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Ovicidal Activity and Its Relation to Chemical Structure for the Two-Spotted Spider Mite (*Tetranychus urticae* Koch) in a New Class of Miticides Containing the Cyclopropyl Group

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Several series of cyclopropyl-containing compounds have been studied and some relationships between chemical structure and direct contact ovicidal activity were found by bioassay on the two-spotted spider mite, *Tetranychus urticae* Koch. Ovicidal activity appears to be the predominant response observed on mites. The data suggest that the ovicidal potency of the compounds is primarily related to the presence of the cyclopropyl group in the molecule, or to the ability of the compounds to be biosynthetically converted in vivo to some toxicant (or toxicants) which probably contains a cyclopropyl ring. General and specific requirements for activity in this class of compounds are presented.

Mites (Acarina) occur throughout the world and can be serious pests of plants, animals, and man (cf. Krantz, 1971). Of the phytophagous mites, members of the Tetranychidae are among the most destructive to agricultural crops. In our work, which was directed toward the chemical control of agriculturally important mites, we used the two-spotted spider mite (*Tetranychus urticae* Koch) and studied (Staal et al., 1975) a new class of cyclopropyl-containing miticides (Henrick and Staal, 1974, 1975a–e; Nelson and Show, 1975; Hurkova and Matolin, 1975) whose action, unlike many present commercial miticides (cf. Billings, 1974; Kenaga and End, 1974), is predominantly ovicidal. Certain members of this class of compounds appear promising for use as commercial miticides judging from the results of large scale field tests. Previously we have discussed the general biological properties of these compounds (Staal et al., 1975) and here we wish to describe some detailed relationships between structure and direct contact ovicidal activity selected from our extensive investigation of this class of compounds.

BIOASSAY PROCEDURE

Assay. All direct ovicidal assays described in this paper were carried out with *Tetranychus urticae* Koch. Our colony, a nonresistant strain, was obtained from Dr. W. W. Allen, University of California, Berkeley, and has been reared in our laboratories on lima bean plants for several years without exposure to chemicals. For the bioassay, compounds were dissolved in acetone. Since many of the compounds in this study were insoluble in water and were solids at room temperature we were unable to find a standard emulsifier base which gave consistent emulsification over a wide range of compounds. Rather than using different emulsifier compositions for different groups of compounds and thus introducing another element of uncertainty, the compounds were all dispensed in acetone solutions after we were satisfied that the differences in activity between a water formulation and an acetone dilution were insignificant in this type of assay. Acetone dipping does kill the plant tissue of the leaf disks, but this did not appear to effect the emergence of the eggs, provided that the leaf disks were allowed to dry out completely. With this technique we were able to ensure that only intrinsic differences in activity, not influenced by differences in dispersion and adjuvants, were studied. Separate solutions with concentrations ranging from 10^{-3} to 10^{-7} g/ml were prepared by successive tenfold dilutions of 1 mg/ml stock solution of compound. Generally, an initial assay series was run using three dilutions (10^{-3}, 10^{-4}, and 10^{-5} g/ml). In some cases where compounds exhibited high ovicidal activity, a more extensive series of fractional dilutions was subsequently applied in order to obtain more precise dose–response curves and LC_{50} values from probit analysis (cf. Finney, 1971).

Approximately 35 eggs, 0–24 h of age, were obtained on the upper surface of a 1.0-cm diameter lima bean primary leaf disk held on moist glass wool, from 24-h oviposition of six female mites. The females were then removed and the egg infested disks were dipped for 2 s into the acetone assay solutions (three disks were treated at each dose level). After dipping the disks were held face down on a paper towel for 1 s and then turned over until the acetone had evaporated. Each disk was then glued (Elmer's Glue-All) individually to a section of a 50-mm disposable plastic petri dish to prevent crumpling while drying out. The eggs were then incubated, after counting, at 25 °C and 68–72% relative humidity for 6 days. The number of unhatched eggs was then recorded and the mortality was calculated using Abbott's correction (Abbott, 1925) for any spontaneous failure to emerge observed in the controls (three disks).

