Synthesis and Insecticidal Activity of Some Pyrethroid-like Compounds Including Ones Lacking Cyclopropane or Ester Groupings

Peter E. Berteau[1] and John E. Casida

Twelve new pyrethroid-like compounds were synthesized, eight of which have insecticidal characteristics similar to that of pyrethrum. The new compounds structurally resemble allethrin or 5-benzyl-3-furylmethyl chrysanthemumate and they include carboxylic acid esters, carbamic acid esters, carboxamides, and ketones. Replacement of the ester oxygen bridge by a methylene group, to form a ketone, or an amino group, to form a carboxamide, does not alter the type of biological activity but greatly reduces the potency. Substitution of the 2,2,3,3-tetramethylcyclopropyl moiety for the 2,2-dimethyl-3-isobutenylcyclopropyl moiety does not greatly alter the insecticidal activity, in any one of the ester, amide, and ketone series. Pyrethroid-like activity, although of low magnitude, persists on replacing the tetramethylcyclopropyl group by a tetramethylaziridino group or, even by a diisopropylamino group. There is limited evidence that the carbonyl group adjacent to the cyclopropane ring, or an activity-retaining replacement of the ring, is a requirement for insecticidal activity, and clearly, the ester linkage is not an essential feature for activity.

Determination of the nature of the insecticidal esters in pyrethrum extract by Staudinger and Ruzicka (1924) led to attempts by these and many other workers to prepare insecticidal cyclopropanecarboxylates of less complex structure, involving modifications in the alcohol or acid moiety (Figure 1). Replacement of the pentadienyl group of pyrethrin I (A) by an allyl group, without resolution of the mixture of eight isomers from synthesis, yielded an important insecticide chemical, allethrin (B), shown as the *dl-trans*-chrysanthemumate (Schechter *et al.*, 1949). High insecticidal activity was retained on replacement of the cyclopentenone ring by certain substituted benzyl groups (Barthel, 1961), by the *N*-tetrahydrophthalimidomethyl group (C) (Kato *et al.*, 1964), or by the benzylfurylmethyl group (D) (Elliott *et al.*, 1967). Attempts to modify the cyclopropane ring without complete loss of activity were not reported prior to the present study. The apparent success in the preparation of the cyclobutane analog of chrysanthemumic acid and its allethronyl ester (Julia and Rouault, 1959; Katsuda *et al.*, 1958a, 1958b) was later contradicted (Crombie *et al.*, 1963; Julia and Rouault, 1960). It was possible to alter the substituents on the cyclopropane ring with retention of significant insecticidal activity in the resulting compounds—e.g., replacement of the geminal dimethyl group by chlorine atoms and of the isobutenyl group by a benzene ring (Novak *et al.*, 1963) or replacement of the isobutenyl group by a second geminal dimethyl group (Matsui and Kitahara, 1967). Thus, it was reported that allethronyl tetramethylcyclopropanecarboxylate (E) approximates the activity of allethrin against houseflies (Matsui and Kitahara, 1967) and, as expected, that benzylfurylmethyl tetramethylcyclopropanecarboxylate (F) is highly insecticidal (Berteau *et al.*, 1968). A few modifications of the ester linkage were made, but the products had little, if any, insecticidal activity. Such products include the ether analog of allethrin (allethronyl chrysanthemumyl ether) (Matsui *et al.*, 1956), an amide (Elliott *et al.*, 1965), and some reverse homoesters (Katsuda, 1961).

A previous publication contains preliminary information concerning pyrethroid-like insecticidal activity shown by certain compounds in which the ester linkage is replaced by a ketone function and, alternatively, in which the tetramethylcyclopropane ring is replaced by a tetramethylaziridino or diisopropylamino group (Berteau *et al.*, 1968). This paper gives the details of the syntheses of these compounds, and of some additional, related ones, and contains more information on their biological activity. Especially, it deals with modifications of the highly insecticidal pyrethroid-like esters B, D, and F.

There are three justifications for the emphasis on structure-activity studies in the benzylfurylmethyl tetramethylcyclopropanecarboxylate (F) series. First, the parent compound is highly insecticidal and this fact allows a large spread in measurable activity of related compounds and derivatives. Second, the lack of aliphatic unsaturation allows great latitude in reaction conditions for preparing possible analogs. Third, there are no asymmetric carbon atoms; and so, resolution of isomers is not a problem in preparing pure derivatives.

PURIFICATION AND ANALYTICAL METHODS

In general, the products of synthesis were purified by column chromatography using Florisil (50- to 100-mesh, Floridin Co., Hancock, W. Va.) or alumina (neutral aluminum oxide WOELM, activity grade I for chromatography, Alupharm Chemicals, New Orleans, La.) or by preparative-scale thin-

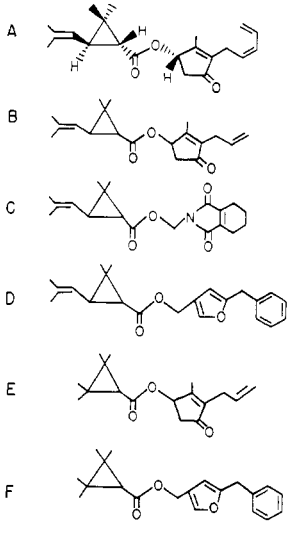


Figure 1. Structures for pyrethrin I (A), allethrin (B), phthalthrin (C), and structurally related insecticide chemicals

Division of Entomology, University of California, Berkeley, Calif. 94720
[1] Present address, Food Additives Unit, World Health Organization, Geneva, Switzerland

layer chromatography (TLC) using plates coated with silica gel G_F (Mallinckrodt Chemical Works, St. Louis, Mo.) at a thickness of 1.0 mm. The Florisil columns were developed, in sequence, with hexane, and ethyl acetate–hexane mixtures of increasing polarity (1 to 100, 1 to 50, 1 to 20, and 1 to 10) until the desired product was eluted. On a comparable basis, benzene and benzene-ether mixtures were used with the alumina column. For preparative-scale TLC, samples of up to 0.1 gram were used and, after development with acetone-hexane (1 to 20) mixture, appropriate fluorescent regions, as evidenced by viewing under short wavelength ultraviolet light, were removed by scraping, and the compounds were eluted from the scrapings with acetone. Whenever possible, the purified products were crystallized prior to analysis or testing.

