SYNTHETIC APPLICATIONS OF KETENE CYCLOADDITIONS;
NATURAL AND NOVEL PYRETHROID INSECTICIDES

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A new synthetic route to natural and novel pyrethroid acids was developed utilizing ketene cycloaddition which is a significant improvement over existing syntheses. The newly synthesized pyrethroid acids were converted to pyrethroid esters and used to study structure-activity relationships.

The cycloaddition of dichloroketene with 2,5-dimethyl-2,4-hexadiene yields (2+2) cycloaddition products, 2,2-dichlorocyclobutanones. The reductive removal of one chlorine atom from these cycloaddition products gave monochlorocyclobutanones which underwent a Favorskii-type ring contraction to yield cis- and trans-chrysanthemic acids. 4-Methyl-1,3-pentadiene was also used as a precursor in this synthetic scheme to yield an analogue of the chrysanthemic acid.

These results are consistent with a concerted cycloaddition process involving a dipolar transition state. The zinc reduction is not a regiospecific reaction which accounts for the two regioisomers of the monochlorocyclobutanones. The Favorskii-type ring contraction is a regiospecific reaction.

A variety of different bicyclo(3.1.0)alkenecarboxylates
and bicyclo(4.1.0)heptenecarboxylates were synthesized from alkylcyclopentadiene and fulvene derivatives. These new bicyclo pyrethroid acids are structurally similar to the natural chrysanthemic acid but are rigid and locked in a single conformation which is likely the least stable conformer of the natural acid. The acids were converted to pyrethroid esters and tested against the housefly and cockroach. The test results indicate that the bicyclo pyrethroids synthesized are not as active as the natural pyrethroid. Apparently, these bicyclo pyrethroids with structures similar to the less stable conformer of the natural pyrethroids are of little consequence as it binds to the target site in the insect.

In an effort to learn more about the conformational requirements of the pyrethroid acid, a new bicyclo-spiro pyrethroid system with a structure similar to the most stable conformation of the natural pyrethroid was designed and synthesized. These bicyclo-spiro pyrethroids were derived from a new isopropylidenecyclobutane derivatives as a starting compound instead of a conjugated diene. The test results of these bicyclo-spiro pyrethroid esters revealed a much greater activity against the housefly and cockroach. This study establishes that the more stable conformer of the natural pyrethroid acid provides a much higher toxicity against the insects tested.
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Ketenes are highly reactive organic compounds which contain a cumulative linkage of an olefinic and carbonyl group. Most of the halogenated ketenes and monosubstituted ketenes are not stable at room temperature and are usually trapped \textit{in situ} by certain substrates. However, there are some dialkylketenes that are relatively stable. The two most common methods for ketene preparation are the dehalogenation or dehydrohalogenation of the corresponding acid halides as illustrated (1, 2, 3, 4, 5, 6, 7, 8, 9).

\[
\begin{align*}
R_1R_2\text{CBr-C-Br} & \xrightarrow{\text{Zn/Cu, ether}} R_1R_2\text{C=C=O} + \text{ZnBr}_2 \\
R_1R_2\text{CH-C-Cl} & \xrightarrow{\text{Et}_3\text{N}} R_1R_2\text{C=C=O} + \text{Et}_3\text{NH}^+\text{Cl}^-
\end{align*}
\]

The most useful ketene reaction is the (2+2) cycloaddition with olefins to form cyclobutanones (10, 11, 12, 13, 14,
Theoretically, the major orbital interaction in ketene cycloaddition reactions is the bond formation between the HOMO of the ketenophile and the LUMO of the ketene. The effect of electron withdrawing groups on the ketene molecule is to lower the energy of the LUMO, and increase the reactivity of the ketene. The reactivity of substituted ketenes in cycloaddition reaction is exemplified by the following order:

\[
\text{Cl}_2\text{C}=\text{C}=\text{O} \quad > \quad \text{Ph}_2\text{C}=\text{C}=\text{O} \quad > \quad \text{Me}_2\text{C}=\text{C}=\text{O} \quad > \quad \text{H}_2\text{C}=\text{C}=\text{O}
\]

The (2+2) cycloaddition of halogenated ketenes and olefins usually provides cycloaddition products that are most useful for the synthesis of a variety of other important compounds. Since the halogen atom provides a good
leaving group, the $\alpha$-halocyclobutanones may undergo a base
catalyzed ring contraction to cyclopropanecarboxylic acids
\((18)\) or easily undergo reductive removal of halogen to give
the dehalogenated product \((19)\).

\[ \text{Br} \quad \text{OH}^- \quad \text{COOH} \]

Several examples have recently appeared in the liter-
ature utilizing the \((2+2)\) cycloaddition reaction of halogen-
ated ketenes to olefinic compounds as a key step in the syn-
thesis of natural products and natural product precursors.
Tanaka \((20)\) reported in 1971 a new synthesis of $\beta$-Thujaplicin
by using the cycloadduct of isopropylcyclopentadiene and
dichloroketene as a precursor.
Fletcher and Hassner (21) reported in 1970 a synthesis of several derivatives of the natural product, 2-cholestene. The addition of dichloroketene to 2-cholestene proceeds in a regioselective manner to give the cyclobutanone in 75% yield. This cycloaddition product was converted to other derivatives of 2-cholestene by ring contraction and ring opening reactions.
Kato and Kido (22) reported in 1974 an efficient route to an important intermediate in the synthesis of colchicine, a natural product with anti-tumor activity. This synthesis utilized the cycloaddition of dichloroketene to a cyclopentadiene derivative as an important step.

\[
\begin{align*}
\text{OCH}_3 & \quad \text{NaOAc} \quad \text{OCH}_3 \\
\text{CH}_3O & \quad \text{Cl} \quad \text{CH}_3O \\
\text{OCH}_3 & \quad \text{Cl} \quad \text{OCH}_3
\end{align*}
\]

Pschorr Cyclization

There has been much interest in recent years in the synthesis of pyrethroid insecticides because these compounds combine a high insect toxicity, low mammalian toxicity and low environmental persistence (23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34). The natural pyrethroid insecticide, an ester, was first isolated from "Pyrethrum Flowers" by Staudinger and Ruzicka (35) in 1924. The acid part of the natural pyrethroid is called "Chrysanthemic Acid" and is a
cyclopropanecarboxylic acid with a disubstituted vinyl substituent on carbon-3 and a geminal dimethyl substituent on carbon-2. The active pyrethroid alcohol usually contains an unsaturated ring with an unsaturated side chain.

Staudinger and Campbell (35, 36) were the first to synthesize ethyl chrysanthemates by reacting 2,5-dimethyl-2,4-hexadiene with diazoacetic ester with or without adding the copper bronze or rhodium acetate as catalysts.

\[
\text{Catalyst} \quad R_1 \quad R_2 = \text{CH}_3, \text{CH}_3; \text{CH}_3, \text{COOC}_2\text{H}_5; \text{Cl, Cl}; \text{Cl, CF}_3
\]

In 1960 Julia et al. (30, 37, 38, 39) prepared Pyrocines, starting with isobutyraldehyde and acetone and after
the ring opening reaction and cyclization obtained ethyl-
trans-chrysanthemate.

Bellus (40) recently reported a newly developed
pathway to permethrinic acid. The addition product (1) of
carbon tetrachloride and acryllyl chloride was treated with
triethylamine to generate the chloro-(2,2,2-trichloro-
ethyl)ketene. Cycloaddition of this ketene with isobutylene,
followed by a cine rearrangement and Favorinskii rearrange-
ment resulted in permethrinic acid.
Based on structure-activity relationship studies, Elliot (41) has proposed that the geminal dimethyl group on the cyclopropanecarboxylic acid is the most important functional group to insecticidal activity. Thus, after 1975, a series of dimethyl and tetramethyl substituted cyclopropanecarboxylic acids (II) were synthesized by Greuter and Holan (32, 42, 43) and proved to have similar insecticidal activity as the natural pyrethroids. In 1978, Serale (44, 45) synthesized spirocyclopropanecarboxylic acids (III) that revealed good activity. Addor et.al. (46, 47, 48)
synthesized the spiro(2,4)heptanecarboxylic acid system (IV) with fairly good activity.

\[
\begin{align*}
\text{II} & \quad R = \text{Me, Et} \\
\text{III} & \quad R = \text{alkyl, dichlorovinyl} \\
& \quad n = 0, 1, 2, 3
\end{align*}
\]

Recently, Fujimoto (34, 49) reported a new pyrethroid system (V) without a cyclopropane ring that proved to have a very high activity. Since this discovery, there has been a renewed interest in conformational structure-activity studies. The high activity of isopropylphenylacetic acid esters may be due to a conformational mimic of the structure of the natural pyrethroid (VI). More recently, Wheeler (50) has synthesized some linear halo-4-alkenoic acids (VII) as novel pyrethroids that showed good broad spectrum insecticidal and some miticidal activity.
The objective of this research is the development of a new synthesis of pyrethroid acids by utilizing the (2+2) ketene cycloaddition reaction as a key step in this synthesis. It is anticipated that such a synthesis will offer an attractive and alternative route to existing pyrethroid acid syntheses and provide for the synthesis of new acids. A further objective will be the conversion of the pyrethroid acids to esters with insecticidal testing on the esters. Hopefully, structure–activity relationships can be developed which will result in potent new insecticides.
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Proton nuclear magnetic resonance (H-NMR) spectra were recorded on a 60 MHz Hitachi Perkin-Elmer R-24B spectrometer employing deuteriochloroform as solvent, with tetramethylsilane as the internal standard. Carbon-13 NMR spectra were recorded on a 90 MHz Jeol-FX-90Q spectrometer. Deuteriochloroform was used as a lock solvent, and all chemical shifts are reported in parts per million. The infrared (IR) spectra were obtained on a Perkin-Elmer 1330 infrared spectrophotometer. All melting points were determined on a Thomas Hoover capillary melting point apparatus. Elemental analyses were carried out by Midwest Microlab, Indiana. The chromatographic separations were performed on Davisil silica gel 62, Davision Chemical, using hexane/ethyl acetate or ethyl acetate/petroleum ether as eluting solvents.

