MATERIALS AND METHODS

Chromatography, Spectroscopy, and Analyses. Thin-layer chromatography (TLC) utilized silica gel F-254 chromatoplates (0.25 mm) (carbon tetrachloride–ether, 5:1, or toluene–ethyl acetate, 6:1) and high-pressure liquid chromatography (HPLC) a μPorasil column (chloroform–acetonitrile, 8:1). Gas–liquid chromatography (GLC) involved the Hewlett-Packard 5830A instrument with a ^{63}Ni electron capture detector and an OV-101/OV-210 (3% each) column (190–240 °C; argon–methane, 20:1) and an on-line computer to calculate normalized peak areas. GLC–chemical ionization mass spectrometry (GLC–CI-MS), as previously reported (Ruzo and Casida, 1982), utilized a 5% OV-101 column (120–240 °C, 8 °C/min). Nuclear magnetic resonance (NMR) spectra for compounds in deuteriochloroform were obtained with the UCB-250 instrument (University of California, Berkeley, Chemistry Department) with chemical shifts for ^{1}H (250 MHz) and ^{13}C (63 MHz) related to tetramethylsilane and for ^{19}F (169 MHz) related to fluorotrichloromethane.

Chemicals. Figure 1 and Tables I and II give the structures of the pyrethroids examined. Pyrethrin I (**1**), jasmolin I (**2**), cinerin I (**3**), and [*propenyl*-3-^{13}C]-*S*-bioallethrin were synthesized in optically pure forms as previously described (Ando and Casida, 1983). Bioallethrin (**4**) and (*RS*)-allethrolone were provided by Roussel-Uclaf (Paris, France). The 3-(3-methyl-2-butenyl) analogue of bioallethrin (**5**) was prepared by a procedure analogous to that reported for **1–3** (Ando and Casida, 1983).

The 3-(3,3-dihalo-2-propenyl) analogues (**6–8**, **10**, and **12**) were synthesized from aldehyde **16** obtained on ozonolysis of (*RS*)-allethronyl acetate in methylene chloride followed by reductive workup with zinc–acetic acid (Okada et al., 1977). Aldehyde **16** was condensed by a Wittig reaction with each of three dihalomethylene ylides as follows: (difluoromethylene)triphenylphosphorane from reaction of dibromodifluoromethane and triphenylphosphine in *N*,*N*-dimethylacetamide containing zinc dust (Hayashi et al., 1979); (dichloromethylene)tris(dimethylamino)phosphorane from bromotrichloromethane and hexamethylphosphorous triamide in methylene chloride (Salmond, 1977); (dibromomethylene)triphenylphosphorane from carbon tetrabromide with triphenylphosphine in methylene chloride (Ramirez et al., 1962). Hydrolysis of the dihaloallethronyl acetates with potassium carbonate in methanol and esterification with (1*R*)-*trans*-chrysanthemic acid chloride gave **6–8**, with (1*R*)-*cis*-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylic acid chloride gave **10**, and with 2,2,3,3-tetramethylcyclopropanecarboxylic acid chloride gave **12**. Allethronyl esters **9** and **11** were obtained by esterification of (*RS*)-allethrolone with suitable acid chlorides.

Cyclopropylallethrin (**13**) was prepared by irradiation (300 nm) of *S*-bioallethrin (Roussel-Uclaf) in degassed *n*-hexane (Ruzo et al., 1980) with retention of the (*S*)-alcohol and (1*R*)-trans-acid configurations (^{1}H and ^{13}C NMR). Epoxyallethrin (**14**, mixture of four diastereoisomers) was obtained by reaction of (*RS*)-allethrolone with excess *m*-chloroperoxybenzoic acid in benzene and coupling the epoxyallethrolone obtained with (1*R*)-*trans*-chrysan-

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Table I. ^1H and ^{13}C NMR Data for Substituted Propenyl Groups or Derivatives Thereof of Rethrins and Rethronyl Acetates