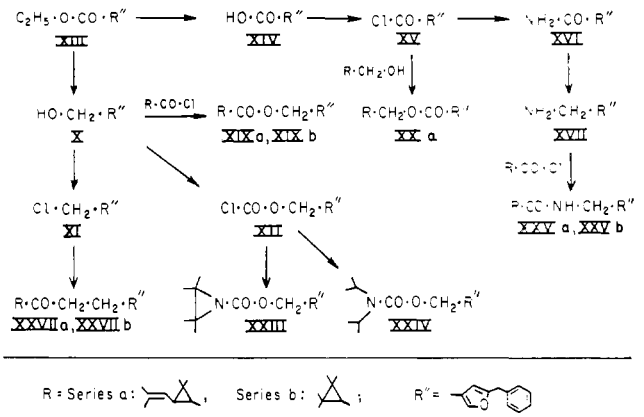
The purity of the reaction products was determined by TLC using silica gel F_{254} precoated plates (Brinkmann Instruments, Inc., Westbury, N.Y.). All reported R_f values were determined using ethyl acetate–hexane (1 to 9) mixture. The plates were sprayed with 20% phosphomolybdic acid in ethanol, then heated at 120° C. for 10 minutes to develop the spots.

Elemental analyses were performed by the Microchemical Laboratory, Department of Chemistry, University of California, Berkeley, Calif. Infrared spectra were measured on a Beckman IR-4 or a Perkin-Elmer 457 spectrometer, using neat films, Nujol mulls, or carbon tetrachloride solutions. Nuclear magnetic resonance (NMR) spectra were obtained on a Varian A60 spectrometer, using deuterochloroform solutions, and were recorded relative to tetramethylsilane ($\delta = 0$ p.p.m.). Mass spectra were obtained by the Department of Chemistry, University of California, Berkeley, Calif., using a Varian M66 or a modified CEC Model 21-103C spectrometer. All melting points were determined on a micro hot stage and were not corrected.

In the toxicity tests, susceptible adult female houseflies (*Musca domestica* L., SCR strain) and adult male and female milkweed bugs (*Oncopeltus fasciatus* Dallas) were treated on the dorsum and the ventrum of the thorax, respectively, with 1.0 μl. of an acetone solution of the test compound. In certain studies with houseflies, 5.0 μg. of piperonyl butoxide synergist were applied as 1.0 μl. of an acetone solution to the abdomen 0.5 to 1.0 hour prior to treatment with the insecticide. The LD_{50} values were determined using a 24-hour holding period at 25° C. in the case of houseflies, and a 48-hour period at 30° C. with milkweed bugs.

METHODS OF SYNTHESIS

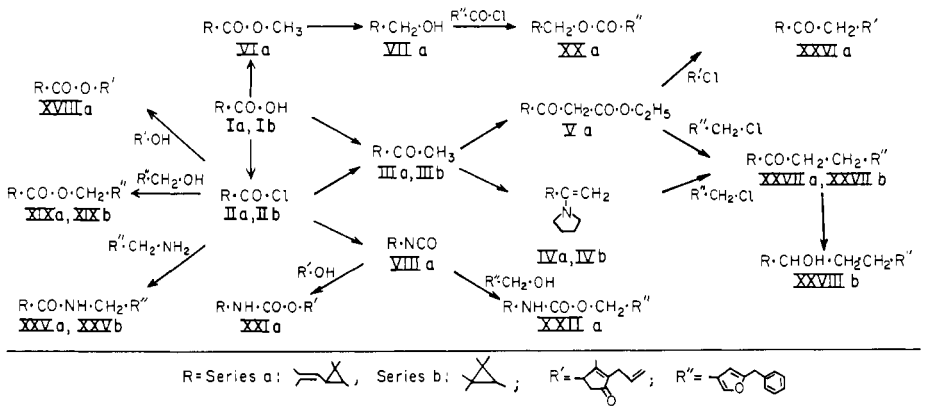
Scheme I outlines the synthesis routes, starting with cyclopropanecarboxylic acids, to prepare the corresponding carboxylic acid esters, carbamic acid esters, carboxamides, and ketones. Scheme II outlines the synthesis routes used to prepare these derivatives which start with ethyl 5-benzyl-3-furoate and 5-benzyl-3-furylmethanol [materials described by Elliott *et al.* (1967)]. These two schemes also give the number designations used for the intermediates as well as for the final products. All compounds derived from chrysanthemumic acid (Ia) are designated as members of the "a" series and are in the *dl*-trans configuration with respect to the cyclopropane ring. Compounds derived from tetramethylcyclopropanecarboxylic acid (Ib) are designated as members of the "b" series. Chemicals prepared from allethrolone are in the *dl*-configuration with respect to the alcohol moiety or replacement groups for the alcohol moiety. The reaction sequences are given, for the most part, in Scheme I for the acid moiety and replacement groups for the acid moiety, and in Scheme II for the alcohol moiety and replacement groups for the alcohol moiety. Analytical data found for the compounds are given in the text or in Table I.



Scheme 2. Synthesis routes for carboxylic acid esters, carbamic acid esters, carboxamides, and ketones, starting from ethyl 5-benzyl-3-furoate (XIII) and 5-benzyl-3-furylmethanol (X)

For structure of the final products, see Table I

Modified Acid Moiety or its Replacement Group. *dl*-trans-Chrysanthemumic acid (Ia) was prepared by epimerization of ethyl *dl-cis, trans*-chrysanthemumate (Benzol Products Co., Newark, N.J.); a 10% solution of the ester in 6*N* sodium ethoxide in absolute ethanol was refluxed for several days (Julia *et al.*, 1959) followed by addition of water, removal of ethanol by distillation, addition of more water, acidification,



Scheme 1. Synthesis routes for carboxylic acid esters, carbamic acid esters, carboxamides, and ketones, starting from cyclopropanecarboxylic acids (Ia and Ib)

For structure of the final products, see Table I

and isolation of the product by the procedure of Campbell and Harper (1945). Distillation (81° to 90° C. at 0.05 mm.) and one recrystallization from ethyl acetate gave the desired acid in 35% yield (m.p. 52–4° C.; lit. 54° C.). 2,2,3,3-Tetramethylcyclopropanecarboxylic acid (Ib) (m.p. 118–9° C.; lit. 121° C.) was obtained by the method of Meshcheryakov and Dolgii (1960) in 75% yield on hydrolysis of the ethyl ester (b.p. 84° to 93° C. at 23 mm.; lit. 76–7° C. at 15 mm.). The yield of the ester was increased to 45% (based on ethyl diazoacetate) by increasing the amount of anhydrous copper sulfate catalyst to 12 grams for a 0.45 mmole run. The method of Crombie *et al.* (1950) was used to convert Ia, in almost quantitative yield, to its acid chloride (IIa) (b.p. 56–60° C. at 0.2 mm.; lit. 50–1° C. at 0.15 mm.) and, with a longer reaction time, Ib to its acid chloride (IIb) (m.p. 31° C.; b.p. 29° C. at 0.1 mm.).