Hexanes, ether, triethylamine, and benzene were dried by distilling from sodium-potassium alloy. All reagents were distilled or recrystallized prior to use. Zinc was activated by copper sulfate. The biological activity of all the pyrethroid esters was evaluated on the female housefly (Musca domestica) and the male German cockroach (Blattella
germanica) by Johnson Wax company. An topical application of each candidate pyrethroid ester was made to determine a LD<sub>50</sub> 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.

2,2-Dichloro-4,4-dimethyl-3-(2-methylpropenyl)cyclobutanone, 2a, and 2,2-Dichloro-3,3-dimethyl-4-(2-methylpropenyl)cyclobutanone, 2a'. A solution of 25 mmol of freshly distilled trichloroacetyl chloride and 25 mmol of POCl<sub>3</sub> in 250 ml of anhydrous ether was added over a 10 hr period to a stirring mixture of 0.10 mol of 2,5-dimethyl-2,4-hexadiene and 25 mmol of activated zinc (1.64 g) in 250 ml of ether at ambient temperature. After the addition was complete, the reaction mixture was stirred for an additional 12 hr. The excess zinc was removed by filtration and the solution concentrated to about 50 ml and then stirred with 100 ml of pentane. The solution was decanted from the zinc chloride etherate and washed with water and a saturated solution of NaHCO<sub>3</sub>. The solvent was removed under reduced pressure and the residue vacuum distilled at 55-58 °C (0.2 mm) to yield 3.1 g (55%); the ratio of 2a/2a' = 3 as evidenced by the <sup>1</sup>H-NMR. The IR and <sup>1</sup>H-NMR data were identical with reported values (1). <sup>13</sup>C-NMR
2-Chloro-4,4-dimethyl-3-(2-methylpropenyl)cyclobutanone, 3a, and 2-Chloro-3,3-dimethyl-4-(2-methylpropenyl)cyclobutanone, 3a'. A 4.0 g (18 mmol) portion of cycloadduct, 2a and 2a', in 50 ml of acetic acid and 5 ml of water was added in portions to 18 mmol of zinc dust over a 1 hr period and then the mixture was stirred for 24 hr at ambient temperature. A 150 ml portion of ether was added to the reaction mixture and the mixture washed with water and a NaHCO₃ solution. The ether solution was dried over anhydrous MgSO₄, the solvent removed under reduced pressure, and the residue vacuum distilled at 58-60°C (0.1 mm) to yield 2.8 g (82%) of 3a and 3a'; IR (film), 1780 cm⁻¹; ¹H-NMR (CDCl₃), δ, 5.3 (d, 2 H, J = 8 Hz), 4.7 (m, 2 H), 3.8 (d, 1 H, J = 6 Hz), 3.0 (m, 1 H), 1.6-1.9 (m, 6 H), 1.0-1.6 (m, 6 H); ¹³C-NMR (CDCl₃), δ, 210.7 (s), 205.5 (s), 138.2 (s), 136.6 (s), 119.5 (d), 117.9 (d), 114.8 (d), 114.1 (d), 69.6 (d), 68.7 (d), 64.7 (d), 63.1-18.3 (overlapped).

cis and trans-Chrysanthemic Acids, 4a. A 2.0 g mixture of monochlorocycloadduct 3a and 3a' was treated with 2 eq of KOH in 50 ml of water at ambient temperature for 24 hrs. The reaction solution was then washed with CHCl₃ to remove unreacted cyclobutanone and/or nonacidic products.
The aqueous reaction solution was then acidified with 2 N HCl and extracted with chloroform, dried over anhydrous MgSO₄ and evaporated under reduced pressure. The residue was vacuum distilled at 95-96°C (0.25 mm) or 138-139°C (10 mm) to yield 1.3 g (73%) of cis- and trans-chrysanthemic acids; (trans/cis = 3). The trans-acid was crystallized from ethyl acetate at -10°C (2 days), washed with petroleum ether and recrystallized from ethyl acetate, m.p. 54°C. The filtrate was cooled to -78°C to yield the cis-acid, m.p. 115-116°C (the m.p. and 1H-NMR data of cis- and trans-chrysanthemic acids are identical with those in the literature) (2). 

2,2-Dichloro-3-(2-methylpropenyl)cyclobutanone, 2b.

From 50 mmol (5.6 ml) of trichloroacety1 chloride, 5 g (60 mmol) of 4-methyl-1,3-pentadiene, 1b, 50 mmol (4.6 ml) of POCl₃ and 5 g (78 mmol) of zinc in 500 ml of ether was obtained 6.8 g (71%) of dichloroketene cycloadduct, 2b, at 65-67°C (0.2 mm); IR (film), 1800 cm⁻¹; 1H-NMR (CDCl₃), δ, 5.2 (d, 1 H, J = 6 Hz), 2.9-3.9 (m, 3 H), 1.9 (m, 3 H), 1.8 (m, 3 H); 13C-NMR (CDCl₃), δ, 192.7 (s), 139.5 (s), 120.5 (d), 90.1 (s), 65.1 (q), 62.6 (d), 48.7 (q), 44.3 (q).
2-Chloro-3-(2-methylpropenyl)cyclobutanone, 3b.

From 5 g (26 mmol) of dichloroketene cycloadduct, 2b, and 1.7 g of zinc in 50 ml of acetic acid and 5 ml of water after 20 hr at ambient temperature there was obtained 3.2 g (79%) of monochlorocycloadduct, 3b, at 52-54°C (0.1 mm); IR (film), 1790 cm⁻¹; ¹H-NMR (CDCl₃), δ, 5.2 (m, 1 H), 4.6 (m, 1 H), 2.6-3.7 (m, 3 H, endo - and exo -), 1.85 (s, 3 H), and 1.75 (s, 3 H); ¹³C-NMR (CDCl₃), δ, (endo- and exo -) 199.7 (s), 198.1 (s), 136.5 (s), 136.4 (s), 124.1 (d), 121.0 (d), 67.1 (d), 65.2 (d), 50.0 (t), 48.9 (t), 35.5 (d), 29.5 (d), 25.3 (q), 25.2 (q), 18.1 (q).

3-(2-Methylpropenyl)cyclobutanone, 3c. From 2 g (10 mmol) of dichlorocyclobutanone, 2b, and 6 g (10 mmol) of zinc in 30 ml of acetic acid and 2 ml of water at ambient temperature after 80 hrs there was obtained 1.2 g (90%) of nonchlorinated cyclobutanone, 3c, at 42°C (3.5 mm); IR (film), 1775 cm⁻¹; ¹H-NMR (CDCl₃), δ, 5.2 (d, 1 H, J = 6.3 Hz), 2.6-3.4 (m, 5 H), 1.7 (s, 3 H), 1.65 (s, 3 H); ¹³C-NMR (CDCl₃), δ, 205.6 (s), 132.4 (s), 128.0 (d), 53.7 (t), 24.8 (q), 21.9 (d), 17.5 (q).

2-(2-Methylpropenyl)cyclopropanecarboxylic Acid, 4b.

From 2 g (12 mmol) of monochlorocyclobutanone, 3b, and 1.6 g (30 mmol) of KOH in 50 ml of water at ambient temperature after 24 hrs there was obtained 1.2 g (75%) of acid, 4b, at 85-86°C (0.1 mm), trans/cis = 10; IR (film), 1680 cm⁻¹; ¹H-NMR (CDCl₃), δ, 12.3 (bs, 1 H), 4.6 (dd, 1 H, J = 8.9 Hz,
\( J = 1.2 \text{ Hz} \), 2.06 (m, 1 H), 1.48 (m, 3 H), 1.4 (m, 3 H), 1.35 (m, 2 H), and 0.9 (m, 1 H); \(^{13}\text{C-NMR (CDCl}_3\), } \delta, \text{ trans-acid: 180.1 (s), 134.0 (s), 124.0 (d), 24.9 (q), 22.3 (d), 21.5 (d), 17.8 (q), 16.3 (q); cis-acid: 178.7 (s), 134.0 (s), 120.7 (d), 20.8 overlapped with 20.3 overlapped with 14.5 (the cis- and trans-acids were not separated).

Anal. Calcd. for C\(_8\)H\(_{12}\)O\(_2\): C, 68.54; H, 8.63. Found: C, 68.23; H, 8.69.

**1,4-Dimethyl-1,3-cyclohexadiene:**

(A) Dehydration of 1,4-Dimethyl-3-cyclohexenol.

1,4-Dimethyl-3-cyclohexenol (10 g, 8 mmol) was added to a solution of 6 ml of concentrated hydrochloric acid in 60 ml of water and refluxed for 14 hrs. Upon cooling to room temperature, this mixture was extracted with two 30 ml portions of ether. The combined ether extracts were extracted with water until neutral and then the ether solution was dried over anhydrous MgSO\(_4\). The ether was evaporated to give a mixture of 1,4-dimethyl-1,3-cyclohexadiene, 14b, and 1,4-dimethyl-1,4-cyclohexadiene, 14a: 7.7 g (89%); the ratio of 14b/14a = 70/30 as evidenced by \(^1\text{H-NMR and }^{13}\text{C-NMR spectra.}

A portion of this mixture, 3 g, was passed through a 20\% impregnated silver nitrate silica gel column (3) (height 40 cm, diameter 20 mm) using petroleum ether to elute 1,4-dimethyl-1,4-cyclohexadiene. The desired 1,4-dimethyl-1,3-cyclohexadiene was eluted with petroleum
ether containing ether (20%) to give 2.1 g. The $^1$H-NMR and $^{13}$C-NMR spectra were identical with those in the literature (4).

(B) Isomerization of 1,4-Dimethyl-1,4-cyclohexadiene. 1,4-Dimethyl-1,4-cyclohexadiene (10 g) was refluxed with 6 ml of concentrated hydrochloric acid in 60 ml of water for 14 hr. This mixture was worked up as described above and passed through the silica gel column impregnated with silver nitrate to give pure 1,4-dimethyl-1,3-cyclohexadiene (6.3 g) as evidenced by the $^1$H-NMR and $^{13}$C-NMR spectral data (4).