LC_{50} Values. These were obtained by interpolation from lines derived from semilog plots of concentration (definition: 1% concentration = 1 g/100 ml) vs. percent response. The activity range of interest for the LC_{50} was

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Table I. Direct Contact Ovicidal Activity of Homologous Aliphatic Cyclopropyl Esters against *T. urticae*

Esters of cyclopropylmethyl alcohol $CH_3(CH_2)_nC(=O)OCH_2C_3H_5$[e]			Esters of cyclopropanecarboxylic acid $CH_3(CH_2)_mOC(=O)C_3H_5$			
No.	n	LC_{50}, % concn[a]	No.	m	LC_{50}, % concn	Mol wt
			17	0	0.86	100.1
			18	1	0.95	114.1
1	1	0.52	**19**	2	0.31	128.1
2	2	>0.10	**20**	3	0.24	142.1
3	3	>0.10	**21**	4	>0.10	156.2
4	4	>0.10	**22**	5	0.076	170.2
			23	6	0.048	184.2
5	6	0.022	**24**	7	0.038	198.3
			25	8	0.035	212.3
			26[c]	9	0.026	226.3
6	10	0.0043[b]	**27**[c]	11	0.014[b]	254.4
7	11	0.0028	**28**[c]	12	0.0039	268.4
8	12	0.0070[b]	**29**[c]	13	0.0052[b]	282.4
9	13	0.0051	**30**[c]	14	0.0017	296.5
10	14	0.0074[b]	**31**[c,d]	15	0.0021[b]	310.5
11	15	0.0041				324.6
12	16	0.0038	**32**[c]	17	0.0025[b]	338.6
13	17	0.0035				352.6
14	18	0.0041	**33**[c]	19	0.0035	366.6
15	20	0.028				394.7
			34	24	0.0050	436.7
			35	27	>0.10	478.8
16	28	>0.10				506.9

[a] Definition: 1% concentration = 1 g/100 ml; note that $LC_{50} \times 10^4$ gives the value (approximately) in parts per million. [b] Data refined by probit analysis (cf. Finney, 1971). [c] Henrick and Staal, 1975d. [d] Trademark Zardex miticide (cycloprate). [e] C_3H_5 = cyclopropyl.

≤0.001 to 0.1%. LC_{50} values for relatively inactive compounds (LC_{50} >0.1%) usually were not determined. In the majority of cases the LC_{50} values reported are from data of at least two separate assays. In ca. 20% of the reported cases the LC_{50} values were refined (indicated in the tables) by probit analyses (cf. Finney, 1971) with a HP 9830 computer program from more extensive bioassay data.

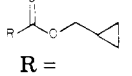
STRUCTURE–ACTIVITY RELATIONSHIPS

Cyclopropylmethyl Esters and Cyclopropanecarboxylates. Examples from a homologous series of esters derived from cyclopropylmethyl alcohol and saturated unbranched acyclic acids (compounds 1 to **16**) and also a series of esters prepared from cyclopropanecarboxylic acid and saturated unbranched acyclic alcohols (compounds **17** to **35**) are presented in Table I. Maximum inhibition of egg hatch is observed in these two series of simple acyclic esters when the chain length is ca. 13 to 20 carbon atoms. In these series, compounds of the same molecular weight sometimes exhibit similar ovicidal activity. The esters containing short chains (≤6 carbon atoms) exhibit low activity (cf. Newallis and Walker, 1966) and the activity also decreases when the chain is much greater than 20 atoms. This dependence of ovicidal activity upon molecular weight appears also in several other series of compounds (see Tables I, III, VII, IX, and Figure 1) of the present study.

It appears that a large variety of aliphatic and aromatic cyclopropylmethyl esters can exhibit high ovicidal activity (cf. Tables II and III) and that, generally, the structural features of the acid portions of these molecules are not critically related to their ovicidal activity other than for the requirement of a certain polarity and an optimum molecular weight range. In a few types of molecules, however, certain structural features are important. For example, the substitution of **10** with an α- or β-methyl substituent (**36** and cf. **37**) does not lower its activity but, whereas the conjugated esters **38** and **41** exhibit high activity, compounds with unsaturation further down the chain (e.g., **42–45**), generally, exhibit lower activity. Esters of various 3,7,11-trimethyl-2-dodecenoic acids (e.g., **40**; see also Staal et al., 1975) exhibit considerably lower activity than the simple unbranched acyclic esters. For monoesters of aromatic acids (Table II) no definite pattern of im-

Table II. Direct Contact Ovicidal Activity of Cyclopropylmethyl Esters against *T. urticae*