Two known cyclopropyl methyl ketones, 1-acetyl-2,2-dimethyl-3-isobutenylcyclopropane (IIIa) and 1-acetyl-2,2,3,3-tetramethylcyclopropane (IIIb) were prepared from the intermediates described above. Chrysanthemumoyl chloride (IIa) was converted, in 45% yield, to the methyl ketone (IIIa) by the method of Eastman and Freeman (1955) (b.p. 41–4° C. at 0.15 mm.; lit. 91° C. at 15 mm.); the acid work-up was done cautiously and the steam distillation step was omitted to prevent artemisyl ring fission (Crombie *et al.*, 1967). The other methyl ketone (IIIb) (b.p. 65–7° C. at 23 mm.; lit. 59.5° C. at 15 mm., Meshcheryakov and Dolgii, 1961) was conveniently obtained, in 80% yield, directly from the acid (Ib) by treating it, in ethereal solution, with two equivalents of methyllithium, using the procedure of DePuy *et al.* (1964) for preparing certain substituted cyclopropanecarboxylic acids.

Compounds IIIa and IIIb were converted to their respective pyrollidine enamines (IVa and IVb) by the method of White and Weingarten (1967), using pentane as the solvent and titanium tetrachloride to abstract water. Distillation gave 2,2-dimethyl-3-isobutenyl-1-(1-pyrollidinovinyl)-cyclopropane (IVa) in 75% yield (b.p. 84–7° C. at 0.1 mm.; C%, calcd. 82.13, found 81.96; H%, calcd. 11.49, found 11.30; N%, calcd. 6.38, found 6.62) and 1-(1-pyrollidinovinyl)-2,2,3,3-tetramethylcyclopropane (IVb) in 40% yield (b.p. 56–60°C. at 0.06 mm.; C% calcd. 80.76, found 79.91; H%, calcd. 11.99, found 11.87; N%, calcd. 7.24, found 7.52). These pyrollidine enamines were stable in the cold when stored in a dry nitrogen atmosphere, but, on exposure to air and moisture, they decomposed as evidenced by rapid darkening of the material. As a result of decomposition during TLC chromatography, the enamines showed spots corresponding to the respective ketones, only. Infrared spectra showed the absence of the ketonic carbonyl band at about 1700 cm.$^{-1}$, and the presence of a new strong band at about 1620 cm.$^{-1}$, as a result of the vinyl grouping of the enamine. Another methyl ketone derivative, ethyl chrysanthemumoylacetate (Va), was made from the corresponding methyl ketone (IIIa), by adding 0.27 mole of the latter compound to a stirred mixture of sodium hydride (60% oil suspension, 0.53 mole) in 75 ml. of dry ether. The mixture was heated to boiling under a nitrogen atmosphere and diethyl carbonate (0.55 mole) was added, dropwise, while maintaining reflux; after the addition was complete, reflux was continued for 4 hours. The mixture was cooled, glacial acetic acid (30 ml.) was added carefully, and the solution was washed with 1.2*M* sodium bicarbonate and water, dried (magnesium sulfate), evaporated, and distilled (89° to 95° C. at 0.03 mm.) to give the desired material in 70% yield (C%, calcd. 70.56, found 70.86; H%, calcd. 9.30, found 9.65). The colorless liquid, which solidified at −15° C., showed a positive test with ferric chloride. The infrared spectrum showed carbonyl bands at 1710 cm.$^{-1}$ and 1750 cm.$^{-1}$, and a wide band at 1610 to 1620 cm.$^{-1}$ as a result of the enolic double bond.

Chrysanthemol (VIIa) (b.p. 107–9° C. at 18 mm.; lit. 73–4° C. at 1 mm.) was prepared in 70% yield from methyl chrysanthemumate (VIa) (obtained by the reaction of diazomethane with Ia) on reduction with lithium aluminum hydride as described by Inouye and Ohno (1956). 2,2-Dimethyl-3-isobutenylcyclopropylisocyanate (VIIIa) was made from IIa (0.32 mole) by adding it to a suspension of activated sodium azide [0.64 mole, made as described by Smith (1946)], in dry benzene (320 ml.), stirring the mixture, and heating under reflux for 18 hours. Completion of the reaction was evident by the absence of a carbonyl band in the 1700- to 1800-cm.$^{-1}$ region of the infrared spectrum. The solid was removed by filtration, the benzene was evaporated, and the residual liquid was distilled (b.p. 87–8° C. at 16 mm.) to give the desired material in 75% yield. The presence of an isocyanate group was confirmed by the strong infrared spectral band at 2300 cm.$^{-1}$. The elemental analyses (C%, calcd. 72.69, found 71.45; H%, calcd. 9.15, found 9.04) were a little too low, probably because the product reacted slightly with moisture. The ethyl urethane (m.p. 61–2° C.) gave appropriate analytical values (C%, calcd. 68.21, found 68.35; H%, calcd. 10.02, found 9.89, N%, calcd. 6.63, found 6.76). Retention of the trans configuration in the isocyanate (VIIIa) and the carbamates (XXIa and XXIIa) prepared from it is assumed on the basis of earlier studies with related compounds (Buchman *et al.*, 1942; Gould, 1959).

Modified Alcohol Moiety or its Replacement Group. The method described for the preparation of 4-bromoallethrone by Matsui *et al.* (1956), modified by replacing phosphorus tribromide by an equivalent molar quantity of phosphorus trichloride, was used to prepare 4-chloroallethrone (IX) in 60% yield (b.p. 69–71° C. at 0.25 mm.; C% calcd. 63.35, found 63.28; H%, calcd. 6.50, found 6.58; Cl%, calcd. 20.78, found 20.38). An alternative route, analogous to that described by LaForge and Barthel (1945) to prepare the chloro-derivative of cinerolone and involving thionyl chloride was attempted but an impure product resulted, as evidenced by the wide boiling range and chromatographic characteristics.

