Ryan, J. J.; Lizotte, R.; Newsome, W. H. *J. Chromatogr.* **1984a**, *303*, 351–360.
Ryan, J. J.; Williams, D. T.; Lau, B. P.-Y.; Sakuma, T. In "Chlorinated Dioxins and Dibenzofurans in the Total Environment, Part II"; Keith, L. H., et al., Eds.; Butterworths: Stoneham, MA, 1984b; pp 205–214.
Sakuma, T.; Gurprasad, N.; Tanner, S. D.; Ngo, A.; Davidson, W. R.; McLeod, H. A.; Lau, B. P.-Y.; Ryan, J. J. In "Chlorinated Dioxins and Dibenzofurans in the Total Environment, Part II"; Keith, L. H., et al., Eds.; Butterworths: Stoneham, MA, 1984; pp 139–152.

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Synthesis and Insecticidal Activities of Pyrethroids Derived from Bicyclo[*n*.1.0]alkenecarboxylic Acids

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Seventeen pyrethroid esters derived from 13 bicyclo[*n*.1.0]alkenecarboxylic acids were synthesized by a newly developed synthetic method. Thus, the cycloaddition products of dichloroketene and substituted cyclopentadienes, dialkylfulvenes, indene, and dialkylbenzofulvenes are used as precursors for the subsequent monodechlorination and Favorskii-type ring contraction to yield the pyrethroid acids. The acids were esterified with a variety of known pyrethroid alcohols. None of the esters showed insecticidal activity in the absence of synergists and very weak synergized insecticidal activity.

INTRODUCTION

The natural pyrethrins have been widely used as effective insecticides due to their high insect toxicity and low mammalian toxicity (Elliott and Janes, 1978). However, a major disadvantage of the natural pyrethrins, especially for use against agricultural pests, lies in the lack of stability in the presence of air and sunlight. The synthesis of new pyrethroid acids and structure–activity studies have received much attention in the literature in recent years (Plummer and Stewart, 1984; Ayad and Wheeler, 1984). A variety of new synthetic pyrethroid esters have been synthesized and reported as effective insecticides with a higher activity and stability than the natural pyrethrins.

We have recently reported a simple yet versatile synthesis of pyrethroid acids (Brady et al., 1983) from conjugated dienes that we believe offers an attractive alternative to existing pyrethroid acid syntheses. This paper describes the synthesis of bicyclo[*n*.1.0]alkenecarboxylic acids, esterification with known pyrethroid alcohols, and the insecticidal activity of the resultant pyrethroid esters.

EXPERIMENTAL SECTION

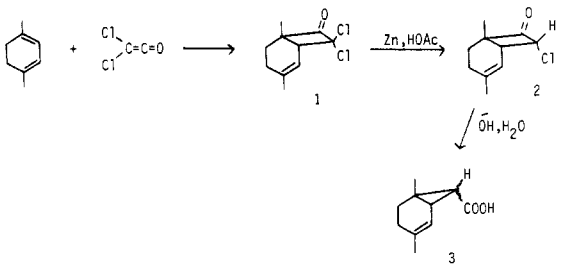
Synthetic Methods. The bicyclo[*n*.1.0]alkenecarboxylic acids were synthesized in three steps as previously described (Scheme I) (Brady et al., 1983).

^{1}H NMR spectra were recorded on a Perkin-Elmer R-248 nuclear magnetic resonance spectrometer, employing deuteriochloroform as the solvent with tetramethylsilane as the internal standard. ^{13}C NMR spectra were recorded on a JEOL FX-90Q FT nuclear magnetic resonance spectrometer.

Ether, hexane, triethylamine, and benzene were dried and purified by distillation from sodium–potassium alloy prior to use.