General Procedure for Cycloadditions of Halogenated Ketenes with Cycloalkadiene Derivatives. To a solution of 0.25 mol of triethylamine and 0.25 mol of the cycloalkadiene derivative in 300 ml of hexane was added 0.25 mol of the appropriate acid chloride (dichloroacetyl chloride for dichloroketene cycloadditions and $\alpha$-chloropropionyl chloride for methylchloroketene cycloadditions) in 100 ml of hexane. The addition was made dropwise over a period of 2 hr with stirring. After the addition was complete, the stirring was continued for 1 h and then the amine salt was filtered and the filtrate washed with two 150 ml portions of water. The filtrate was dried over MgSO$_4$ and the solvent removed under reduced pressure and the residue vacuum distilled to yield the cycloaddition product.
7,7-Dichloro-4-isopropylidenebicyclo(3.2.0)hept-2-en-6-one. A solution of 13.8 g (93 mmol) of dichloroacetyl chloride in 10 ml of hexane was added dropwise to a warm (40°) solution of 10 g (94 mmol) of 6,6-dimethylfulvene and 9.5 g (94 mmol) of triethylamine in 500 ml of hexane during a 5 hr period. The amine salt was removed under reduced pressure and the residue vacuum distilled at 94° C (0.25 mm) or 100° C (0.7 mm) to yield 18.2 g (89%); (5) IR (film), 1802 cm⁻¹; ¹H-NMR (CDCl₃), δ, 6.5 (m, 1 H), 5.9 (m, 1 H), 4.7 (m, 1 H), 4.1 (m, 1 H), 1.8 (s, 6 H); ¹³C-NMR (CDCl₃), δ, 193.9 (s), 136.2 (d), 133.4 (s), 129.7 (s), 129.4 (d), 87.7 (s), 62.3 (d), 58.1 (d), 21.9 (q), 20.8 (q).

7,7-Dichloro-4-diethylmethylenebicyclo(3.2.0)hept-2-en-6-one. A 50 g (0.37 mol) portion of 6,6-diethylfulvene, (6) 36 ml (0.37 mol) of dichloroacetyl chloride and 51 ml (0.37 mol) of triethylamine gave 60 g (66%) of the cycloadduct; bp 120° C (0.2 mm), IR (film), 1800 cm⁻¹, ¹H-NMR (CDCl₃), δ, 1.0 (m, 6 H), 2.2 (q, 4 H), 4.1 (m, 1 H), 4.8 (d, 1 H, J = 6 Hz), 5.9 (m, 1 H), 6.6 (d, 1 H, J = 6 Hz); ¹³C-NMR (CDCl₃), δ, 193.7 (s), 141.3 (s), 136.1 (d), 132.9 (s), 129.7 (d), 87.4 (s), 62.1 (d), 58.0 (d), 26.4 (t), 24.8 (t), 13.3 (q), 12.3 (q).

7-Chloro-7-methyl-4-diethylmethylenebicyclo(3.2.0)hept-2-en-6-one. A solution of 28 g (0.2 mol) of 6,6-diethylfulvene, 20.2 g (0.2 mol) of triethylamine and 25.4 g
(0.2 mol) of 2-chloropropionyl chloride in hexane was refluxed for 24 hrs. The crude cycloadduct in hexane was passed through a silica gel column to give 27 g (60%); IR (film), 1800 cm$^{-1}$; $^1$H-NMR (CDCl$_3$), $\delta$, 1.0 (m, 6 H), 1.5 (s, 3 H), 2.2 (q, 4 H), 3.7 (d, 1 H, J = 7 Hz), 4.7 (d, 1 H, J = 7 Hz), 5.9 (s, 1 H), 6.6 (d, 1 H, J = 6 Hz); $^{13}$C-NMR (CDCl$_3$), $\delta$, 202 (s), 139.7 (s), 135.9 (d), 131.7 (s), 130.6 (d), 77.9 (s), 63.4 (d), 53.8 (d), 26.6 (t), 24.9 (t), 19.5 (q), 13.6 (q), 12.5 (q).

7,7-Dichloro-4-cyclopentylidenebicyclo(3.2.0)hept-2-en-6-one. From 30 g (0.22 mol) of 6,6-tetramethylenefulvene, (6) 33.4 g (0.22 mol) of dichloroacetyl chloride and 22.2 g (0.22 mol) of triethylamine in refluxing hexane, there was obtained 33 g (61%); b.p. 130°C (0.15 mm); IR (film), 1800 cm$^{-1}$; $^1$H-NMR (CDCl$_3$), $\delta$, 2.0-3.0 (m, 8 H), 4.2-4.4 (m, 2 H), 5.8 (m, 2 H).

7-Chloro-7-methyl-4-isopropylidenebicyclo(3.2.0)hept-2-en-6-one. From 15 g (0.14 mol) of 6,6-dimethylfulvene, (7) 14.5 g (0.14 mol) of triethylamine and 18 g (0.14 mol) of 2-chloropropionyl chloride, there was obtained 19.6 g (70%); b.p. 92-4°C (0.25 mm); IR (film), 1790 cm$^{-1}$; $^1$H-NMR (CDCl$_3$), $\delta$, 1.5 (s, 3 H), 1.8 (s, 6 H), 3.7 (m, 1 H), 4.7 (m, 1H), 5.8 (m, 1 H), 6.5 (d, 1 H, J = 6 Hz); $^{13}$C-NMR (CDCl$_3$), $\delta$, 202.9 (s), 135.9 (d), 130.3 (d), 78.2 (s), 63.6 (d), 53.9 (d), 22.2 (q), 20.9 (q), 19.6 (q).
2,3-Benzo-7,7-dichloro-4-isopropylidenebicyclo(3.2.0)-heptan-6-one. From 40 g (0.25 mol) of dimethylbenzofulvene, 37.7 g (0.25 mol) of dichloroacetyl chloride, and 25.2 g (0.25 mol) of triethylamine, there was obtained 26.7 g (40%); m.p. 105-7 °C after recryst. from hexane; IR (film), 1800 cm⁻¹; ¹H-NMR (CDCl₃), δ, 2.0 (s, 3 H), 2.1 (s, 3 H), 4.4 (d, 1 H, J = 9 Hz), 5.0 (d, 1 H, J = 9 Hz), 7.5 (m, 4 H); ¹³C-NMR (CDCl₃), δ, 194.1 (s), 142.1 (s), 132.7 (s), 129.4 (s), 128.9 (d), 128.5 (d), 126.9 (d), 124.7 (d), 88.3 (s), 64.4 (d), 55.5 (d), 25.2 (q), 21.5 (q).

7-Chloro-7-methyl-4-diphenylmethylenebicyclo(3.2.0)-hept-2-en-6-one. From 14 g (0.06 mol) of 6,6-diphenylfulvene (8), 6 g (0.06 mol) of triethylamine and 7.6 g (0.06 mol) of 2-chloropropanoyl chloride, there was obtained 7.6 g (40%); m.p. 117-8 °C, recryst. from acetone; IR (film), 1780 cm⁻¹; ¹H-NMR (CDCl₃), δ, 1.55 (s, 3 H), 3.9 (m, 1 H), 4.8 (d, 1 H, J = 7 Hz), 6.0 (m, 1 H), 6.45 (d, 1 H, J = 6 Hz), 7.2 (m, 10 H); ¹³C-NMR (CDCl₃), δ, 202.1 (s), 125-141 (m), 77.8 (s), 65.8 (d), 54.8 (d), 19.3 (q).

8,8-Dichloro-3,6-dimethylbicyclo(4.2.0)octa-2-en-7-one. To a mixture of 5 g (0.046 mol) of 1,4-dimethyl-1,3-cyclohexadiene (9) and 3.5 g of activated zinc in 250 ml of ether was added over a 6 hr 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 hrs. 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 residue vacuum distilled, b.p. 69-72°C (0.10 mm), to give 6 g (59%); \textsuperscript{1} H-NMR (CDCl\textsubscript{3}), ¥, 1.0-3.0 (m, 11 H), 5.25 (m, 1 H); \textsuperscript{13} C-NMR (CDCl\textsubscript{3}), ¥, 193.0 (s), 139.4 (s), 124.4 (d), 84.2 (s), 65.1 (d), 20-40 (m).

**General Procedure of the Reduction of the Dichloroketene Cycloadducts.** To a solution of 0.1 mol of the dichlorocyclobutanone derivatives in 300 ml of acetic acid is added 0.1 mol of zinc dust in portions over a 1 hr period. The mixture is then stirred at ambient temperature for 24 hr. A 200 ml portion of ether is added to the reaction mixture and then it is washed with water until neutral. The ether solution is then dried over anhydrous MgSO\textsubscript{4} and the solvent is removed under reduced pressure. The residue was used without further purification in the next step (ring contraction step).

**7-Chloro-3-methylbicyclo(3.2.0)hept-2-en-6-one.** From 6 g (0.031 mol) of 7,7-dichloro-3-methylbicyclo(3.2.0)hept-2-en-6-one and 2.0 g of zinc in 30 ml of acetic acid was obtained 4.2 g (86.5%), bp 63 °C (0.1 mm); IR (film), 1780 cm\textsuperscript{-1}; \textsuperscript{1} H-NMR (CDCl\textsubscript{3}), ¥, 1.7 (s, 3 H), 2.4 (m, 2 H), 3.6 (m, 2 H),
4.8 (dd, 1 H, J = 6 Hz, J = 6 Hz), 5.1 (m, 1 H); \textsuperscript{13}C-NMR (CDCl\textsubscript{3}), \delta, 204.7 (s), 146.0 (s), 121.9 (d), 65.1 (d), 58.6 (d), 45.8 (d), 39.1 (t), 16.3 (q).

\textbf{7-Chlorobicyclo(3.2.0)hept-2-en-6-one.} From 10 g of 7,7-dichloro-bicyclo(3.2.0)hept-2-en-6-one and 3.7 g of zinc in 50 ml of acetic acid there was obtained 7.2 g (90%); IR (film), 1790 cm\textsuperscript{-1}; \textsuperscript{1}H-NMR (CDCl\textsubscript{3}), \delta, 2.5 (m, 2 H), 3.7 (m, 2 H), 4.9 (m, 1 H), 5.6 (m, 2 H); \textsuperscript{13}C-NMR (CDCl\textsubscript{3}), \delta, 204.3 (s), 135.3 (d), 128.0 (d), 65.2 (d), 58.0 (d), 45.7 (d), 35.3 (t).