Intermediates or the final product in the synthetic route for 5-benzyl-3-furylmethanol (X) reported by Elliott *et al.* (1967) were used to prepare 5-benzyl-3-furylmethyl chloride (XI), and a number of related compounds (XII–XVII). For the preparation of 5-benzyl-3-furylmethyl chloride (XI), a mixture of dry benzene (5 ml.), phosphorus trichloride (0.04 mole), and pyridine (2 ml.) was cooled in an ice-bath, and 5-benzyl-3-furylmethanol (X) (0.05 mole) in dry benzene (50 ml.) was added, dropwise, with stirring. The mixture was stirred for 16 hours, poured into 1.2*M* sodium bicarbonate, extracted with benzene, the benzene washed with water, dried (sodium sulfate), evaporated, and the residue distilled (99–100° C. at 0.03 mm.) to give the desired product in 75% yield (C%, calcd. 69.73, found 69.58; H%, calcd. 5.37, found 5.22; Cl%, calcd. 17.16, found 17.25). The chloroformate ester (XII) of 5-benzyl-3-furylmethanol (X) was prepared by dissolving 5 mmoles of the latter compound in dry benzene (6 ml.), adding phosgene (6.6 mmoles in 6 ml. of benzene), and allowing the mixture to react for 20 hours at 25° C. The reaction vessel was immersed in a water bath at 50° C. and high vacuum was applied to remove the solvent, excess phosgene, and hydrochloric acid gas. The chloroformate was not further purified. (Treatment of allethrolone with phosgene under a variety of conditions produced a complex mixture, from which it was not possible to isolate allethronyl chloroformate.)

Ethyl 5-benzyl-3-furoate (XIII) (Elliott *et al.*, 1967) was

hydrolyzed to 5-benzyl-3-furoic acid (XIV) by refluxing 0.1 mole of the ester with 100 ml. of 2*N* potassium hydroxide in 50% aqueous ethanol for 3 hours. The ethanol was evaporated off and the unsaponified material was removed by extraction with benzene. The aqueous phase was acidified with dilute sulfuric acid, extracted with a large volume of benzene, and the benzene was washed with water, dried (sodium sulfate), evaporated, and the solid crystallized from ethyl acetate–hexane mixture, to give the desired product in 80% yield. An analytical sample was obtained by recrystallization from a large volume of hexane to give m.p. 130–1° C. (C%, calcd. 71.28, found 71.72; H%, calcd. 4.98, found 5.12). Conversion to the acid chloride (XV) in 95% yield was accomplished by stirring XIV (0.05 mole) in thionyl chloride (50 ml.) for 3 days at 25° C., evaporating the excess thionyl chloride, and distilling the product (93° to 100° C. at 0.03 mm.). 5-Benzyl-3-furamide (XVI) was prepared by dropwise addition of the furoyl chloride (XV) (20 mmoles) to 30 ml. of vigorously stirred 15*N* ammonium hydroxide, continuing the stirring for 20 minutes after the addition was complete. On dilution with water, the solid precipitate was filtered off and recrystallized from ethanol-chloroform mixture (80% yield) and then from a large volume of aqueous ethanol to give XVI, m.p. 189–90° C. (C%, calcd. 71.63, found 71.82; H%, calcd. 5.51, found 5.35; N%, calcd. 6.96, found 6.36). 5-Benzyl-3-furamide (XVI) (15 mmoles) was reduced to 5-benzyl-3-furylmethylamine (XVII) by adding it in small portions to a stirred suspension of powdered lithium aluminum hydride (100 mmoles) in dry ether (100 ml.) at 25° C., with additional stirring for 16 hours at 25° C. Water was very cautiously added under a nitrogen atmosphere, followed by addition of 2*N* sodium hydroxide. The ether layer was washed with water, dried (magnesium sulfate), and evaporated to give a yellowish oil which solidified at −15° C. and which was not further purified.

Carboxylic Acid Esters, Carbamic Acid Esters, and Carboxamides. The carboxylic acid esters (XVIIIa, XIXa, XIXb, and XXa) were obtained by treating the acid chloride (IIa, IIa, IIb, and XV, respectively) with the appropriate alcohol (*dl*-allethrolone, X, X, and VIIa, respectively) in benzene solution in the presence of one equivalent of pyridine. The benzene solution was washed with dilute hydrochloric acid (cautiously), 1.2*M* sodium bicarbonate, and water, dried (sodium sulfate), and evaporated. Yields for the products, purified by column chromatography on Florisil, ranged from 80 to 95%. The carboxylic acid ester, XIXa, was recrystallized from hexane, after additional purification on an alumina column, whereas XIXb crystallized directly as a pure compound on removal of the solvent from Florisil column chromatography. Additional chromatography on alumina was also necessary to obtain a pure sample of the reverse-ester (XXa). The *N*-(2,2-dimethyl-3-isobutenyl-1-cyclopropyl)-carbamates (XXIa and XXIIa) were prepared by reaction of 2,2-dimethyl-3-isobutenylcyclopropylisocyanate (VIIIa) (12 mmoles) with allethrolone (10 mmoles) to obtain XXIa or with 5-benzyl-3-furylmethanol (X) (10 mmoles) to obtain XXIIa. The reactions were run in dry benzene (3 ml.) containing one drop of triethylamine, by refluxing for 16 hours. The solvent was evaporated, and the products, obtained in almost quantitative yields based on the alcohols, were recrystallized from hexane. The 2,2,3,3-tetramethylaziridinecarboxylate (XXIII) and *N,N*-diisopropylcarbamate (XXIV) of 5-benzyl-3-furylmethanol (X) were prepared by dissolving 5-benzyl-3-furylmethyl chloroformate (XII) in benzene and adding equivalent amounts of 2,2,3,3-tetramethylaziridine (Closs and Brois, 1960) and triethylamine, or greater than two equivalents of dry diisopropylamine. After a reaction time of 3 hours for XXIII and 3 days for XXIV, the precipitate was filtered off, the solvent evaporated, and the oily products purified by passing them two times through Florisil columns. The yields obtained were 20% for XXIII and 16% for XXIV. (The comparable series of allethronyl carbamates were not made because it was not possible to prepare allethronyl chloroformate as previously noted.) Formation of the carboxamides (XXVa, XXVb) was accomplished by dissolving 5-benzyl-3-furylmethylamine (XVII) and one equivalent of dry pyridine in 10 volumes of dry benzene followed by dropwise addition, with stirring and cooling, of slightly less than one equivalent of the acid chloride (IIa and IIb, respectively) and subsequent stirring for 18 hours at 25° C. The reaction mixtures were washed with water, dilute hydrochloric acid, 1.2*M* sodium bicarbonate, and water, dried (sodium sulfate), and evaporated. The chrysanthemumic acid derivative (XXVa) was recrystallized from hexane and the tetramethylcyclopropanecarboxylic acid derivative (XXVb), an oil, was purified by column chromatography on Florisil. The yields were 40% for XXVa and 30% for XXVb.