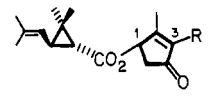
$-CH_2CH=CH_2$ or derivatives thereof		chemical shifts, ppm[a]				
no.	R	C(1')H_2	C(2')H	C(1')	C(2')	C(3')
4, 9, 11, 15, Ac[b]	$-CH_2CH=CH_2$	3.00 (d)	5.75 (d, d, t)[c]	27.1	133.5	115.9
5, Ac	$-CH_2CH=C(CH_3)_2$	2.95 (d)	5.05 (distorted t)[d]	25.6	119.7	133.0
6, 10, 12, Ac	$-CH_2CH=CF_2$[e]	2.90 (d)	4.25 (d, d, t)[f]	16.3 (d)[g]	75.1 (q)[g]	156.6 (t)[g]
7, Ac	$-CH_2CH=CCl_2$	3.10 (d)	5.90 (t)[d]	23.8	125.3	121.4
8, Ac	$-CH_2CH=CBr_2$	3.05 (d)	6.45 (t)[d]	27.3	133.8	90.4
13				7.4	4.5[h]	5.0[h]
14				26.1	50.1	46.7

[a] Spectra were measured in deuteriochloroform with tetramethylsilane as the internal standard. ^1H NMR: ±0.05 ppm. ^{13}C NMR: ±0.1 ppm. ^{13}C data for individual compounds are given in Table I of the supplementary material. For data on related compounds see Ando and Casida (1983), Bramwell et al. (1969), and Janes (1977). [b] Ac is the corresponding acetate. [c] J = 17, 10, and 6 Hz. [d] J = 7 Hz. [e] Similar ^{19}F NMR spectra (deuteriochloroform with fluorotrichloromethane as the internal standard) are obtained for 6, 10, 12, and their alcohol intermediate, i.e., (*Z*)-F ca. −91 ppm [dd, J_{F-F} ~ 44 Hz, J_{H-F} ~ 24.5 Hz (trans)], (*E*)-F ca. −89 ppm (d, J_{F-F} ~ 44 Hz). [f] J_{H-F} = 23.5 Hz (trans) and 2.5 Hz (cis); J_{H-H} = 7.5 Hz. [g] $^1J_{C-F}$ = 287 Hz; $^2J_{C-F}$ = 24 Hz (trans) and 20 Hz (cis); $^3J_{C-F}$ = 5 Hz. [h] These assignments are arbitrary.

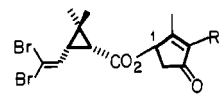
Table II. Toxicity to Houseflies and Photoreactivity as Thin Films of Pyrethrins, Allethrin, Terallethrin, and Their Analogues

rethronyl esters[a]		topical LD_{50}, μg/g			contact, μg/cm²		rel photoreaction rate[b]
no.	R	alone	PB	alone/PB	LD_{50}	KD_{50}	
	Chrysanthemates						
1	$-CH_2CH=CHCH=CH_2$ (Z)	26	0.08	325	>0.3	0.13	17.7
2	$-CH_2CH=CHCH_2CH_3$ (Z)	95	0.68	140	0.23	>0.6	2.0
3	$-CH_2CH=CHCH_3$ (Z)	85	0.27	315	0.22	0.14	4.2
4	$-CH_2CH=CH_2$	29[c]	0.68[c]	43	0.04	0.10	1.0
5	$-CH_2CH=C(CH_3)_2$	265	0.70	379	>0.6	>0.6	1.3
6	$-CH_2CH=CF_2$	12	0.60	20	0.03	0.08	0.7
7	$-CH_2CH=CCl_2$	50	0.55	91	0.13	0.34	0.2
8	$-CH_2CH=CBr_2$	45	1.2	38	0.25	>0.6	0.2
	Dibromovinyldimethylcyclopropanecarboxylates						
9	$-CH_2CH=CH_2$	14	0.43	33	0.05	0.06	0.4
10	$-CH_2CH=CF_2$	9	0.43	21	0.04	>0.4	1.0
	Tetramethylcyclopropanecarboxylates						
11	$-CH_2CH=CH_2$	35	0.75	47	0.07	0.07	0.3
12	$-CH_2CH=CF_2$	10	0.70	14	0.03	0.05	0.3