8,8-Dichloro-3,6-dimethylbicyclo[4.2.0]oct-2-en-7-one (1). (This procedure is typical of the in situ cycloaddition of dichloroketene with a diene to yield the α,α-dichlorocyclobutanone.) To a mixture of 5 g (0.046 mol) of 1,4-dimethyl-1,3-cyclohexadiene and 3.5 g of activated zinc in 250 mL of anhydrous ether was added over a 6-h period a solution of freshly distilled 5.2 mL (0.046 mol) of trichloroacetyl chloride and 4.3 mL (0.046 mol) of phosphoryl chloride in 250 mL of anhydrous ether at ambient temperature. After the addition was complete, the mixture was stirred for an additional 2 h. The excess zinc was removed by filtration and the solution concentrated to about 50 mL and then mixed with 150 mL of hexane. The solution was decanted from the zinc chloride etherate and washed with a solution of sodium bicarbonate and water until neutral. The solvent was removed under reduced pressure and the residue vacuum distilled: bp 69–72 °C (0.10 mm); 6 g (59%); ^{1}H NMR ($CDCl_3$) δ 1.0–3.0 (m, 11 H), 5.25 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 193 (s), 139.4 (s), 124.4 (d), 84.2 (s), 65.1 (d), 20–40 (m).

Scheme I



8-Chloro-3,6-dimethylbicyclo[4.2.0]oct-2-en-7-one (2). (This procedure is typical of the selective reductive removal of only one chlorine atom from the α,α-dichlorocyclobutanones.) To a solution of 4 g (0.0182 mol) of 1 in 100 mL of acetic acid was added 1.15 g (0.0176 mol) of zinc dust in portions over a 1-h period. The mixture was then stirred at ambient temperature for 24 h. A 200-mL portion of ether was added to the reaction mixture, and then it was washed with water until neutral. The ether solution was then dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure: yield 3.1 g (93%) of **2**; IR (film) 1785 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.0–2.5 (m, 10 H), 2.7 (m, 1 H), 4.5 (m, 1 H), 5.3 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 199.0 (s), 139.4 (s), 124.4 (d), 68.8 (d), 20–40 (m).

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3,6-Dimethylbicyclo[4.1.0]hept-2-ene-7-carboxylic Acid (3). (This procedure is typical of the base-catalyzed Favorskii-type ring contraction reactions of the α-chlorocyclobutanones to yield the bicyclo[*n*.1.0]alkenecarboxylic acids.) A mixture of 9.2 g (0.05 mol) of **2** and 0.10 mol of sodium hydroxide in 50 mL of water was refluxed for 6 h. Upon cooling, the mixture was washed with 100 mL of chloroform to remove any unreacted cyclobutanone and/or nonacidic products. The aqueous solution was acidified with 2 N HCl and extracted with 200 mL of ether. The extract was dried over anhydrous magnesium sulfate, and then the solvent was removed under reduced pressure. The residue was vacuum distilled: 4.1 g (50%) of an oil; ^{1}H NMR ($CDCl_3$) δ 1.2–2.5 (m, 12 H), 5.3 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 178.1 (s), 132.2 (s), 119.8 (d), 23–33 (m), 22.9 (q), 18.3 (q).

5-Benzyl-3-furylmethyl 3,6-Dimethylbicyclo[4.1.0]-hept-2-ene-7-carboxylate (4). *m*-Phenoxybenzyl, 5-benzyl-3-furylmethyl, and 3′,4′,5′,6′-tetrahydrophthalimidomethyl alcohols were used for the pyrethroid ester preparations. (This procedure is typical of the pyrethroid ester preparations from the bicyclo[*n*.1.0]alkenecarboxylic acids.) To a refluxing solution of 50 mL of benzene containing 9.5 g (0.08 mol) of freshly distilled thionyl chloride was added 3.3 g (0.02 mol) of the acid **3** in 50 mL of benzene over a 30-min period. This solution was refluxed for 3 h and cooled to ambient temperature. The excess thionyl chloride and benzene were removed under reduced pressure to give the corresponding acid chloride.