Monoesters

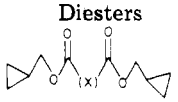


No.	R =	LC_{50}, % concn
10	$CH_3(CH_2)_{14}$	0.0074[a]
36	$CH_3(CH_2)_{13}CH(CH_3)$	0.0027
37	$CH_3(CH_2)_{11}CH(CH_3)CH_2$	0.0039
38	(E)-$CH_3(CH_2)_{12}CH=C(CH_3)$	0.0038
39	$CH_3(CH_2)_{11}C(CH_3)=CH$	0.013
40	(E)-$(CH_3)_2CH(CH_2)_3CH(CH_3)$-$(CH_2)_3C(CH_3)=CH$	0.060
41	$CH_3(CH_2)_{12}C\equiv C$	0.0029
42	(E)-$CH_3(CH_2)_7CH=CH(CH_2)_7$	0.034
43	(Z)-$CH_3(CH_2)_7CH=CH(CH_2)_7$	0.025
44	(Z)-$CH_3(CH_2)_{10}CH=CH(CH_2)_4$	0.026[a]
45	$CH_3(CH_2)_7C\equiv C(CH_2)_7$	0.028
46	$CH_3(CH_2)_{12}OCH_2$	0.0054
47	C_6H_5	0.031
48	p-$CH_3CH_2C_6H_4$	0.017
49	p-$(CH_3)_2CHC_6H_4$	0.030
50[b]	p-$CH_3(CH_2)_7C_6H_4$	0.0063
51[b]	p-$C_6H_5C_6H_4$	0.0088[a]
52	p-$CH_3OC_6H_4$	0.023
53	m-$CH_3OC_6H_4$	0.024
54	p-$CH_3(CH_2)_7OC_6H_4$	0.026
55	p-$C_6H_5OC_6H_4$	0.028
56	p-$C_6H_4CH_2OC_6H_4$	0.0048
57[b]	(E)-$C_6H_5CH=CH$	0.011
58[b]	(E)-p-$ClC_6H_4CH=CH$	0.0031[a]
59[b]	(E)-p-$CH_3C_6H_4CH=CH$	0.010[a]

[a] Data refined by probit analysis (Finney, 1971). [b] Henrick and Staal, 1975e.

Table III. Direct Contact Ovicidal Activity of Bis(cyclopropylmethyl) Esters against *T. urticae*

Diesters



No.	X =	LC_{50}, % concn
60[a]	1,4-Benzene	0.0038[b]
61[a]	1,3-Benzene	0.020
62[a]	1,2-Benzene	0.045
63[a]	1,4-(2,5-Dimethylbenzene)	0.012[b]
64[a]	1,4-(2,5-Dichlorobenzene)	0.0084[b]
65[a]	1,4-(2-Nitrobenzene)	0.0037[b]
66	$(CH_2)_0$	0.062
67[c]	$(CH_2)_1$	0.024
68[c]	$(CH_2)_2$	0.017
69[c]	$(CH_2)_3$	0.016
70[c]	$(CH_2)_4$	0.0092[b]
71[c]	$(CH_2)_5$	0.0075[b]
72[c]	$(CH_2)_6$	0.0055
73[c]	$(CH_2)_7$	0.0037[b]
74[c]	$(CH_2)_8$	0.0061[b]
75[c]	$(CH_2)_{10}$	0.0054
76[c]	$(CH_2)_{12}$	0.0066[b]
77[c]	(*E*)-CH=CH	0.023
78[c]	C≡C	0.082
79	*trans*-1,4-Cyclohexane	0.0023[b]
80	$CH_2(1,4\text{-}C_6H_4)CH_2$	0.0040[b]
81	2,6-Pyridine	0.0092
82	2,5-Pyridine	0.0031[b]
83	2,5-Thiophene	0.0029[b]
84	4,4′-Biphenyl	0.015

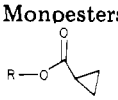
[a] Henrick and Staal, 1975a. [b] Data refined by probit analysis. [c] Henrick and Staal, 1975c.