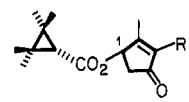
[a] For structures see Figure 1. Compounds 1–3 are optically pure esters of the (1*S*)-alcohols and compounds 4–12 are esters of the (1*RS*)-alcohols. Common names are as follows: 1, pyrethrin I; 2, jasmolin I; 3, cinerin I; 4, bioallethrin; 11, terallethrin. [b] Rates as thin films irradiated at 360 nm are relative to 4 with a reactivity of 5.6 nmol cm^{-2} h^{-1}. [c] Topical LD_{50} values for epoxyallethrin 14 are >500 μg/g alone and 90 μg/g with PB.



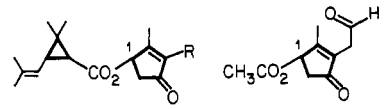
1-8, 13, 14



9, 10



11, 12



15 16

Figure 1. Structures of rethronyl esters studied (1–15) and formylmethyl intermediate 16. See Tables I–III for the identity of the R substituents and common names. Compounds 1–3, 13, and 15 are used as (1*S*)-alcohols and others as (1*RS*)-alcohols.

themic acid chloride. *cis*-Allethrin (15) was made by esterification of (*S*)-allethrolone with (1*RS*)-*cis*-chrysanthemic acid chloride.

Table I gives the ^1H and ^{13}C NMR assignments for the substituted propenyl groups of rethronyl acetates and rethrins 4–15. Tables I and II of the supplementary material give complete ^{13}C NMR data for these compounds (see paragraph at end of paper regarding supplementary material).

Photochemical Studies. For comparisons of photoreactivity the pyrethroids were irradiated at 360 nm as thin films on glass (16 μg/cm²) through Pyrex in a Rayonet photoreactor equipped with RPR 3500 lamps (The Southern N.E. Ultraviolet Co., Middletown, CT). Photolyzed mixtures were dissolved in acetonitrile (5 mL) for GLC of a 2-μL aliquot. Reaction rates were calculated relative to allethrin with duplicate samples irradiated for 0.1–0.5 h (3–45% conversion). Photolyses were also carried out at 32 μg/cm² for 1–2 h for tentative characterization of photoproducts from esters 4 and 6–10 by TLC (carbon tetrachloride–ether, 5:1) with the epoxide-sensitive 4-(*p*-nitrobenzyl)pyridine reagent (Hammock et al., 1974) or by their GLC–CI-MS quasimolecular ions, i.e., $[M + 1]^+$ and

$[M + 29]^+$. In a final study, [^{13}C]-*S*-bioallethrin was irradiated at 300 nm for 2.5 h either as a 0.7 mM solution in degassed hexane or as a 200 $\mu g/cm^2$ thin film on glass, and the products were examined by TLC (toluene–ethyl acetate, 6:1; detection with aqueous potassium permanganate spray or viewing under UV light) and ^{13}C NMR.

Bioassays. Adult female houseflies (*Musca domestica* L., SCR strain, 4–6 days after emergence, ~20 mg each) were treated topically on the abdomen with the test compound in 0.5 μL of acetone or, to determine synergized toxicity, with 5 μg of piperonyl butoxide (PB) in 0.5 μL of acetone and 30 min later with the pyrethroid in 0.5 μL of acetone; mortality was recorded at 24 h. For contact tests the pyrethroid in acetone was placed in the bottom of a Petri dish (60 cm^2), the solvent was evaporated, 10 flies were introduced, and the knockdown (KD) was recorded at 15 min and the kill at 18 h. Adult German cockroaches (*Blattella germanica* L., ~85 mg each, provided by the Vector Control Section, Alameda Naval Air Station, Alameda, CA) were introduced in groups of four into 8-mL vials containing pyrethroid films on all glass surfaces, noting the KD at 1 h and the mortality at 24 h. Male albino mice (13–15 g) were treated intraperitoneally (ip) with the pyrethroid dissolved in 50 μL of methoxytriglycol with mortality determinations 24 h later.