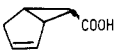
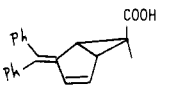
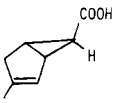
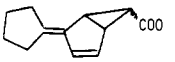
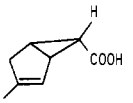
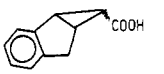
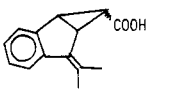
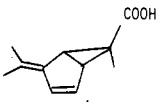
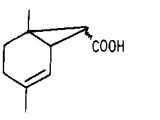
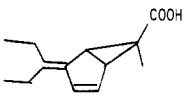
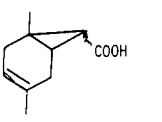
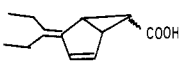
To a 50-mL benzene solution containing 5.64 g (0.03 mol) of 5-benzyl-3-furylmethyl alcohol and 1.6 g (0.02 mol) of pyridine was added the above described acid chloride in 25 mL of benzene over a 15-min period at ambient temperature. The mixture was stirred for 6 h and the pyridine salt removed by filtration. The solvent was removed under reduced pressure and the residue passed through a silica gel column. The ester could be eluted with hexane/ethyl acetate (10/1) solvent system: yield 5.5 g (82%) of a colorless oil; IR (film) 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.2–2.3 (m, 12 H), 3.9 (s, 2 H), 4.8 (s, 2 H), 5.3–5.9 (m, 3 H), 7.2 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 172.2 (s), 154.9 (s), 139.8 (d), 137.2 (s), 133–117 (m), 106.9 (d), 57.0 (t), 33.9 (t), 32–18 (m). Anal. Calcd for $C_{22}H_{24}O_3$: C, 78.57; H, 7.14. Found: C, 78.67; H, 7.29.

Biological Methods. The biological activity of all the pyrethroid esters was evaluated on the female housefly and the male German cockroach. A topical application of an acetone solution of each candidate pyrethroid ester was made to determine an LD_{50} value. Each ester was tested both unsynergized and synergized with piperonyl butoxide, an oxidative inhibitor, and with NIA-16388, an esterase inhibitor. Both synergists were applied at the 1/4 toxicant/synergist ratio to block the two major metabolic pathways known for pyrethroid detoxification. A 24-h percent mortality was determined for each dosage by applying 0.5 μL onto the ventral abdomen of the test insect that is anesthetized by carbon dioxide. Each treatment was replicated twice, using either 25 adult male German cockroaches or 25 female houseflies. The average percent 24-h kill was then plotted on logarithimic probability graph paper to estimate both the LD_{50} and LD_{84} values, or the dosages of active ingredient that are lethal to 50% and 84% of the test insects.

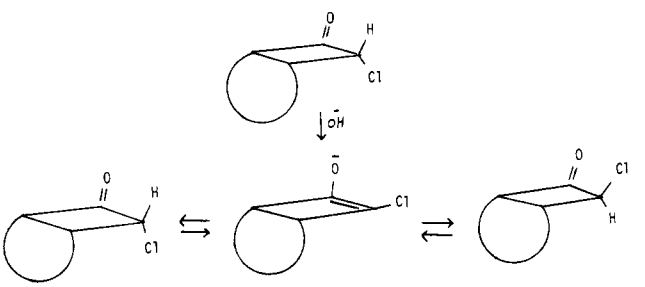
RESULTS AND DISCUSSION

The three-step synthesis described in Scheme I for the bicyclo[*n*.1.0]alkenecarboxylic acids represents a versatile synthesis of pyrethroid acids from conjugated dienes and offers an attractive alternative to existing pyrethroid syntheses. The acids described in Table I were prepared in yields ranging from 20 to 45% (most were in the 40–45% range) for all three steps.