portant structural features is discernible other than that compounds of higher molecular weight such as, for example, cyclopropylmethyl 4-octylbenzenecarboxylate (**50**), 4-biphenylcarboxylate (**51**), and *p*-chlorocinnamate (**58**), generally exhibit higher activity. In the diesters of benzenedicarboxylic acid (Table III), the terephthalic acid diester (**60**) is considerably more active than is the isophthalic acid diester (**61**) or the phthalic acid diester (**62**). Mononitro, dichloro, or dimethyl substitution in the aromatic ring of the terephthalate **60** does not remove the activity (**63**–**65**), but the 2,3,5,6-tetrachloro and tetramethyl analogues of **60** are much less active (LC_{50} >0.1%). Compounds in this series with more than two ester functions show low activity; the 1,2,4-benzenetricarboxylate is moderately active (LC_{50} = 0.035%) but the 1,3,5-benzenetricarboxylate, the 1,2,4,5-benzenetetracarboxylate, and the 1,2,3,4,5,6-benzenehexacarboxylate are relatively inactive (LC_{50} >0.1%). In the homologous series of bis(cyclopropylmethyl) alkanedicarboxylates **66** to **76** (Table III) the activity is similar from 1,4-butanedicarboxylate to 1,12-dodecanedicarboxylate. For more complex diesters, such as **79**–**84** (Table III), high ovicidal activity is obtained for esters such as the *trans*-1,4-cyclohexanedicarboxylate (**79**), and the 2,5-thiophenedicarboxylate (**83**), but no definite pattern of important structural features is discernible.

For the aliphatic cyclopropanecarboxylic acid monoesters (Table IV), branching at the α carbon of the alcohol chain (e.g., **85** and **87**) gives compounds of lower activity. The esters of terpenoid alcohols such as 3,7-dimethyloctanol (**89**) also generally show a low activity while the 2-methyl substituted ester **86** still has high activity. We investigated several esters derived from polar alcohols (e.g., **93**) and found, in general, low ovicidal activity for this group of compounds. Most of the phenyl (cf. Janiak, 1972) and benzyl monocyclopropanecarboxylates examined (e.g., **94**–**105**) show only moderate (LC_{50} ≥0.01%) ovicidal activity (Table IV) and the various ring substituents are generally unimportant (with the exception of 2,4-dinitro-6-alkylphenyl cyclopropanecarboxylates which appear to have a different action; cf. Janiak, 1972). Esters such as the *p*-chlorocinnamyl (**107**) and the 4-(*p*-methylphenyl)propyl (**108**), however, exhibit higher activity.

Table IV. Ovicidal Activity of Certain Cyclopropanecarboxylates against *T. urticae*

Monoesters

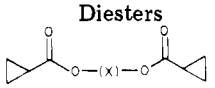


No.	R =	LC_{50}, % concn
31	$CH_3(CH_2)_{15}$	0.0021[a]
85[b]	$CH_3(CH_2)_{11}CH(CH_3)$	0.030
86[b]	$CH_3(CH_2)_{13}CH(CH_3)CH_2$	0.0035
87[b]	$CH_3(CH_2)_{12}C(CH_3)_2$	>0.10
88[b]	$CH_3(CH_2)_{11}CH(CH_3)CH(CH_3)CH_2$	0.015
89[b]	$(CH_3)_2CH(CH_2)_3CH(CH_3)(CH_2)_2$	>0.10
90[b]	$(Z)\text{-}CH_3(CH_2)_7CH{=}CH(CH_2)_8$	0.0070[a]
91	$CH_3(CH_2)_{12}O(CH_2)_2$	0.0036
92	$CH_3(CH_2)_{11}S(CH_2)_2$	0.0069
93	$CH_3(CH_2)_3O(CH_2)_2O(CH_2)_2O(CH_2)_2$	0.024
94	C_6H_5	0.063
95	$p\text{-}CH_3CH_2C_6H_4$	0.027
96	$p\text{-}CH_3(CH_2)_7C_6H_4$	0.019
97	$p\text{-}C_6H_5C_6H_4$	0.0087[a]
98	$p\text{-}CH_3OC_6H_4$	0.032
99	$p\text{-}HOC_6H_4$	>0.10
100	2,5-Dichlorophenyl	0.027
101	$C_6H_5CH_2$	0.050
102	$p\text{-}CH_3OC_6H_4CH_2$	0.010[a]
103	$m\text{-}CH_3OC_6H_4CH_2$	0.024
104	$p\text{-}ClC_6H_4CH_2$	0.012[a]
105	$p\text{-}C_6H_5C_6H_4CH_2$	0.0056
106	$(E)\text{-}C_6H_4CH{=}CHCH_2$	0.012
107	$(E)\text{-}p\text{-}ClC_6H_4CH{=}CHCH_2$	0.0041
108	$p\text{-}CH_3C_6H_4(CH_2)_3$	0.0051

[a] Data refined by probit analysis. [b] Henrick and Staal, 1975d.