Ketones and an Alcohol. Two methods, leading to the ketone analogs (XXVIa, XXVIIa, and XXVIIb), involved substitution reactions of 4-chloroallethrone (IX) or 5-benzyl-3-furylmethyl chloride (XI) at the methyl group of the cyclopropyl methyl ketones (IIIa, IIIb). This substitution was achieved either from the pyrollidine enamines of the methyl ketones (IVa, IVb), by refluxing with the chloro-derivative in dry methanol, or, alternatively, by converting the methyl ketone to its ethoxycarbonyl derivative (Va), using diethyl carbonate and sodium hydride. The resulting β-keto-ester (Va) was allowed to react with the chloro-derivative in the presence of sodium ethoxide; hydrolysis and thermal decarboxylation gave the desired product.

To prepare the ketone analog of allethrin, 1-(4-allethronyl)-acetyl-2,2-dimethyl-3-isobutenylcyclopropane (XXVIa), by the keto-ester route, clean sodium (reagent spheres, 0.05 gram-atom) was dissolved in dry absolute ethanol, ethyl chrysanthemumoyl acetate (Va) (0.055 mole) was added, and the mixture was refluxed for 10 minutes. 4-Chloroallethrone (IX) (0.05 mole) was added, dropwise and with stirring, to the boiling solution; reflux was maintained for 2 hours, the heating was discontinued, and the mixture was stirred for 20 hours, while standing at 25° C. Sodium chloride, formed during the reaction, was filtered off, the ethanol was removed by evaporation, and the residue was taken up in dichloromethane which was then washed successively with 2*N* hydrochloric acid, 1.2*M* sodium bicarbonate, and water, dried (sodium sulfate), and evaporated. The residual yellow oil was hydrolyzed by stirring at 25° C. for 20 hours with 1*N* sodium hydroxide (65 ml.). The unsaponified material (mostly dehydroallethrolone dimers as discussed below) was removed by extraction with benzene. To the aqueous phase, which contained the sodium salt of the allethronyl substituted keto-acid in solution, was added 18*N* sulfuric acid (5 ml.), and the mixture was stirred at 80° to 90° C. When frothing, due to decarboxylation, had ceased (about 30 minutes), the mixture was cooled and extracted with benzene, and the benzene was washed successively with 1.2*M* sodium bicarbonate and water, dried (sodium sulfate), and evaporated. The residual oil was heated at 100° C. under high vacuum to remove methyl ketone (IIIa) which had been regenerated due to hydrolysis and decarboxylation of any unsubstituted keto-ester (Va). The remaining material was purified by Florisil column chromatography, to obtain the pure compound as a colorless, slightly translucent oil. Distillation under reduced pressure, of a portion of the material, resulted in decomposition.

The enamine route is less favorable than the keto-ester route to prepare the ketone analog of allethrin (XXVIa), because of the nature of the products formed by competing reactions. Enamines are known to undergo both C-alkylation and N-alkylation; the products of the N-alkylation reduce the yield of the substituted ketone (Szmuszkovicz, 1963). A polar solvent appears to be better than a nonpolar solvent for the enamine route because the yield of XXVIa, or at least the insecticidal activity of the products obtained, was highest with methanol and was progressively lower with acetonitrile and benzene. Although it was not investigated, the effect of solvent polarity on the yield of desired product possibly is related to a change in the ratio of C-alkylation to N-alkylation. However, even with methanol as the reaction solvent, it was not possible to isolate the desired product because of the nature of the attendant impurities. The pyrollidine enamine (IVa) (0.06 mole) in dry methanol (75 ml.) was heated under reflux with 4-chloroallethrone (IX) (0.06 mole) for 20 hours. After this period, water (75 ml.) was added and reflux was continued for 2 hours; the methanol was evaporated, saturated aqueous sodium carbonate (100 ml.) was added, and the mixture was extracted with chloroform. The chloroform phase was dried (sodium sulfate) and evaporated. It was possible to purify this product by Florisil column chromatography and preparative TLC to the extent that it gave one spot on TLC, identical to the desired product (XXVIa) as obtained by the keto-ester route. However, the product was not the same as that obtained by the keto-ester route, in that, among other differences, a strong band was present at 1780 $cm.^{-1}$ in the infrared spectrum for the material from the enamine route. This band is characteristic of the strained bridge carbonyl group in 2,4-diallyl-3,5-dimethyl-3a,4,7,7a-tetrahydro-4,7-methanoindene-1,8-dione (referred to as the dehydroallethrolone dimer molecule). In fact, the infrared spectrum of the material from the enamine route was very similar to the noninsecticidal dehydroallethrolone dimer obtained on alkaline treatment of allethronyl acid phthalate (LaForge *et al.*, 1952), with the exception that weak bands or shoulders were present in appropriate regions to indicate the presence of XXVIa as a minor contaminant. When recrystallized from hexane, the material from the enamine route gave a m.p. of 62–4° C. and an infrared spectrum identical to that of the LaForge dimer which has a m.p. of 66–8° C. Insecticidal activity resided in the mother liquor and not in the crystals. Even after removal of much of the dimer by crystallization, no chromatographic solvent was found that would separate XXVIa from the remaining portion of dimer; distillation in a short-path still was ineffective for separation. Another dehydroallethrolone dimer was also formed, because a second crystalline material (m.p. 46–8° C.) of higher R_f value but with an almost identical infrared spectrum was isolated from a comparable reaction mixture (C%, calcd. 80.56, found 80.85; H%, calcd. 7.51, found 7.30) (Berteau *et al.*, 1967). [Although LaForge *et al.* (1952) reported only one dehydroallethrolone dimer, they noted that four stereoisomeric forms can theoretically exist, designated as the exo-cis, exo-trans, endo-cis, and endo-trans forms; it is probable that this second crystalline material is one of these forms but different from that previously reported.] Dehydroallethrolone dimers also are formed by a competing elimination reaction, when substituting 4-chloroallethrone (IX), in the keto-ester route; however, they do not interfere with isolation of XXVIa because they are easily removed before decarboxylation by extracting them out with benzene, leaving the sodium salt of the β-keto-acid in the aqueous phase. The keto-ester route is the method of choice for preparation of XXVIa because of the ease of removal of dehydroallethrolone dimers prior to formation of the substituted ketone.