\textbf{7-Chloro-4-isopropylidenebicyclo(3.2.0)hept-2-en-6-one.} From 10 g (46 mmol) of 7,7-dichloro-4-isopropylidenebicyclo(3.2.0)hept-2-en-6-one and 3.0 g (46 mmol) of zinc in 100 ml of acetic acid and 10 ml of water at ambient temperature, after 24 hrs there was obtained 6.8 g (82%), m.p. 63°C (from petroleum ether); IR (film), 1780 cm\textsuperscript{-1}; \textsuperscript{1}H-NMR (CDCl\textsubscript{3}), \delta, 6.1 (m, 1 H), 5.9 (m, 1 H), 5.0 (m, 1 H), 4.4 (m, 1 H), 3.95 (m, 1 H), 1.8 (s, 6 H); \textsuperscript{13}C-NMR (CDCl\textsubscript{3}), \delta, 201.9 (s), 135.7 (d), 135.1 (s), 129.9 (d), 127.4 (s), 64.4 (d), 63.1 (d), 44.3 (d), 21.7 (q), 20.6 (q).

\textbf{7-Chloro-4-diethylmethylenebicyclo(3.2.0)hept-2-en-6-one.} From 50 g (0.20 mol) of 7,7-dichloro-4-diethylmethylenebicyclo(3.2.0)hept-2-en-6-one and 13.3 g of zinc in 240 ml of acetic acid, there was obtained 38.7 g (92%), b.p. 110°C (0.25 mm); IR (film), 1790 cm\textsuperscript{-1}; \textsuperscript{1}H-NMR (CDCl\textsubscript{3}), \delta, 1.05 (m, 6 H), 2.25 (q, 4 H), 4.0 (m, 1 H), 4.5 (m, 1 H), 5.0
(dd, 1 H, J = 9 Hz, J = 5 Hz), 5.95 (m, 1 H), 6.55 (m, 1 H); ^13^C-NMR (CDCl\textsubscript{3}), \delta, 201.4 (s), 141.4 (s), 138.8 (s), 135.4 (d), 130.2 (d), 64.0 (d), 62.6 (d), 44.1 (d), 26.0 (t), 24.6 (t), 13.1 (q), 12.3 (q).

7-Chloro-4-cyclopentylidenebicyclo(3.2.0)hept-2-en-6-one. From 25 g (0.102 mol) of 7,7-Dichloro-4-cyclopentylidenebicyclo(3.2.0)hept-2-en-6-one and 6.7 g of zinc in 150 ml of acetic acid, there was obtained 15.9 g (75%), m.p. 132°C (recryst. from hexane/benzene); IR (film), 1790 cm\textsuperscript{-1}; \textsuperscript{1}H-NMR (CDCl\textsubscript{3}), \delta, 1.8-3.1 (m, 8 H), 4.0 (m, 2 H), 5.1 (m, 1H), 5.7 (m, 2 H); ^13^C-NMR (CDCl\textsubscript{3}), \delta, 204.5 (s), 144.8 (s), 139.2 (s), 130.4 (d), 122.3 (d), 65.2 (d), 58.3 (d), 46.0 (d), 35.6 (t), 33.1 (t), 32.7 (t), 23.1 (t).

2,3-Benzo-7-chlorobicyclo(3.2.0)heptan-6-one. From 21.6 g (0.095 mol) of 2,3-benzo-7,7-dichlorobicyclo(3.2.0)-heptan-6-one and 6.2 g of zinc in 200 ml of acetic acid, there was obtained 16.4 g (90%) of white solid, m.p. 112°C after recryst. from hexane. The reaction solution was treated with 200 ml of chloroform rather than ether as noted above in general procedure; IR (film), 1790 cm\textsuperscript{-1}; \textsuperscript{1}H-NMR (CDCl\textsubscript{3}), \delta, 2.9-4.4 (m, 4 H), 5.2 (dd, J = 9 Hz, J = 3 Hz), 7.2 (m, 4 H); ^13^C-NMR (CDCl\textsubscript{3}), \delta, 203.7 (s), 143.5 (s), 137.6 (s), 128.1 (d), 127.9 (d), 126.5 (d), 125.1 (d), 65.3 (d), 58.6 (d), 44.7 (d), 34.5 (t).

2,3-Benzo-7-chloro-4-isopropylidenebicyclo(3.2.0)heptan-6-one. From 1.24 g of zinc and 5 g (0.019 mol) of
2,3-benzo-7,7-dichloro-4-isopropylidenebicyclo(3.2.0)heptan-6-one in 50 ml of acetic acid and using a chloroform extract instead of ether, there was obtained 4.2 g (95%), m.p. 168-170°C; IR (film), 1790 cm⁻¹; ¹H-NMR (CDCl₃), δ, 2.0 (s, 2 H), 2.1 (s, 3 H), 4.3 (m, 1 H), 4.7 (m, 1 H), 5.2 (dd, 1 H, J = 9 Hz, J = 3 Hz), 7.4 (m, 4 H); ¹³C-NMR (CDCl₃), δ, 203.0 (s), 142.1 (s), 140.1 (s), 130.7 (s), 127.8 (d), 126.5 (d), 124.7 (d), 64.4 (d), 38.5 (d), 25.2 (q), 21.5 (q).

8-Chloro-3,6-dimethylbicyclo(4.2.0)octa-2-en-7-one.

From 4 g (0.018 mol) of 8,8-dichloro-3,6-dimethylbicyclo(4.2.0)octa-2-en-7-one and 1.15 g of zinc in 100 ml of acetic acid, there was obtained 3.1 g (93%); IR (film), 1785 cm⁻¹; ¹H-NMR (CDCl₃), δ, 1.0-2.5 (m, 10 H), 2.7 (m, 1 H), 4.5 (m, 1 H), 5.3 (m, 1 H); ¹³C-NMR (CDCl₃), δ, 199.0 (s), 139.4 (s), 124.4 (d), 68.8 (d), 20-40 (m).

General Procedure for the Bicyclo(n.1.0)alkenecarboxylic Acid. A mixture of 0.05 mol of the corresponding monochlorocyclobutanone and 0.10 mol of sodium hydroxide in 50 ml of water was refluxed for 6 hr. 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 or chloroform. The extract was dried over anhydrous MgSO₄ and then the solvent was removed under reduced pressure. The residue was vacuum distilled or recrystallized. (The crude acids could be used for the
ester preparation without further purification). The spectral data and the yield of a variety of different new acids are described below.

**4-Isopropylidenebicyclo(3.1.0)hex-2-en-6-carboxylic Acid.** A yield of 86% was obtained with m.p. 135-137°C (recryst. from hexane/benzene); IR (film), 1680 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\)), \(\delta\), 6.15 (dd, 1 H, \(J = 7.5\) Hz, \(J = 1.2\) Hz), 5.8 (m, 1 H), 2.65 (dd, 2 H, \(J = 9.6\) Hz, \(J = 1.2\) Hz), 2.0 (d, 1 H, \(J = 3\) Hz), 1.9 (s, 6 H); \(^1^3\)C-NMR (CDCl\(_3\)), \(\delta\), 169.5 (s), 137.1 (s), 130.2 (d), 126.7 (s), 30.1 (d), 29.6 (d), 25.1 (d), 21.6 (q), 20.8 (q).

Anal. Calcd. for C\(_{10}\)H\(_{12}\)O\(_3\): C, 73.17; H, 7.31. Found: C, 73.09; H, 7.45.

**3-Methylbicyclo(3.1.0)hex-2-en-6-carboxylic Acid.** A yield of 65% was obtained with b.p. 130°C (0.1 mm); cis/trans = 1; \(^1\)H-NMR (CDCl\(_3\)), \(\delta\), 1.1-2.7 (m, 16 H), 5.2 (m, 1 H), 5.5 (m, 1 H); \(^1^3\)C-NMR (CDCl\(_3\)), \(\delta\), 179.8 (s), 177.0 (s), 144.6 (s), 141.4 (s), 125.3 (d), 119.3 (d), 40.1 (t), 35.5 (d), 32.9 (d), 31.0 (d), 27.4 (d), 23.3 (t), 22.9 (t), 15.8 (q), 15.6 (q).

Anal. Calcd. for C\(_8\)H\(_{10}\)O\(_2\): C, 69.54; H, 7.29. Found: C, 69.28; H, 7.32.

The trans isomer crystallized from the cis/trans mixture after 5 days under -10°C. After recrystallization from petroleum ether a 25% yield was obtained (based on the mono-chlorocyclobutanone) with a m.p. of 85-87°C; \(^1\)H-NMR (CDCl\(_3\)), \(\delta\), 1.65 (s, 3 H), 2.0-2.7 (m, 5 H), 5.2 (s, 1 H); \(^1^3\)C-NMR
4-Diethylmethylenebicyclo(3.1.0)hex-2-en-6-carboxylic Acid. A 51% yield was obtained at b.p. 120 °C (0.1 mm); cis/trans = 1; $^1$H-NMR (CDCl$_3$), $\delta$, 1.0 (m, 12 H), 2.2-2.9 (m, 14 H), 6.2-6.4 (m, 4 H); $^{13}$C-NMR (CDCl$_3$), $\delta$, 179.2 (s), 175.3 (s), 140.9 (s), 137.7 (s), 135.4 (s), 133.2 (d), 131.2 (d), 128.8 (s), 128.4 (d), 25-34 (m), 13.4 (q), 12.4 (q), 12.2 (q).

Anal. Calcd. for C$_{12}$H$_{16}$O$_2$: C, 75.0; H, 8.33. Found: C, 74.82; H, 8.50.

4-Diethylmethylene-6-methylbicyclo(3.1.0)hex-2-en-6-carboxylic acid. A 56% yield was obtained with m.p. 132-134 °C after recrystallization from hexane/benzene; $^1$H-NMR (CDCl$_3$), $\delta$, 1.2 (m, 9 H), 2.2 (q, 4 H), 2.8 (s, 2 H), 5.8 (d, 1 H, J = 6 Hz), 6.3 (d, 1 H, J = 6 Hz); $^{13}$C-NMR (CDCl$_3$), $\delta$, 182.1 (s), 144.2 (s), 135.8 (s), 132.2 (d), 130.2 (d), 39.7 (d), 34.7 (d), 31.4 (s), 26.5 (t), 25.8 (t), 14.1 (q), 12.9 (q), 7.28 (q).