Table I. Bicyclo[*n*.1.0]alkenecarboxylic Acids Used To Prepare Pyrethroids

Compound No.	Structure	Compound No.	Structure
5		12	
6		13	
7		14	
8		15	
9		3	
10		16	
11			

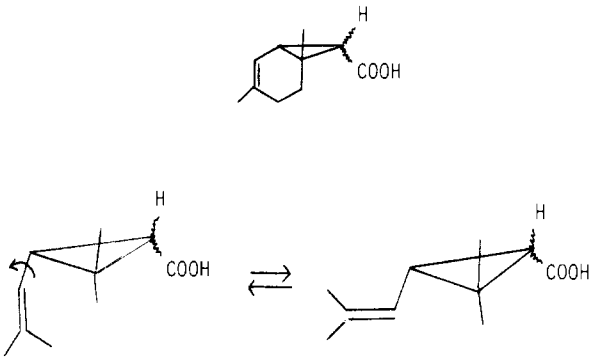
Scheme II



The key step in this synthesis is the reductive removal of only one chlorine atom from the α,α-dichlorobutanone with 1 equiv of zinc dust in acetic acid. This reduction results in only one regioisomer, *endo*-chlorocyclobutanone (Rey et al., 1968), which is also the same regioisomer as obtained from the reduction when tri-*n*-butyltin hydride (Brady and Hoff, 1970) is employed. The subsequent Favorskii-type ring contraction is regiospecific (Salaun and Conia, 1968; Conia and Salaun, 1972) but affords both cis- and trans-substituted bicyclo[*n*.1.0]alkenecarboxylic acids (cis/trans = 1) due to epimerization via the enolate ion under the basic reaction conditions prior to the ring contraction reaction as illustrated in Scheme II (Rey et al., 1982).

In addition to dichloroketene, methylchloroketene was also used in the cycloaddition step with several of the disubstituted fulvenes. Only the corresponding *endo*-methyl-*exo*-chlorocyclobutanones (Brady and Hieble, 1972) were obtained which underwent a regiospecific ring contraction to yield only one regioisomer of the pyrethroid acid, the *endo*-methyl isomer. Since the *endo*-methyl-

Scheme III



exo-chlorocyclobutanones cannot undergo the *endo*- and *exo*-chloro epimerization as noted above for the monochlorocyclobutanones, these regioisomers gave only the *trans*-cyclopropanecarboxylic acids after ring contraction. (Only one regioisomer was found as evidenced by ^{13}C NMR.)

Seventeen pyrethroid esters derived from the 13 bicyclo[*n*.1.0]alkenecarboxylic acids in Table I were prepared by reaction of the acid chlorides with *m*-phenoxybenzyl, 5-benzyl-3-furylmethyl, and 3′,4′,5′,6′-tetrahydrophthalimidomethyl alcohols. These esters were tested for insecticidal activity by determining the 24-h kill by a 0.5-μL topical application on the housefly and the German cockroach. All of the candidate pyrethroids synthesized are nontoxic to both these insects when applied either unsynergized or synergized with piperonyl butoxide. Housefly toxicity is demonstrated at the 5-μg level by several of the pyrethroids (the *m*-phenoxybenzyl ester of compound **5** and the 5-benzyl-3-furylmethyl ester of compounds **3**, **5**–**7**, **14**, and **16**) only when synergized with the esterase inhibitor NIA 16388. These results indicate that metabolic hydrolysis is the major detoxification route for these pyrethroids. However, for the application of 0.5 μL/insect this level of housefly toxicity results in less than 1% the activity of the permethrin standard.

The acid derived from 1,4-dimethyl-1,3-cyclohexadiene (**3**) is worthy of particular note. This acid is very similar to the naturally occurring chrysanthemic acid except it is locked in one particular conformation and lacks the freedom of rotation about the vinyl group as in the natural acid as illustrated in Scheme III. It was anticipated that this acid could give some very specific information about the conformational requirements of the pyrethroid acid as it binds to the target site in the insect. However, since the pyrethroid ester derived from this acid revealed little insecticidal activity, this particular conformation is apparently of little consequence. Certainly this locked conformation would be the least stable of the conformations that the naturally occurring chrysanthemic acid could assume.