1-[3-(5-Benzyl-3-furyl)-propionyl]-2,2-dimethyl-3-isobutenylcyclopropane (XXVIIa) was prepared by the keto-ester route, in a manner similar to that described above for XXVIa, except that the reaction scale was 4.4 mmoles. The substituted keto-ester was more resistant to hydrolysis than the corresponding allethronyl derivative and remained almost unaffected by stirring at 25° C. with 1*N* sodium hydroxide; consequently, it was necessary to reflux the material with 1*N* sodium hydroxide for 3 hours, during which time both hydrolysis and decarboxylation were achieved. The product was extracted and washed in the usual manner and was purified by chromatography both on a Florisil column and on thin-layer. The resulting yield was very low (5%), and the enamine route proved to be the method of choice for preparing compound (XXVIIa). The pyrollidine enamine of 1-acetyl-2,2-dimethyl-3-isobutenylcyclopropane (IVa) (5 mmoles) along with 5-benzyl-3-furylmethyl chloride (XI) (5 mmoles) in dry methanol (7 ml.) were refluxed for 16 hours in a nitrogen atmosphere, during which time the reaction mixture became dark red in color. At the end of this period, water (7 ml.) was added and reflux was continued for 2 hours. The solution was evaporated, the residue taken up in dichloromethane, the dichloromethane washed with 1.2*M* sodium bicarbonate and water, dried (sodium sulfate), and evaporated. Purification by column chromatography (Florisil and alumina) and on thin-layer resulted in a pure product (XXVIIa) (single spot on TLC), isolated in 20% yield as an oil which did not crystallize; it was identical, in every respect, to the material obtained by the keto-ester route.

1-[3-(5-Benzyl-3-furyl)-propionyl]-2,2,3,3-tetramethylcyclopropane (XXVIIb) was made from the pyrollidine enamine of 1-acetyl-2,2,3,3-tetramethylcyclopropane (IVb) (25 mmoles) and 5-benzyl-3-furylmethyl chloride (XI) (25 mmoles) in dry methanol (35 ml.) by refluxing for 2 days in a nitrogen atmosphere, during which time the mixture became dark red in color. After this reflux period, water (35 ml.) was added and reflux was maintained for 3 hours. Water and methanol were removed by evaporation and the tarry residue was extracted first with benzene and water, and then with dichloromethane; the dichloromethane dissolved a gum which was insoluble in both water and benzene. The benzene and dichloromethane extracts were separately washed, in the usual manner, dried (sodium sulfate), and evaporated. TLC indicated the presence of the desired product in both extracts; however, the benzene extract showed the presence of an impurity with a R_f value close to that of the product, whereas, the impurities in the dichloromethane extract were of much lower R_f values. Both extracts were separately subjected to Florisil column chromatography, and the desired material was crystallized once from hexane. Almost equal amounts of the desired product (XXVIIb), as a white crystalline solid, were recovered from the dichloromethane and benzene extracts, in an over-all yield of 30%. The material of higher purity was obtained from the dichloromethane extract. In another experiment, preparative TLC was necessary to obtain material of satisfactory purity.

A material tentatively identified as 3-(5-benzyl-3-furyl)-1-(2,2,3,3-tetramethylcyclopropyl)-propanol (XXVIIIb) was prepared from XXVIIb (1.0 mmole) by adding it, in small portions, with stirring, to a suspension of lithium aluminum hydride (2.6 mmoles) in dry ether. A brisk evolution of hydrogen occurred on each addition. After the addition was complete, the mixture was stirred for 16 hours. Then ethyl acetate was cautiously added, followed by saturated aqueous

ammonium chloride. The ethereal phase was separated, washed with 1.2*M* sodium bicarbonate, dried (sodium sulfate), and evaporated. The product (XXVIIIb) was isolated as a noncrystalline material in almost quantitative yield, after purification by Florisil column chromatography. On conversion to the alcohol, the infrared spectral peak at 1710 $cm.^{-1}$ associated with the carbonyl group of the ketone completely disappeared and a new peak appeared at 3400 $cm.^{-1}$ due to the hydroxyl group. Insufficient material was available for further characterization.

SPECTRAL IDENTIFICATION

Crombie *et al.* (1967) have observed that, in the case of certain chrysanthemumic acid derivatives, where a carbonium ion is easily generated on the carbon atom adjacent to the 1-position of the cyclopropane ring, artemisyl ring fission is likely to occur in the presence of acid. The occurrence of this type of fission can be easily detected from the NMR spectrum by a quartet centered at $\delta = 5.85$ p.p.m. arising from the olefinic protons of the diene formed (Crombie, 1967). In all compounds where this isomerization is likely to occur (IIIa, IVa, Va, VIIa, XXa, XXVIa, and XXVIIa), the cyclopropane ring was found to be intact because the aforementioned quartet was absent. On a similar basis, ring fission in the tetramethylcyclopropanecarboxylic acid series did not occur in the preparation of IIIb, IVb, XXVIIb, and XXVIIIb because the signals anticipated downfield for the olefinic protons which would arise from such isomerization were not observed. Both the cyclopropane and furan rings remained intact in the carboxamide series, as determined by a NMR spectrum on XXVa. In the carbamic acid ester series, the cyclopropane ring was found to be intact in XXIa and in ethyl *N*-(2,2-dimethyl-3-isobutenyl-1-cyclopropyl)-carbamate. In the preparation of the tetramethylaziridinecarboxylate (XXIII), acidic ring cleavage might occur (Bestian *et al.*, 1950) and so triethylamine was added as an acid acceptor; this procedure was successful in preventing ring cleavage as evidenced by a NMR spectrum on the product, which showed a signal corresponding to 12 protons which were not resolved at $\delta = 1.15$ p.p.m., attributable to the four methyl groups on the tetramethylaziridine ring.

The mass spectral data supported the structures assigned to compounds XVIIIa, XXIII, XXIV, XXVb, XXVIa, XXVIIa, and XXVIIb because, in each case, the *m/e* value for the parent peak was identical to the anticipated molecular weight. In addition, the infrared spectral bands of each new compound were consistent with the structure assigned.