Anal. Calcd. for C$_{13}$H$_{18}$O$_2$: C, 75.73; H, 8.37. Found: C, 75.53; H, 8.93.

4-Cyclopentylidenebicyclo(3.1.0)hex-2-en-6-carboxylic Acid. A 55% yield was obtained with m.p. 116 °C after recrystallization from petroleum ether; $^1$H-NMR (CDCl$_3$), $\delta$, 1.5-3.0 (m, 22 H), 5.5 (m, 4 H); $^{13}$C-NMR (CDCl$_3$), $\delta$, 179.3 (s), 176.5 (s), 143.8 (s), 140.9 (s), 139.5 (s), 139.3 (s), 127.5 (d), 127.2 (d), 126.2 (d), 120.7 (d), 23-36 (m).
Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.78; H, 7.37. Found: C, 75.50; H, 7.34.

5-Isopropylidene-6-methylbicyclo(3.1.0)hex-2-en-6-carboxylic Acid. A 65% yield was obtained with a m.p. of 107-108°C after recrystallization from petroleum ether; $^1$H-NMR (CDCl$_3$), $\delta$, 0.9 (s, 3 H), 1.85 (s, 6 H), 2.85 (s, 2 H), 5.8 (d, 1 H, $J = 6$ Hz), 6.2 (d, 1 H, $J = 6$ Hz); $^{13}$C-NMR (CDCl$_3$), $\delta$, 182.1 (s), 136.5 (s), 132.3 (d), 131.7 (s), 129.9 (d), 39.9 (d), 34.9 (d), 31.1 (s), 21.9 (q), 20.9 (q), 7.28 (q).

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.15; H, 7.86. Found: C, 74.18; H, 8.02.

4-Diphenylmethylene-6-methylbicyclo(3.1.0)hex-2-en-6-carboxylic Acid. A yield of 40% was obtained with a m.p. 230°C after recrystallization from hexane/benzene; $^1$H-NMR (CDCl$_3$), $\delta$, 1.8 (s, 3 H), 3.4 (s, 2 H), 6.8-7.6 (m, 12 H); $^{13}$C-NMR (DMSO-d$_6$), $\delta$, 168.4 (s), 154.0 (s), 141.5 (s), 140.4 (s), 137.0 (d), 134.1 (s), 129.7 (d), 129.0 (d), 128.2 (d), 128.1 (d), 126.9 (d), 116.3 (s), 36-41 (m), 16.1 (s).

Anal. Calcd. for $C_{21}H_{18}O_2$: C, 83.40; H, 5.96. Found: C, 83.65; H, 6.08.

2,3-Benzobicyclo(3.1.0)hexan-6-carboxylic Acid. A yield of 65% was obtained with a m.p. 134°C after recrystallization from hexane/benzene; cis/trans = 1; $^1$H-NMR (CDCl$_3$), $\delta$, 1.1-3.4 (m, 10 H), 7.2 (m, 8 H); $^{13}$C-NMR (CDCl$_3$), $\delta$, 179.1 (s), 176.0 (s), 145.0 (s), 143.1 (s), 141.5 (s), 126.5 (d),
126.4 (d), 125.9 (d), 125.2 (d), 124.5 (d), 123.9 (d), 123.8 (d), 35.2 (t), 35.1 (t), 32.9 (d), 32.1 (d), 30.5 (d), 27.1 (d), 24.6 (d), 24.0 (d).

Anal. Calcd. for C_{11}H_{10}O_{2}:  C, 75.80;  H, 5.74.  Found:  C, 75.70;  H, 5.75.

2,3-Benzo-4-isopropylidenebicyclo(3.1.0)hexan-6-carboxylic Acid.  A yield of 52% with m.p. 193-195 °C was obtained after recrystallization from hexane/benzene; $^1$H-NMR (CDCl$_3$), δ, 1.9 (s, 3 H), 2.0 (s, 3 H), 2.1-3.3 (m, 3 H), 7.2 (m, 4 H); $^{13}$C-NMR (DMSO-d$_6$), δ, 169.6 (s), 142.3 (s), 141.7 (s), 132.6 (s), 129.7 (s), 126.1 (d), 125.6 (d), 125.1 (d), 123.4 (d), 28.9 (d), 28.7 (d), 28.3 (d), 24.4 (q), 21.3 (q).

Anal. Calcd. for C_{14}H_{14}O_{2}:  C, 78.50;  H, 6.54.  Found:  C, 78.37;  H, 6.39.

3,6-Dimethylbicyclo(4.1.0)hept-2-en-7-carboxylic Acid. A yield of 50% of an oil was obtained; $^1$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). This acid was used to prepare the pyrethroid ester without further purification.

General Procedure for Pyrethroid Esters. The active m-phenoxybenzyl alcohol, 5-benzyl-3-furymethyl alcohol and 3',4',5',6'-tetrahydrophthalimidomethyl alcohol were used for the pyrethroid ester preparations. To a refluxing solution of 50 ml of benzene containing 0.08 mol of freshly
distilled thionyl chloride was added 0.02 mol of the pyrethroid acid in 50 ml of benzene over a 30 min. period. The solution was refluxed for 3 hr and cooled to ambient temperature. The excess thionyl chloride and benzene were removed under reduced pressure to give the corresponding acid chloride as evidenced by IR and $^1$H-NMR spectrum.

To a 50 ml benzene solution containing 0.03 mol of the appropriate alcohol and 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 hr and the pyridine salt removed by filtration. The solvent was removed under reduced pressure and the residue passed through a silica gel column. The esters could be eluted with hexane/ethyl acetate (10/1) solvent system. The spectral data and yields of a variety of different pyrethroid esters which were prepared from the above described pyrethroid acids are described below.

**m-Phenoxybenzyl Bicyclo(3.1.0)hex-2-en-6-carboxylate.**

There was obtained a colorless oil in an 84% yield; cis/trans = 1; IR (film), 1700 cm$^{-1}$; $^1$H-NMR (CDCl$_3$), $\delta$, 0.9-2.5 (m, 10 H), 5.1 (d, 4 H, J = 6 Hz), 5.9 (m, 4 H), 7.2 (m, 18 H);

$^{13}$C-NMR (CDCl$_3$), $\delta$, 172.1 (s), 168.3 (s), 157.0 (s), 156.6 (s), 138.1 (s), 137.9 (s), 132-126 (m), 122.9 (d), 122.2 (d), 118.6 (d), 117.8 (d), 65.0 (t), 64.7 (t), 35.7 (d), 34.1 (d), 32.5 (d), 31.2 (d), 29.8 (d), 25.8 (d), 22.6 (t), 21.8 (t).

Anal. Calcd. for C$_{20}$H$_{18}$O$_3$: C, 78.43; H, 5.88. Found:
5-Benzyl-3-furylmethyl Bicyclo(3.1.0)hex-2-en-6-carboxylate. An 87% yield of a colorless oil was obtained (cis/trans = 1); IR (film), 1700 cm⁻¹; \(^1\)H-NMR (CDCl\(_3\)), \(\delta\), 0.9-2.5 (m, 10 H), 4.8 (s, 4 H), 5.6 (d, 4 H, J = 6 Hz), 5.9-6.0 (m, 6 H), 7.2 (m, 12 H); \(^{13}\)C-NMR (CDCl\(_3\)), \(\delta\), 172.7 (s), 168.8 (s), 155.2 (s), 140.0 (s), 137.5 (d), 132-121.2 (m), 121.0 (s), 107.0 (d), 57.6 (t), 57.1 (t), 35.8-31.3 (m), 30.0 (d), 25.9 (d), 22.8 (d), 21.9 (d).


m-Phenoxybenzyl 3-Methylbicyclo(3.1.0)hex-2-en-6-carboxylates. A 79% yield of a colorless oil was obtained (cis/trans = 1); IR (film), 1700 cm⁻¹; \(^1\)H-NMR (CDCl\(_3\)), \(\delta\), 1.0-2.3 (m, 16 H), 5.0 (s, 4 H), 5.4 (m, 2 H), 7.2 (m, 18 H); \(^{13}\)C-NMR (CDCl\(_3\)), \(\delta\), 172.6 (s), 172.3 (s), 157.2 (s), 156.6 (s), 144.4 (s), 141.0 (s), 140.7 (s), 138.5 (s), 129-105 (m), 65.0 (t), 64.5 (t), 39-26 (m), 15.5 (q), 12.1 (q).

Anal. Calcd. for C\(_{21}\)H\(_{20}\)O\(_3\): C, 78.75; H, 6.25. Found: C, 78.45; H, 5.97.

5-Benzyl-3-furylmethyl 3-Methylbicyclo(3.1.0)hex-2-en-6-carboxylate. An 87% yield of a colorless oil was obtained (cis/trans = 1); IR (film), 1700 cm⁻¹; \(^1\)H-NMR (CDCl\(_3\)), \(\delta\), 1.0-3.0 (m, 16 H), 3.9 (m, 4 H), 4.8 (m, 4 H), 5.2-6.0 (m, 4 H), 7.2 (m, 12 H); \(^{13}\)C-NMR (CDCl\(_3\)), \(\delta\), 172.5 (s), 171.5 (s), 155.1 (s), 140-139 (m), 137.4 (d), 128-121
trans-3',4',5',6'-Tetrahydrophthalimidomethyl 3-
Methylbicyclo(3.1.0)hex-2-en-6-carboxylate. An 88% yield
of a colorless oil was obtained; IR (film), 1700 cm\(^{-1}\);
\(^1\)H-NMR (CDCl\(_3\)), \(\delta\), 1.7-2.4 (m, 16 H), 5.4 (m, 3 H);
\(^{13}\)C-NMR (CDCl\(_3\)), \(\delta\), 168.7 (s), 168.1 (s), 143.5 (s), 142.0
(s), 119.4 (d), 59.5 (t), 36.4 (t), 31.7 (d), 22.7-19.6 (m),
15.1 (q).

Anal. Calcd. for C\(_{17}\)H\(_{19}\)N\(_3\): C, 67.77; H, 6.31. Found:
C, 67.88; H, 6.48.