RESULTS

Biological Activity. In housefly topical assays, the three most potent chrysanthemates are pyrethrin I (**1**), bioallethrin (**4**), and particularly the difluoropropenyl analogue (**6**) (Table II). On analogy with *S*-bioallethrin and its less toxic (1*R*)-allethronyl isomer (Elliott, 1954), it appears likely that the major insecticidal component is the (*S*)-rethronyl ester of *RS* compounds **4–12**, thereby further favoring **4** and **6** in comparison with *S*-rethronyl compounds **1–3**. The difluoropropenyl compounds are more potent than their propenyl analogues in all three series examined (**6** vs. **4**, **10** vs. **9**, and **12** vs. **11**) without a large influence of the acid moiety on the toxicity. The least toxic compounds topically to flies are **2**, **3**, and **5** with terminal alkyl substituents and **14** with an epoxyalkyl group. PB increases the topical activity of pyrethroids **1–12** by 20–379-fold and brings all the compounds to essentially the same level of activity except for **1** which is severalfold more potent. Contact toxicity to houseflies, both KD_{50} and LD_{50} values, are generally equivalent for the difluoropropenyl compounds and their propenyl counterparts. Pyrethroids giving lower KD_{50} than LD_{50} values are pyrethrin I (**1**) and cinerin I (**3**) (Table II).

The chrysanthemates are more toxic than the tetramethylcyclopropanecarboxylates to German cockroaches and conversely to mice (Table III).

Photochemical Reactions. Pyrethrin I (**1**) is much more reactive than jasmolin I (**2**) and cinerin I (**3**) which in turn are more reactive than allethrin (**4**) and its methylbutenyl and difluoropropenyl analogues (**5** and **6**). The dichloro- and dibromopropenyl derivatives (**7** and **8**) are the most photostable rethrins examined (Table II). The tetramethylcyclopropanecarboxylates (**11** and **12**) are somewhat more stable than the corresponding chrysanthemates (**4** and **6**) and (dibromovinyl)dimethylcyclopropanecarboxylates (**9** and **10**) (Table II).

Chrysanthemates **4** and **6–8** undergo extensive epoxidation in the acid moiety without other structural modifications (TLC, GLC–CI-MS). [^{13}C]-*S*-Bioallethrin in hexane photolyzes to its cyclopropyl derivative (**13**) (TLC, ^{13}C NMR) and a minor product with a ^{13}C NMR signal appropriate for *cis*-allethrin (**15**) (115.78-ppm signal completely distinct from the 115.96-ppm signal of **4**). When irradiated as a thin film until the parent compound is almost completely decomposed, [^{13}C]allethrin gives a small amount of cyclopropylallethrin (**13**) and a multitude of products of lower TLC R_f including epoxyallethrin (**14**) (TLC, toluene–ethyl acetate, 6:1, R_f 0.16 vs. 0.39 for allethrin). ^{13}C NMR revealed the major signal at 115.97 ppm for allethrin, minor signals at 115.41, 116.19, 116.26, and 116.52 ppm for photoproducts with the unmodified propenyl substituent, and trace signals at 4.5 and 5.1 ppm and at 46.7 ppm appropriate for cyclopropyl and epoxypropyl substituents, respectively. Thus, the propenyl group is not a primary site for photodegradation of bioallethrin as thin films.

Table III. Toxicity to German Cockroaches and Mice of Allethrin, Terallethrin, and Their Difluoropropenyl Analogues

rethronyl esters		LD_{50}	
no.	R	cockroach contact, $\mu g/cm^2$ [a]	mouse ip, mg/kg
	Chrysanthemates		
4	$-CH_2CH=CH_2$	0.33	38
6	$-CH_2CH=CF_2$	0.20	28
	Tetramethylcyclopropanecarboxylates		
11	$-CH_2CH=CH_2$	0.83	5
12	$-CH_2CH=CF_2$	0.57	6

[a] Males are slightly more sensitive than females, and the 15-min KD_{50} dose was about twice the 24-h LD_{50} dose.