STRUCTURE-ACTIVITY RELATIONSHIPS

Insecticidal activity data for the carboxylic acid esters, carbamic acid esters, carboxamides, and ketones are given in Table I. The insecticidal activity of the carboxamide (XXVa) was not due to a trace of the ester analog (XIXa) present as an impurity because, when repurified by TLC in a system which would remove any ester present, the insecticidal activity was not reduced. Nearly equivalent insecticidal activity is conferred by the 2,2-dimethyl-3-isobutenylcyclopropyl and 2,2,3,-3-tetramethylcyclopropyl groupings as demonstrated in the 5-benzyl-3-furylmethyl series with carboxylic acid esters (XIXa *vs.* XIXb), carboxamides (XXVa *vs.* XXVb), and ketones (XXVIIa *vs.* XXVIIb). These results confirm and extend the finding of Matsui and Kitahara (1967) in the allethronyl carboxylic acid ester series and give further emphasis to the importance of the geminal dimethyl groupings. The degree of synergism by piperonyl butoxide is high in all three series and, for the most part, is independent of the substituents on the cyclopropane ring, suggesting that the isobutenyl grouping is not the limiting factor in the rate of metabolism of compounds in the 5-benzyl-3-furylmethyl series. This finding is contradictory to expectation based on metabolic studies with pyrethrin I, allethrin, phthalthrin, and dimethrin (Yamamoto and Casida, 1966). Although the site of metabolic attack in the 5-benzyl-3-furylmethyl series is not known, the structure-activity studies relative to degree of synergism indicate that the position most rapidly attacked by the microsome-mixed function oxidase enzymes of houseflies probably is a site common to each of the chemicals in the series of compounds XIXa, XIXb, XXVa, XXVb, XXVIIa, and XXVIIb.

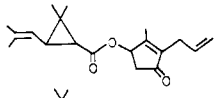
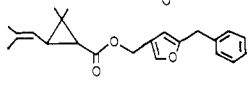
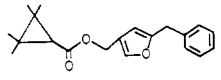
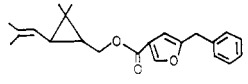
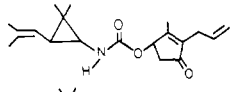
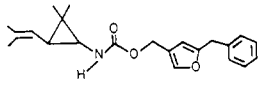
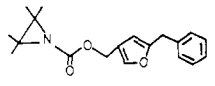
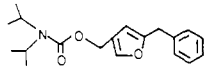
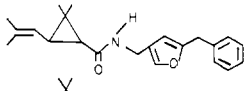
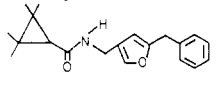
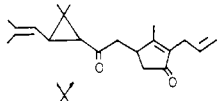
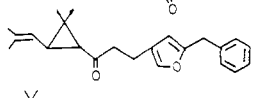
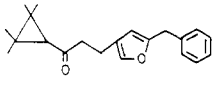
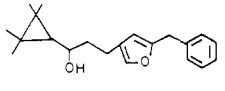
An almost equivalent reduction in biological activity on replacement of the ester group by either an amide or a ketone group is evident from the 5-benzyl-3-furylmethyl series described above and from comparison of allethrin (XVIIIa) with its ketone analog (XXVIa).

The carbonyl group adjacent to the cyclopropane ring or a grouping of equivalent configuration undoubtedly is an important structural feature because almost total loss of activity results in reduction of compound XXVIIb to compound XXVIIIb; a shift in the position of the carbonyl group from adjacent to the cyclopropane (XIXa) to adjacent to the furan ring (XXa); and insertion of a NH-group between the carbonyl function and the cyclopropane ring (XXIa and XXIIa versus XVIIIa and XIXa, respectively). However, the latter carbamates possibly do not have appropriate spatial configuration and distance between the cyclopropane ring and the 5-benzyl-3-furylmethyl group to have the expected activity. In addition, Matsui and Kitamura (1955) report that the allethronyl ester of homochrysanthemumic acid is inactive.

Clearly, from the present and earlier structure-activity studies, pyrethroid-like biological activity is dependent on a specific spatial configuration conferring possible points of attachment or binding at two or more positions on the molecule. Detailed considerations of these features are mentioned in the introduction and are discussed by Barthel (1961), Matsui and Kitahara (1967), and Elliott (1967). The present study deals primarily with replacement groupings for the ester linkage and the cyclopropane ring. The ester grouping can be replaced by an amide or ketone grouping with retention of the same type of biological activity, although of a lower magnitude. This finding definitely establishes that potential cleavage of the ester grouping or the action of a fragment liberated on its hydrolysis is not an essential feature for insecticidal activity. The cyclopropane ring is not absolutely essential for activity; apparently, it can be replaced by a nitrogen-containing ring, or a nitrogen-containing ring-opened analog with retention of significant activity, albeit drastically reduced activity. The ketone analog of allethrin and the tetramethylaziridinecarboxylate and diisopropylcarbamate analogs of another ester (XIXb) are less active than their respective ester analogs when assayed at both the organismal and nerve axon levels (Berteau *et al.*, 1968), indicating that the major effect of the substituent changes is due to a difference in combination with or binding at the site of physiological disruption and not to the penetration rate into the organism. All available evidence indicates that the carbonyl group adjacent to the cyclopropane ring or a grouping of equivalent spatial configuration is essential for pyrethroid-like activity; however, data relevant to this hypothesis exist for only a few compounds.

It is probable that optimal insecticidal activity in the pyrethroid-like materials has not yet been achieved because even with the most insecticidal compounds, the esters of 5-benzyl-

Table I. Analytical Data and Insecticidal Activity Found for Carboxylic Acid Esters, Carbamic Acid Esters, Carboxamides, and Ketones

Compound No.	Structure	M.P., °C.	R_f Values for TLC		Elemental Analyses, % Calcd.	Found	Toxicity, Topical LD_{50} (Mg./Kg) Milkweed bug	Housefly Without synergist	Housefly With synergist
				Carboxylic Acid Esters					
XVIIIa		Oil	0.34	C	75.46	75.13	30	21	0.8
				H	8.67	8.96			
XIXa		54–5	0.61	C	78.07	77.98	20	0.8	0.07
				H	7.74	8.01			
XIXb		34	0.64	C	76.89	76.88	9	0.7	0.05
				H	7.74	7.73			
XXa		Oil	0.63	C	78.07	78.09	>1000	>1000	>1000
				H	7.74	7.86			
				Carbamic Acid Esters					
XXIa		72–4	0.08	C	71.89	72.13	>1000	>1000	>1000
				H	8.57	8.59			
				N	4.41	4.68			
XXIIa		43	0.25	C	74.76	74.28	>1000	>1000	>1000
				H	7.70	7.83			
				N	3.96	3.89			
XXIII		Oil	0.36	C	72.82	72.43	300	228	13
				H	7.40	7.39			
				N	4.47	4.31			
XXIV		Oil	0.42	C	72.35	72.40	800	750	30
				H	7.99	7.98			
				N	4.44	4.55			
				Carboxamides					
XXVa		76–8	0.14	C	78.30	78.21	>1000	63	0.6
				H	8.06	8.10			
				N	4.15	4.28			
XXVb		Oil	0.16	C	77.14	75.94	>1000	65	0.6
				H	8.09	8.10			
				Ketones and Derivative					
XXVIa		Oil	0.25	C	79.96	79.74	200	171	5
				H	9.39	9.52			
XXVIIa		Oil	0.62	C	82.10	81.49	64	17	1.2
				H	8.39	8.39			
XXVIIb		53–4	0.62	C	81.25	81.08	>1000	39	1.7
				H	8.44	8.38			
XXVIIIb		Oil	0.27	C	80.73	80.24	>1000	>1000	530
				H	9.03	9.09			

3-furylmethanol, there is a significant increase in toxicity on treatment with a high level of synergist, indicating that detoxification is still a limiting factor. Thus, there is a need to continue in the search for compounds that combine rapid penetration, slow detoxification rates, and optimal fit at the receptor site leading to maximum physiological disruption.