5-Benzyl-3-furylmethyl 4-Diethylmethylene-6-methyl-
bicyclo(3.1.0)hex-2-en-6-carboxylate. An 80% yield of a
colorless oil was obtained; IR (film), 1700 cm\(^{-1}\); \(^1\)H-NMR
(CDCl\(_3\)), \(\delta\), 0.9 (m, 9 H), 2.2 (m, 4 H), 2.8 (m, 2 H), 3.9
(s, 2 H), 4.9 (s, 2 H), 6.2 (m, 3 H), 7.2 (m, 6 H); \(^{13}\)C-NMR
(CDCl\(_3\)), \(\delta\), 174.6 (s), 155.3 (s), 143.3 (s), 139.8 (s),
137.6-126 (m), 121.4 (s), 106.9 (d), 58.1 (t), 38.8 (t),
34-25 (m), 14.0 (q), 12.7 (q), 7.51 (q).

Anal. Calcd. for C\(_{25}\)H\(_{28}\)O\(_3\): C, 79.78; H, 7.45. Found:
C, 79.92; H, 7.56.

m-Phenoxybenzyl 4-Diethylmethylene-6-methylbicyclo-
(3.1.0)hex-2-en-6-carboxylate. A yield of 84% of a color-
less oil was obtained; IR (film), 1700 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\)),
\(\delta\), 1.0 (m, 9 H), 2.3 (m, 4 H), 2.8 (m, 2 H), 5.1 (s, 2 H),
35

6.7 (m, 1 H), 7.1 (m, 9 H); _1^3C-NMR (CDCl₃), δ, 174.5 (s), 157.5 (s), 156.8 (s), 143.5 (s), 138.4 (s), 135.8 (s), 132.0 (d), 130-117 (m), 65.5 (t), 38.9 (d), 34.0 (d), 31.6 (s), 26.4 (t), 25.6 (t), 13.9 (q), 12.8 (q), 7.49 (q).


_m-Phenoxybenzyl 2,3-Benzobicyclo(3.1.0)hexan-6-carboxylate._ A colorless oil in an 84% yield was obtained (cis/trans = 1); IR (film), 1700 cm⁻¹; H-NMR (CDCl₃), δ, 1.0-3.2 (m, 10 H), 4.8 (s, 2 H), 5.1 (s, 2 H), 7.2 (m, 26 H); _1^3C-NMR (CDCl₃), δ, 171.8 (s), 168.7 (s), 157.2 (s), 157.0 (s), 156.9 (s), 156.7 (s), 144.3 (s), 143.1 (s), 141.4 (s), 139.3 (s), 137-122 (m), 118.6 (d), 118.0 (d), 65.5 (t), 64.9 (t), 35-30 (m), 26.3 (s), 24-23 (m).


_5-Benzyl-3-furylmethyl 2,3-Benzobicyclo(3.1.0)hexan-6-carboxylate._ An 85% yield of a colorless oil was obtained (cis/trans = 1); IR (film), 1700 cm⁻¹; H-NMR (CDCl₃), δ, 1.2-3.5 (m, 10 H), 3.9 (s, 4 H), 4.6 (s, 2 H), 4.9 (s, 2 H), 5.7 (s, 1 H), 6.0 (s, 1 H), 7.2 (m, 20 H); _1^3C-NMR (CDCl₃), δ, 172.0 (s), 168.8 (s), 155.3 (s), 155.2 (s), 143.1 (s), 141.7 (s), 138.4 (s), 137.4 (s), 129-120 (m), 107.0 (d), 57.7 (t), 57.0 (t), 34-23 (m).

5-Benzyl-3-furylmethyl 3,6-Dimethylbicyclo(4.1.0)-
hept-2-en-7-carboxylate. A yield of 82% of a colorless
oil was obtained; IR (film), 1700 cm$^{-1}$; $^1$H-NMR (CDCl$_3$), $\delta$
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$_3$), $\delta$, 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.

7-Isopropylidenebicyclo(4.2.0)octane. To a solution
of 4.7 g (37 mmol) of bicyclo(4.2.0)octan-7-one (1) and 60
ml of dimethyl sulfoxide was added 28 g (64 mmol) of (iso-
propyl)triphenylphosphonium iodide and 7.1 g (64 mmol) of
t-BuOK over 1 h period. The solution was stirred overnight
and then heated for 15 h at 90°C. The resultant solution
was extracted with petroleum ether, after removing the
solvent, the residue was passed through silica gel column
by using petroleum ether as eluting solvent to give 2.3 g
(40%) of pure olefin. IR (film), 1600 cm$^{-1}$; $^1$H-NMR (CDCl$_3$),
$\delta$, 1.1-2.9 (m, 18 H); $^{13}$C-NMR (CDCl$_3$), $\delta$, 135.1 (s), 120.8
(s), 39.9 (d), 32.7 (t), 28-18 (m).

2,2-Dichloro-3,3-dimethyl-5,6-tetramethylenespiro-
(3,3)heptan-1-one. To a solution of 1.7 g (11.3 mmol) of
7-isopropylidenebicyclo(4.2.0)octane and 2 g of activated
zinc in 100 ml ether was added over a 6 h period a solution
of 1.7 ml (15 mmol) trichloroacetyl chloride, after work up,
there was obtained 2.4 g (81%); IR (film), 1800 cm$^{-1}$; $^1$H-NMR (CDCl$_3$), $\delta$, 1.3-2.8 (m, 18 H); $^{13}$C-NMR (CDCl$_3$), $\delta$, 201.6 (s), 91.5 (s), 68.9 (s), 47.4 (s), 39.4 (d), 20-30 (m).

2-Chloro-3,3-dimethyl-5,6-tetramethylenespiro(3,3)-heptan-1-one. To a solution of 2.0 g of 2,2-dichloro-3,3-dimethyl-5,6-tetramethylenespiro(3,3)heptan-1-one and 50 ml of acetic acid was added 0.5 g of zinc. After stirring overnight and work up, there was obtained 1.5 g (90%); IR (film), 1780 cm$^{-1}$; $^1$H-NMR (CDCl$_3$), $\delta$, 1.0-2.8 (m, 18 H), 4.4 (s, 1 H); $^{13}$C-NMR (CDCl$_3$), $\delta$, 205.2 (s), 69.7 (d), 47.2 (s), 20-30 (m).

2,2-Dimethyl-4,5-tetramethylenespiro(2,3)hexan-1-carboxylic acid. A solution of 1.2 g of 2-chloro-3,3-dimethyl-5,6-tetramethylenespiro(3,3)heptan-1-one in 15 ml of water containing 1 g of NaOH was stirred for 6 h. After work up there was obtained 0.8 g (80%); IR (film), 1680 cm$^{-1}$; $^1$H-NMR (CDCl$_3$), $\delta$, 1.1-2.9 (m, 19 H), 9.9 (s, 1 H); $^{13}$C-NMR (CDCl$_3$), $\delta$, 178.9 (s), 44.4 (s), 44.2 (s), 14.9-36 (m).

5-Benzyl-3-furylmethyl 2,2-Dimethyl-4,5-tetramethylenespiro(2,3)hexan-1-carboxylate. The 2,2-dimethyl-4,5-tetramethylenespiro(2,3)hexan-1-carboxylic acid was converted to the acid chloride and then reacted with 5-benzyl-3-furylmethyl alcohol by following the described general procedure. Thus, a 70% of a colorless ester was obtained; IR (film), 1700 cm$^{-1}$; $^1$H-NMR (CDCl$_3$),
δ, 1.0-2.4 (m, 19 H), 3.7 (s, 2 H), 4.7 (s, 2 H), 7.0 (m, 6 H); $^{13}$C-NMR (CDCl$_3$), δ, 171.5 (s), 155.2 (s), 139.8 (s), 137.5 (d), 128.4 (d), 128.2 (d), 126.2 (d), 121.4 (s), 107.0 (d), 56.9 (t), 42.8 (s), 15-36 (m).

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CHAPTER III

RESULTS AND DISCUSSION

Chrysanthemic acid and certain analogues have been known for many years to be effective components of pyrethroid esters which are potent insecticides (1). In this dissertation we describe a simple yet versatile synthesis of pyrethroid acids from conjugated dienes which we believe will offer an attractive alternative to existing pyrethroid acid syntheses. The procedure is based on the finding that 2,2-dichloro-3-vinylcyclobutanones, readily available cycloaddition products from dichloroketene and conjugated dienes, will undergo a selective reductive removal of one chlorine atom. The resultant monochlorocyclobutanones undergo a facile Favorskii-type ring contraction to the pyrethroid acids.

In previous studies in this laboratory on dichloroketene-hindered olefin cycloadditions, the dichloroketene cycloadducts of 2,5-dimethyl-2,4-hexadiene, 2a and 2a' were prepared (2). These cycloaddition products are now an important precursor to chrysanthemic acid, 4a. Dichloroketene is generated in situ from trichloroacetyl chloride with zinc in ether containing phosphorous oxychloride (a
slight modification of existing literature procedure (2, 3) in the presence of the diene. Both regioisomers are obtained;

\[ \text{R} \begin{array}{c} \text{R} \\ \text{R} \end{array} \] + \text{Cl}_3\text{CCOCl} \\
1a, R = \text{CH}_3 \\
b, R = \text{H} \\
\overset{\text{Zn/POCl}_3}{\downarrow} \\
\text{R} \begin{array}{c} \text{R} \\ \text{R} \end{array} \text{CO} + \text{R} \begin{array}{c} \text{Cl} \\ \text{Cl} \end{array} \\
2a, R = \text{CH}_3 \\
b, R = \text{H} \\
\overset{\text{Zn/HOAc}}{\downarrow} \\
\text{R} \begin{array}{c} \text{R} \\ \text{R} \end{array} \text{CO} + \text{R} \begin{array}{c} \text{H} \\ \text{Cl} \end{array} \\
2a', R = \text{CH}_3 \\
\overset{-\text{OH}}{\downarrow} \\
\text{R} \begin{array}{c} \text{R} \\ \text{R} \end{array} \text{CO} + \text{R} \begin{array}{c} \text{Cl} \\ \text{Cl} \end{array} \\
3a, R = \text{CH}_3 \\
b, R = \text{H} \\
3a', R = \text{CH}_3 \\
\overset{4a, R = \text{CH}_3}{\downarrow} \\
\text{R} \begin{array}{c} \text{R} \\ \text{R} \end{array} \text{COOH} \\
b, R = \text{H} \]
2,2-dichloro-4,4-dimethyl-3-(2-methylpropenyl)cyclobutanone, 2a, in 40% yield and 2,2-dichloro-3,3-dimethyl-4-(2-methylpropenyl)cyclobutanone, 2a', in 15% yield. Theoretically, orbital interaction of the LUMO of the ketene and the HOMO of the olefin allows two dipolar transition states in which 2a forms from an allylic cation-type transition state, 2e, and 2a' forms from a tertiary carbon cation-type transition state, 2f, as illustrated. Since the allylic cation-type transition state is more stable than the tertiary carbon cation-type transition state, the yield of the regioisomer, 2a, is higher. Apparently the energy difference between these two transition states is not sufficient to eliminate the pathway leading to 2a'.