In summary, 17 pyrethroid esters derived from 13 bicyclo[*n*.1.0]alkenecarboxylic acids were synthesized and converted into insecticidal pyrethroid esters. None of the esters affords an activity advantage to structurally similar known compounds.

ACKNOWLEDGMENT

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Registry No. **1**, 98874-83-0; **2**, 98874-86-3; **3** (isomer 1), 98874-99-8; **3** (isomer 2), 98973-66-1; **3** (acid chloride) (isomer 1), 98875-03-7; **3** (acid chloride) (isomer 2), 98973-72-9; **4** (isomer 1), 98875-13-9; **4** (isomer 2), 98973-78-5; **5** (isomer 1), 4971-27-1; **5** (isomer 2), 4971-26-0; **5** (acid chloride) (isomer 1), 98973-68-3; **5** (acid chloride) (isomer 2), 98973-69-4; **6**, 98874-92-1; **6** (acid chloride), 98875-01-5; **7**, 98973-61-6; **7** (acid chloride), 98973-73-0; **8** (isomer 1), 98973-62-7; **8** (isomer 2), 98973-63-8; **9**, 98874-93-2; **10**, 98874-94-3; **10** (acid chloride), 98875-02-6; **11** (isomer 1), 98874-95-4; **11** (isomer 2), 98973-64-9; **12**, 98874-96-5; **13** (isomer 1), 98874-97-6; **13** (isomer 2), 98973-65-0; **14** (isomer 1), 31481-64-8; **14** (isomer 2), 31481-65-9; **14** (acid chloride) (isomer 1), 98973-70-7; **14** (acid chloride) (isomer 2), 98973-71-8; **15**, 98874-98-7; **16** (isomer 1), 98875-00-4; **16** (isomer 2), 98973-67-2; dichloroketene, 4591-28-0; 1,4-dimethyl-1,3-cyclohexadiene, 26120-52-5; trichloroacetyl chloride, 76-02-8; 7,7-dichloro-4-(diethylmethylene)bicyclo-[3.2.0]hept-2-en-6-one, 98874-84-1; 6,6-diethylfulvene, 7301-16-8; dichloroacetyl chloride, 79-36-7; 7,7-dichloro-4-cyclopentylidenebicyclo[3.2.0]hept-2-en-6-one, 84257-14-7; 6,6-tetramethylenefulvene, 4727-24-6; 2,3-benzo-7,7-dichloro-4-isopropylidenebicyclo[3.2.0]heptan-6-one, 98874-85-2; dimethylbenzofulvene, 34472-48-5; 7-chloro-7-methyl-4-(diphenylmethylene)bicyclo[3.2.0]hept-2-en-6-one, 98874-91-0; 6,6-diphenylfulvene, 2175-90-8; 2-chloropropanoyl chloride, 7623-09-8; 6,6-dimethylfulvene, 2175-91-9; 7-chloro-4-(diethylmethylene)-bicyclo[3.2.0]hept-2-en-6-one, 98874-87-4; 7-chloro-4-cyclopentylidenebicyclo[3.2.0]hept-2-en-6-one, 98874-88-5; 2,3-benzo-7-chlorobicyclo[3.2.0]heptan-6-one, 76612-37-8; 2,3-benzo-7,7-dichlorobicyclo[3.2.0]heptan-6-one, 7316-61-2; indene, 95-13-6; 2,3-benzo-7-chloro-4-isopropylidenebicyclo[3.2.0]heptan-6-one, 98874-89-6; 7-chloro-3-methylbicyclo[3.2.0]hept-2-en-6-one, 98874-90-9; 7,7-dichloro-3-methylbicyclo[3.2.0]hept-2-en-6-one, 36842-13-4; 5-methylcyclopentadiene, 96-38-8; 7-chlorobicyclo-[3.2.0]hept-2-en-6-one, 25169-61-3; 7,7-dichlorobicyclo[3.2.0]-hept-2-en-6-one, 5307-99-3; cyclopentadiene, 542-92-7; *m*-phenoxybenzyl 2,3-benzobicyclo[3.1.0]hexane-6-carboxylate (isomer 1), 98875-04-8; *m*-phenoxybenzyl 2,3-benzobicyclo[3.1.0]hexane-6-carboxylate (isomer 2), 98973-74-1; 5-benzyl-3-furylmethyl 2,3-benzobicyclo[3.1.0]hexane-6-carboxylate (isomer 1), 98875-05-9; 5-benzyl-3-furylmethyl 2,3-benzobicyclo[3.1.0]hexane-6-carboxylate (isomer 2), 98973-75-2; *m*-phenoxybenzyl bicyclo-[3.1.0]hex-2-ene-6-carboxylate (isomer 1), 98875-06-0; *m*-phenoxybenzyl bicyclo[3.1.0]hex-2-ene-6-carboxylate (isomer 2), 98974-79-9; 5-benzyl-3-furylmethyl bicyclo[3.1.0]hex-2-ene-6-carboxylate (isomer 1), 98974-80-2; 5-benzyl-3-furylmethyl bicyclo[3.1.0]hex-2-ene-6-carboxylate (isomer 2), 98875-07-1; *m*-phenoxybenzyl 3-methylbicyclo[3.1.0]hex-2-ene-6-carboxylate (isomer 1), 98875-08-2; *m*-phenoxybenzyl 3-methylbicyclo-[3.1.0]hex-2-ene-6-carboxylate (isomer 2), 98973-76-3; 5-benzyl-3-furylmethyl 3-methylbicyclo[3.1.0]hex-2-ene-6-carboxylate (isomer 1), 98875-09-3; 5-benzyl-3-furylmethyl 3-methylbicyclo-[3.1.0]hex-2-ene-6-carboxylate (isomer 2), 98973-77-4; *trans*-3′,4′,5′,6′-tetrahydrophthalimidomethyl 3-methylbicyclo[3.1.0]-hex-2-ene-6-carboxylate, 98875-10-6; 5-benzyl-3-furylmethyl 4-(diethylmethylene)-6-methylbicyclo[3.1.0]hex-2-ene-6-carboxylate, 98875-11-7; *m*-phenoxybenzyl 4-(diethylmethylene)-6-methylbicyclo[3.1.0]hex-2-ene-6-carboxylate, 98875-12-8.