ACKNOWLEDGMENT

The authors gratefully thank the following persons for their suggestions, assistance and/or contribution of materials; Y.-L. Chen, L. C. Gaughan, H. T. Gordon, Louis Lykken, and Izuru Yamamoto, Division of Entomology, University of California, Berkeley; Yoshihiko Nishizawa, Sumitomo Chemical Co., Osaka, Japan; Michael Elliott, Rothamsted Experimental Station, Harpenden, England; Leslie Crombie, University of South Wales and Monmouthshire, Cardiff, Wales.

LITERATURE CITED

Barthel, W. F., *Adv. Pest Control Res.* **4,** 33 (1961).

Berteau, P. E., Casida, J. E., Narahashi, T., *Science* **161,** 1151 (1968).

Berteau, P. E., Crombie, L., Casida, J. E., Pacific Conference on Chemistry and Spectroscopy, 3rd Western Regional Meeting, ACS, Anaheim, Calif., October 1967.

Bestian, H., Heyna, J., Bauer, A., Ehlers, G., Hirsekorn, B., Jacobs, T., Noll, W., Weibezahn, W., Römer, F., *Ann.* **566,** 210 (1950).

Buchman, E. R., Reims, A. O., Skei, T., Schlatter, M. J., *J. Am. Chem. Soc.* **64,** 2696 (1942).

Campbell, I. G. M., Harper, S. H., *J. Chem. Soc.*, **1945,** p. 283.
Closs, G. L., Brois, S. J., *J. Am. Chem. Soc.* **82,** 6068 (1960).
Crombie, L., University of South Wales and Monmouthshire, Cardiff, Wales, private communication, 1967.
Crombie, L., Crossley, J., Mitchard, D. A., *J. Chem. Soc.* **1963,** p. 4957.
Crombie, L., Edgar, A. J. B., Harper, S. H., Lowe, M. W., Thompson, D., *J. Chem. Soc.* **1950,** p. 3552.
Crombie, L., Houghton, R. P., Woods, D. K., *Tetrahedron Letters* **46,** 4553 (1967).
DePuy, C. H., Dappen, G. M., Eilers, K. L., Klein, R. A., *J. Org. Chem.* **29,** 2813 (1964).
Eastman, R. H., Freeman, S. K., *J. Am. Chem. Soc.* **77,** 6642 (1955).
Elliott, M., *Science J.*, pp. 3–8, March 1967.
Elliott, M., Farnham, A. W., Janes, N. F., Needham, P. H., Pearson, B. C., *Nature* **213,** 493 (1967).
Elliott, M., Janes, N. F., Jeffs, K. A., Needham, P. H., Sawicki, R. M., *Nature* **207,** 938 (1965).
Gould, E. S., "Mechanism and Structure in Organic Chemistry," pp. 623–7, Holt, Rinehart, and Winston, New York, 1959.
Inouye, Y., Ohno, M., *Bull. Agr. Chem. Soc. Japan* **20,** 25 (1956).
Julia, M., Julia, S., Bémont, B., Tchernoff, G., *Compt. Rend.* **247,** 242 (1959).
Julia, M., Rouault, A., *Bull. Soc. Chim. France* **1959** p. 1833.
Julia, M., Rouault, A., *Bull. Soc. Chim. France* **1960,** p. 979.
Kato, T., Ueda, K., Fujimoto, K., *Agr. Biol. Chem. Japan* **28,** 914 (1964).
Katsuda, S. (to Dainippon Jotyugiku Co., Ltd.), Japanese Patent **8948** (June 28, 1961).
Katsuda, Y., Chikamoto, T., Inouye, Y., *Bull. Agr. Chem. Soc. Japan* **22,** 185 (1958a).
Katsuda, Y., Chikamoto, T., Nagasawa, S., *Bull. Agr. Chem. Soc. Japan* **22,** 393 (1958b).
LaForge, F. B., Barthel, W. F., *J. Org. Chem.* **10,** 114 (1945).
LaForge, F. B., Green, N., Schechter, M. S., *J. Am. Chem. Soc.* **74,** 5392 (1952).
Matsui, M., Kitahara, T., *Agr. Biol. Chem. Japan* **31,** 1143 (1967).
Matsui, M., Kitamura, S., *Bull. Agr. Chem. Soc. Japan* **19,** 42 (1955).
Matsui, M., Yamashita, K., Miyano, M., Kitamura, S., Suzuki, Y., Hamuro, M., *Bull. Agr. Chem. Soc. Japan* **20,** 89 (1956).
Meshcheryakov, A. P., Dolgii, I. E., *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk* **1960,** p. 931.
Meshcheryakov A. P., Dolgii, I. E., *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk* **1961,** 496.
Novak, J., Farkas, J., Sorm, F. (Ceskoslovenska Akademie Ved.), German Patent **1,154,463** (September 19, 1963).
Schechter, M. S., Green, N., LaForge F. B., *J. Am. Chem. Soc.* **71,** 3165 (1949).
Smith, P. A. S., *Org. Reactions* **3,** 337 (1946).
Staudinger, H., Ruzicka, L., *Helv. Chim. Acta* **7,** 177 (1924).
Szmuszkovicz, J., in "Advances in Organic Chemistry. Methods and Results," Vol. **IV**, p. 25. Interscience, New York, 1963.
White, W. A., Weingarten, H., *J. Org. Chem.* **32,** 213 (1967).
Yamamoto, I., Casida, J. E., *J. Econ. Entomol.* **59,** 1542 (1966).

Received for review February 12, 1969. Accepted April 21, 1969. Paper was presented in part before the Division of Agricultural and Food Chemistry, 156th National Meeting, ACS, Atlantic City, N. J., September 1968. Study supported in part by grants from the U. S. Department of Agriculture (Grant No. 4) and the U. S. Public Health Service, National Institutes of Health (Grant No. ESGM 00049).