A key step in the synthesis of chrysanthemic acid is the reductive removal of only one chlorine atom (3-15) in 2a and 2a' by treating the dichloroketene cycloaddition product with one equivalent of zinc dust in acetic acid. After 24
h at ambient temperature, a mixture of monochlorocyclobutanones, 3a and 3a', is obtained in 82\% yield. The structures of 3a and 3a' were determined by $^1$H-NMR and $^{13}$C-NMR spectrometry. The reduction step is not regiospecific and yields two stereomers for each regioisomer of the cycloadduct thus accounting for the four signals for the carbon bearing the chlorine atom in the $^{13}$C-NMR spectrum. The mechanism of the zinc reduction is shown below (8, 16):
The Favorskii-type ring contraction reaction is a regio-specific reaction (17-27) and the four monochlorocyclobutanones yield cis- and trans-chrysanthemic acid, 4a, in 73% yield. The cis-acid was obtained from cis-chlorocyclobutanone and the trans-acid was obtained from trans-chlorocyclobutanone. The isomeric chrysanthemic acids may be separated by crystallization from ethyl acetate (28).

\[ \text{cis} \]

\[ \text{trans} \]

In order to verify the versatility of this synthetic sequence, 4-methyl-1,3-pentadiene, 1b, was also used to prepare the pyrethroid acid analogue, 4b. Obviously the allylic cation-type dipolar transition state would be much
more stable than the primary carbon cation-type dipolar transition state; thus, only one regioisomer of dichloro-ketene cycloadduct, 2b, is observed. To prove that 2b is in fact the regioisomer obtained, the cycloaddition product was reduced with an excess of zinc/acetic acid to remove both chlorine atoms to yield 3c. The symmetric structure of 3c was mainly characterized by the appearance of only 7 carbon peaks in the completely decoupled $^{13}$C-NMR spectrum as illustrated.

The advantages of this three-step reaction sequence are that the reagents are readily available, the procedure is simple and requires only mild conditions, and the reaction can be performed with a wide variety of conjugated dienes. This method should compete quite favorably with existing procedures in the literature in terms of simplicity and availability of starting compounds for a broad range of pyrethroid
acids (29-32).

Although the natural pyrethrins have been widely used as effective insecticides, a major disadvantage of the natural pyrethrins, especially for the use against agricultural pests, lies in the lack of stability in the presence of air and sunlight. In order to overcome this drawback, the synthesis of new systems of pyrethroid acids and the structure-activity studies have received much more attention in the literature in recent years (33, 34). A variety of new synthetic pyrethroid esters have been synthesized and reported as effective insecticides with a higher activity and stability compared to the natural pyrethrins.

In our efforts to develop a new system of pyrethroid insecticides, we found that the bicyclo(n.1.0)alkenecarboxylates are quite similar to the natural pyrethroids and also can be synthesized by utilizing our recently developed synthetic method described above (35). Thus, alkylcyclopentadienes were used as starting materials for the dichloroketene cycloadditions. The alternate method of generating dichloroketene from dichloroacetyl chloride with triethylamine was used in this in situ cycloaddition to provide the cycloaddition products, 3-alkyl-7,7-dichlorobicyclo(3.2.0)-hept-2-en-6-ones, in 70-75% yield. Monodechlorination and the Favorovskii-type ring contraction resulted in the formation of 3-alkylbicyclo(3.1.0)hex-2-en-6-carboxylic acids, 6a-6c.
While the zinc reduction step is generally not regio-specific, the reduction of 3-alkyl-7,7-dichlorobicyclo-(3.2.0)hept-2-en-6-one results in only one regioisomer, the endo-chlorocyclobutanone, 5, which is also the same regioisomer as obtained from the reduction when tri-n-butyltin hydride is employed (36, 37). Apparently in this bicyclic system the exo-chloro substituent is much more susceptible to reductive removal. The subsequent Favorskii-type ring contraction of the endo-chlorocyclobutanone affords both cis- and trans-substituted bicyclo(3.1.0)-alkenecarboxylic acids (cis/trans = 1). The Favorskii ring
contraction is a regiospecific reaction (38, 39). Hence, the formation of approximately equal amounts of the cis- and trans-isomers of the cyclopropanecarboxylic acids is due to the epimerization of monochlorocyclobutanone under the basic reaction conditions (40) prior to the ring contraction reaction as illustrated.

A variety of dialkyfulvenes derived from cyclopentadiene were also used as precursors in this synthetic sequence.
to prepare the new pyrethroid-like acids as illustrated, 8a, 8d, 8e.

In addition to dichloroketene, methylchloroketene was used in the cycloaddition step with several disubstituted fulvenes as illustrated, 8b, 8c, 8f. In the methylchloroketene cycloadditions, only the endo -methyl- exo -chloro-cyclo- butanones, 7, were obtained which underwent a regiospecific
ring contraction to yield only one regioisomer of the pyr-ethroid acid, the endo -methyl isomer (41). Since the endo -methyl- exo -chlorocyclobutanones cannot undergo the endo - and exo -chloroepimerization as noted above for the mono-chlorocyclobutanones, these regioisomers gave only the trans -cyclopropanecarboxylic acids after ring contraction (Only one regioisomer was found as evidenced by the C-NMR spectrum). In an extension of this study, the cyclopentadiene derivatives, indene and dimethylbenzofulvene, were also used to prepare the corresponding analogues of bicyclo(3.1.0)-alkenecarboxylic acids, 9 and 10, by following the same scheme. Thus, eleven new bicyclo(3.1.0)alkenecarboxylic acids were prepared successfully as listed in Table I.
TABLE I
NEW BICYCLO(3.1.0)ALKENECARBOXYLIC ACIDS SYNTHESIZED

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>R₁</th>
<th>Physical State</th>
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<tr>
<td>6a</td>
<td>H</td>
<td>H</td>
<td>mp 112</td>
</tr>
<tr>
<td>6b</td>
<td>Me</td>
<td>H</td>
<td>mp 85-7 (trans)</td>
</tr>
<tr>
<td>6c</td>
<td>Me</td>
<td>H</td>
<td>oil (cis)</td>
</tr>
<tr>
<td>8a</td>
<td>Me</td>
<td>H</td>
<td>mp 135-7</td>
</tr>
<tr>
<td>8b</td>
<td>Me</td>
<td>Me</td>
<td>mp 107-8</td>
</tr>
<tr>
<td>8c</td>
<td>Et</td>
<td>Me</td>
<td>mp 132-4</td>
</tr>
<tr>
<td>8d</td>
<td>Et</td>
<td>H</td>
<td>bp 120/0.1 mm</td>
</tr>
<tr>
<td>8e</td>
<td>H</td>
<td>H</td>
<td>mp 116</td>
</tr>
<tr>
<td>8f</td>
<td>Ph</td>
<td>Me</td>
<td>mp 230</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>H</td>
<td>mp 134</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>H</td>
<td>mp 193-5</td>
</tr>
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</table>

In the synthesis of the pyrethroid esters of the above described acids, the acids were converted to pyrethroid esters by conversion to the corresponding acid chlorides by treatment with thionyl chloride or oxalyl chloride. The
acid chlorides were then allowed to react with active pyrethroid alcohols in benzene solution containing pyridine to give the pyrethroid esters. The three active pyrethroid alcohols used were m-phenoxybenzyl alcohol, 5-benzyl-3-furylmethyl alcohol and 3',4',5',6'-tetrahydrophthalimidomethyl alcohol. The insecticidal activity test results of six representative esters against the housefly (Musca domestica) and German cockroach (Blattell germanica) are listed in Table II. All of the candidate pyrethroids synthesized are non-toxic to the housefly when applied either unsynergized or synergized with piperonyl butoxide. Housefly toxicity is demonstrated at the 5 µg/insect level by several of the pyrethroids 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. Neither the unsynergized nor synergized formulations of the new pyrethroids demonstrate any activity when applied on German cockroach.

Since the bicyclo(3.1.0)alkenecarboxylates had shown little insecticidal activity, we continued our efforts to find a new system with a specific configuration which is more similar to the naturally occurring pyrethroid. After a careful consideration, we found that the 3,6-dimethyl-bicyclo(4.1.0)hept-2-en-7-carboxylic acid, 11, is worthy
### TABLE II

**TEST RESULTS OF NEW BICYCLO(3.1.0)ALKENECARBOXYLATES**

<table>
<thead>
<tr>
<th>Toxicant</th>
<th>Housefly LD50 mg(1)</th>
<th>Roach LD50 mg(1)</th>
</tr>
</thead>
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<tr>
<td></td>
<td>1.0 PB(1:4) N(1:4)</td>
<td>1.0 PB(1:4) N(1:4)</td>
</tr>
<tr>
<td>Pyrethrins</td>
<td>0.125 0.132 &lt;0.5 &lt;0.5</td>
<td></td>
</tr>
<tr>
<td>NA NA 1.6 NA NA NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA NA 1.4 NA NA NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA NA 2.6 NA NA NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA 1.85 1.90 NA NA NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA 1.84 1.90 NA NA NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA NA 2.90 NA NA NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(1) 1.0 = unsynergized, PB = piperonyl butoxide, N = NIA 16388, NA = no activity.

\[ R = -CH_2- \text{structure} \quad R_1 = -CH_2- \text{structure} \]
of particular note. This acid is very similar to the natural chrysanthemic acid except it is locked in one particular conformation, 12, and lacks the freedom of rotation about the vinyl group as in the natural acid as illustrated. 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.