Supplementary Material Available: Yields, IR, ^1H NMR, ^{13}C NMR, and elemental analysis data on the cyclobutanones and pyrethroid acids (8 pages). Ordering information is given on any current masthead page.

LITERATURE CITED

Ayad, H. M.; Wheeler, T. N. *J. Agric. Food Chem.* **1984**, *32*, 85.
Brady, W. T.; Norton, S. J.; Ko, J. *Synthesis* **1983**, 1002.
Brady, W. T.; Hieble, J. P. *J. Am. Chem. Soc.* **1972**, *94*, 4278.
Brady, W. T.; Hoff, E. F. J. *J. Org. Chem.* **1970**, *35*, 3733.
Conia, J. M.; Salaun, J. R. *Acc. Chem. Res.* **1972**, *5*, 33.
Elliott, M.; Janes, N. F. *Chem. Soc. Rev.* **1978**, *7*, 473.
Plummer, E. L.; Stewart, R. R. *J. Agric. Food Chem.* **1984**, *32*, 1116.
Rey, M.; Huber, U. A.; Dreiding, A. S. *Tetrahedron Lett.* **1968**, *32*, 3583.
Rey, M.; Roberts, S. M.; Dreiding, A. S. *Helv. Chim. Acta* **1982**, *65*, 703.
Salaun, J.; Conia, J. M. *Bull. Soc. Chim. Fr.* **1968**, 3735.

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