Photochemical ester cleavage is a major reaction for both (dibromovinyl)dimethylcyclopropanecarboxylates **9** and **10** and chrysanthemates **4** and **6–8** (GLC–CI-MS of acid moiety). Caronic acid is also detected (GLC–CI-MS) from **4** and **6–8**. Dihaloallethrolones, but not allethrolone itself, are observed as photoproducts. Dibromopropenyl derivative **8** is a special case, yielding eight products (separated by HPLC but cochromatographing on GLC), each modified in the acid moiety and with $[M + 1]^+$ 2 amu lower than **8**. These reactions are completely quenched with 2,4,6-tri-*tert*-butylphenol, suggesting the involvement of a free radical process. Reaction of **8** with *N*-bromosuccinimide in carbon tetrachloride on sunlamp irradiation yields four products identical with those obtained on photolysis (HPLC followed by CI-MS). It appears likely that the first four products arise from bromine radical induced unsaturation or new ring formation and the latter four products from secondary photocyclization reactions.

DISCUSSION

The insecticidal activity and stability of the rethrins are influenced by the 3-substituent of the alcohol moiety due in part to the metabolic and photochemical reactivity conferred by this site. Most of the present studies used houseflies which show a relatively higher potency for **4** vs. **1** than some other insects (Elliott, 1954, 1971). The order for ease of synergism of housefly toxicity by PB approximates that for photoreactivity, i.e., **1** and **3** > **2** and **4** ≥ **6–8**. The greater synergism of **1** than of **4** agrees with an earlier study (Elliott, 1971) and probably reflects their relative ease of biooxidation. Larger LD_{50} and KD_{50} values for **1** and **3** also indicate their rapid metabolism. The high degree of synergism of methylbutenyl compound **5** probably results from oxidatively sensitive allylic methyl substituents at both ends of the molecule. The high photoreactivity of **1** is due to the conjugated *cis*-diene chromophore, and the greater reactivity of **2** and **3** than of **4** may result from the larger number of allylic hydrogens available for free radical abstraction. Replacement of the propenyl

group with a 3,3-dihalopropenyl substituent has relatively little effect on the synergizability but with the dichloro- and dibromopropenyl compounds greatly reduces the photoreactivity.

Allethrin photooxidation yields epoxides at three sites, i.e., the acid moiety methylpropenyl group (Ruzo et al., 1980; Ueda et al., 1974), the cyclopentenolone ring (Kimmel et al., 1982), and the alcohol moiety propenyl substituent (this study). A dihalopropenyl group stabilizes the alcohol moiety to photodecomposition; i.e., dihaloallethrolones but not allethrolone itself are detected as photoproducts, perhaps by minimizing the possibility of epoxidation or ozonolysis reactions at this substituent. Two observations indicate that the alcohol moiety propenyl group may be involved in oxidative detoxification in houseflies, e.g., methylene hydroxylation or epoxidation (Elliott et al., 1972; Yamamoto, 1973). First, the toxicity and degree of synergism are almost independent of the acid moiety, thereby focusing attention on the alcohol moiety. Second, the differential difluoropropenyl vs. propenyl toxicity in topically treated houseflies disappears on PB synergism. In contrast, there is a large toxicity difference between the chrysanthemates and tetramethylcyclopropanecarboxylates in mice, suggesting that detoxification in this case may involve primarily the acid moiety methylpropenyl substituent.

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Registry No. 1, 121-21-1; **2**, 4466-14-2; **3**, 25402-06-6; **4**, 28434-00-6; **5**, 84558-59-8; **6**, 84621-31-8; **7**, 84558-60-1; **8**, 84558-61-2; **9**, 84558-62-3; **10**, 84558-63-4; **11**, 33855-51-5; **12**, 84558-64-5; **13**, 50414-68-1; **14**, 84558-65-6; **15**, 584-79-2; [*propenyl*-3-^{13}C]-*S*-bioallethrin, 83478-01-7; (*RS*)-allethrolone, 29605-88-7.

Supplementary Material Available: Two tables giving complete ^{13}C NMR data for the acid and alcohol moieties of rethronyl acetates and rethrins (2 pages). Ordering information is given on any current masthead page.

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