In order to synthesize this particular acid, 1,4-dimethyl-1,3-cyclohexadiene was the ideal precursor for our three-step synthetic sequence. Unfortunately, the two most often cited references for the preparation of this diene require several steps and suffer from difficulty of yield reproducibility and starting material availability (42, 43).
Therefore, we developed a simple and efficient procedure for the preparation of pure 1,4-dimethyl-1,3-cyclohexadiene uncontaminated with 1,4-dimethyl-1,4-cyclohexadiene from readily available compounds. Thus, 4-methyl-3-cyclohexen-1-one, 13a, was prepared by the Birch Reduction and hydrolysis of commercially available p-methylanisole as previously described (44). 1,4-Dimethyl-3-cyclohexenol, 13b, was readily available from 13a by the usual method of adding methylmagnesium iodide to the ketone in good yield (45). Several different procedures were tried for the dehydration process (46, 47), and the optimum procedure was found to be refluxing the alcohol with 3-5% aqueous hydrochloric acid for two hours. Both 1,4-dimethyl-1,4-cyclohexadiene, 14a, and 1,4-dimethyl-1,3-cyclohexadiene, 14b, were formed in a 90% yield in a ratio of 45/55 respectively based on the \textsuperscript{1}H-NMR spectrum. Upon heating the dehydration mixture for 14 hr, the ratio of dienes changed to 14b/14a of 70/30. Apparently, isomerization of 14a to the more thermodynamically stable 14b occurred during this heating period. The separation of 14a from 14b is difficult by fractional distillation but a silica gel column impregnated with silver nitrate was found to be very suitable for the separation of these two isomers using a petroleum ether/ether solvent system (48). The overall yield of pure 14b from 13a is about 50\%.
In further studies on the isomerization of 14a to 14b, the pure 14a was prepared by the Birch Reduction of p-xylene in near quantitative yield (49). Refluxing the pure 14a under the same acidic conditions as described above for 14 hr resulted in a ratio of 14b/14a of 70/30 as evidenced by $^1$H-NMR spectrum. Obviously, 14a is being isomerized to 14b under the acidic conditions described at about 100°C in 14 hr to the extent of 70%. Efforts to increase the percentage of 14b above 70% were unsuccessful.

The overall yield of pure 14b from p-xylene is 63%. Clearly, the method of choice for the preparation of 14b is the isomerization of pure 14a prepared by the Birch Reduction
of p-xylene because only two steps are involved and the better overall yield. The key to this preparative procedure is the efficient separation of 14b from 14a by the silver nitrate impregnated silica gel column. We have utilized this procedure to prepare several grams of pure 14b free from any 14a.

The advantages of this isomerization procedure for the preparation of 1,4-dimethyl-1,3-cyclohexadiene over existing literature procedures are that the starting compounds are
readily available, the procedure is simple, short and requires only mild conditions to produce the pure diene on a preparative scale.

The 1,4-dimethyl-1,3-cyclohexadiene obtained by this method was allowed to react with dichloroketene to give the cycloadduct, 8,8-dichloro-3,6-dimethylbicyclo(4.2.0)octa-2-en-7-one. This cycloaddition product upon reduction and ring contraction gave the expected 3,6-dimethylbicyclo-(4.1.0)hept-2-en-7-carboxylic acid, 11, in 50% yield. The pyrethroid acid derived from 1,4-dimethyl-1,4-cyclohexadiene was also prepared. These acids were converted to esters of
5-benzyl-3-furylmethyl alcohol and tested against the common housefly and German cockroach. The esters revealed little activity as indicated in Table III.

TABLE III

TEST RESULTS OF DIMETHYLBICYCLO(4.1.0)HEPTENECARBOXYLATES

<table>
<thead>
<tr>
<th>Toxicant</th>
<th>Housefly LD50 μg(1)</th>
<th>Roach LD50 μg(1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrethrins</td>
<td>1.6 0.125 0.16</td>
<td>0.132</td>
</tr>
<tr>
<td></td>
<td>&gt;5.0 5.2 1.6</td>
<td>NA NA NA</td>
</tr>
</tbody>
</table>

(1) 1.0 = unsynergized, PB = piperonyl butoxide, N = NIA 16388, NA = no activity.

R = -CH₂\(\text{-C}=\text{O}\)\(\text{C}\)\(\text{-C}=\text{O}\)\

Apparently, this particular conformation of the acid is of little consequence as it binds to the target site in the insect. Certainly this locked conformation would be the least stable of the conformations that the naturally occurring chrysanthemic acid could assume. These results led us to believe that substituted spirocyclopropanecarboxylic acid systems, 15, with the structure similar to
the more stable conformer, 16, of natural pyrethroid acid, would be good candidates for pyrethroids and should provide a higher toxicity against insects.

![Chemical structures](image)

After an examination of the literature, it was found that only a limited number of simple spirocarboxylic acids have been synthesized as pyrethroid insecticides. All of these spirocarboxylic acids were derived from commercial available olefins. Apparently, the limited development in the synthesis of spiro-pyrethroid acids is due to the lack of availability of the appropriate olefins. In our efforts to synthesize some new spiro-pyrethroids, we found that a variety of bicyclic olefins can be derived from the cyclo-addition product of cycloalkenes and dichloroketene fairly easy in good yield. Thus, cyclohexene was allowed to react with dichloroketene to give the corresponding cyclobutanone.
After a reductive removal of the two chlorine atoms, and a Wittig reaction, there was obtained 7-isopropylidenebicyclo-(4.2.0)octane. This olefin was cycloadded to dichloro-ketene, selectively monodechlorinated and ring contracted to yield 2,2-dimethyl-5,6-tetramethylenespiro(2,3)hexan-1-carboxylic acid, 17. Molecular models of this cyclopropane-carboxylic acid do in fact reveal a locked conformation quite similar to the expected most stable conformation of the natural chrysanthemic acids.
The pyrethroid esters of this acid demonstrate a toxicity against the housefly of about 0.5 times as active as pyrethrin. On German cockroaches these esters demonstrated a minimal amount of toxicity and only when synergized with the esterase inhibitor - Niagara 16388 as indicated in Table IV. Although the bicyclic spiro pyrethroids synthesized are not as active as natural pyrethrin, this test result obviously showed that the bicyclic spiro-pyrethroids are more insecticidally active than the synthesized bicyclic pyrethroids as we expected.

**TABLE IV**

**TEST RESULTS OF BICYCLO SPIRO PYRETHROIDS**

<table>
<thead>
<tr>
<th>Toxicant</th>
<th>Synergist</th>
<th>Housefly LD50 μg</th>
<th>Roach LD50 μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrethrin</td>
<td>PB</td>
<td>0.15</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>2.60</td>
<td>&gt;5.0</td>
</tr>
<tr>
<td></td>
<td>PB</td>
<td>0.34</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>NI</td>
<td>0.27</td>
<td>2.55</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>2.16</td>
<td>&gt;5.0</td>
</tr>
<tr>
<td></td>
<td>PB</td>
<td>0.35</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>NI</td>
<td>0.28</td>
<td>1.7</td>
</tr>
</tbody>
</table>

(1) PB = piperonyl butoxide, NI = NIA 16388

![Chemical structures](image)
In summary, the results described in this study indicate that the newly developed synthetic sequence for pyrethroid acids is a significant improvement over existing syntheses in the literature. This synthesis has the advantage of utilizing readily available starting compounds, the procedure is simple and requires only mild conditions and the reaction can be performed with a wide variety of conjugated dienes. The scope of the synthesis was examined by studying various conjugated dienes and the results were very positive with good to excellent yields being obtained of the cyclopropanecarboxylic acids for all three steps.

The new cyclopropanecarboxylic acids that were synthesized were used to study structure-activity relationships of pyrethroid insecticides. The bicyclo pyrethroids have structures similar to the naturally occurring pyrethroid acid except for a methyl group on carbon 3 or 5. However, the test results revealed little activity against the housefly and cockroach. In an effort to more closely mimic the natural pyrethroid, 3,6-dimethylbicyclo(4.1.0)hept-2-en-7-carboxylic acid was synthesized by our new synthesis. This acid, with methyl groups on carbon atom 3 and 6, closely resembles the natural pyrethroid acid and was expected to provide information concerning the structural requirements as it binds to the target site in the insect.

1,4-Dimethyl-1,3-cyclohexadiene was required as the
conjugated diene for the synthesis of the above described acid. It was necessary to develop a new synthesis of this diene free from any 1,4-dimethyl-1,4-cyclohexadiene. This preparation involved the Birch Reduction of p-xylene to 1,4-dimethyl-1,4-cyclohexadiene, isomerization of this diene to a mixture of 1,4-dimethyl-1,3-cyclohexadiene and 1,4-dimethyl-1,4-cyclohexadiene and then an efficient separation of the dienes by a silica gel column chromatography impregnated with silver nitrate.

The test results of the pyrethroid esters derived from 3,6-dimethylbicyclo(4.1.0)hept-2-en-7-carboxylic acid revealed a low toxicity. It is important to note that this cyclopropanecarboxylic acid is identical to the naturally occurring chrysanthemic acid except it is locked in a single conformation and this conformation would be expected to be the least stable conformation. Therefore, these results indicate for the first time that this conformer is not the active form of the pyrethroid.

A new cyclopropanecarboxylic acid was designed and synthesized with a rigid structure which closely resembles the more stable conformer of the natural pyrethroid acid. This acid was a spiro acid and was prepared from an isopropylidencyclobutane derivative. Consistent with our expectations the pyrethroid ester derived from this spiro acid revealed a much greater toxicity against the housefly and cockroach.
Clearly, based on the insecticidal activity test results, it can be concluded that the pyrethroid ester derived from the more stable conformer of the natural pyrethroid acid provides the greater toxicity against the insects tested. These results also suggest that in the synthesis of potent new pyrethroid acids, the acids should have structures that mimic the major conformation of the natural pyrethroid acid.
CHAPTER BIBLIOGRAPHY


BIBLIOGRAPHY


Shell Oil Company.