Table V. Ovicidal Activity of Certain Bis(cyclopropanecarboxylates) against *T. urticae*[a]

Diesters



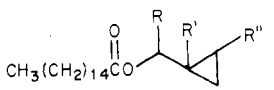
No.	X =	LC_{50}, % concn
109	$CH_2C{\equiv}CCH_2$	0.015
110	$CH_2C{\equiv}CC{\equiv}CCH_2$	0.0018[b]
111	$(CH_2)_{10}$	0.0025[b]
112	$(CH_2)_{12}$	0.0060
113	*trans*-1,4-Cyclohexylene	0.0077[b]
114	$CH_2\text{-}(trans\text{-}1,4\text{-}C_6H_{10})CH_2$	0.0031
115	$CH_2\text{-}(cis\text{-}1,4\text{-}C_6H_{10})CH_2$	0.0034
116	$1,4\text{-}C_6H_4$	0.0030[b]
117	$CH_2\text{-}(1,4\text{-}C_6H_4)CH_2$	0.0040[b]
118	4,4′-Biphenyl	0.0090

[a] Henrick and Staal, 1975d. [b] Data refined by probit analysis.

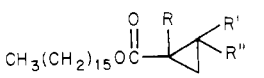
In the various bis(cyclopropanecarboxylates) which we investigated, some of which are shown in Table V, moderate to good activity is generally observed although diesters from naphthalenic and simple tertiary diols generally exhibit low activity. The steric arrangement of the carbon atoms in the six-membered ring systems of the alcohol portion of the esters is apparently not strongly related to activity since the diesters of *trans*-1,4-cyclohexanediol and 1,4-benzenedimethanol (**113** and **117**, respectively) have high activity as do the diesters prepared from both *trans*- and *cis*-1,4-cyclohexanedimethanol (**114** and **115**, respectively).

Thus it appears, from the above consideration of ovicidal activity data, that the acid portions of the cyclopropylmethyl esters (Tables I, II, and III) and the alcohol portions of the cyclopropanecarboxylates (Tables I, IV, and V) serve an important function as carriers for the toxicant which is either cyclopropylmethanol, cyclopropanecarboxylic acid, or some compound or compounds biosynthetically derived from these [cyclopropylmethanol, cyclopropanecarboxylic acid, and lower esters (e.g. **1–4**, **17–21**, Table I) are relatively inactive as ovicides (LC_{50} >0.1%)].

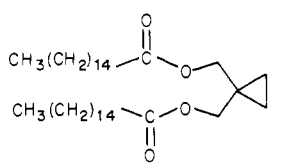
Compounds Related to Cyclopropylmethyl Esters and Cyclopropanecarboxylates. That the cyclopropylmethanol and cyclopropanecarboxylic acid groups are the uniquely active portions of the previously discussed compounds is further suggested by the low ovicidal activity of esters when the cyclopropane ring is further substituted. For example, **119b** shows an LC_{50} of 0.015% and **119a**, **119c**, and **120a–c** show LC_{50} >0.1% (cf. **10** and **31**, Table I). The diesters **121** and **122**, with two ester groups attached to the one ring, are inactive although this may be due to their high molecular weight (578); cf. Table I. Chrysanthemyl hexadecanoate and the esters **123** and **124** are also inactive (LC_{50} >0.1%) as mite ovicides.



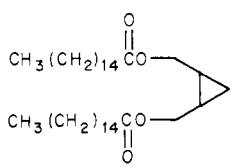
119a, R = CH_3; R′ = R″ = H
b, R = H; R′ = CH_3; R″ = H
c, R = R′ = H; R″ = CH_3



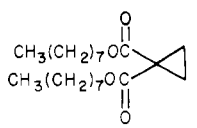
120a, R = CH_3; R′ = R″ = H
b, R = H; R′ = CH_3; R″ = H
c, R = H; R′ = R″ = CH_3

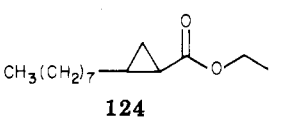


121



122





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Furthermore, a wide variety of related esters prepared from alcohols similar to cyclopropylmethanol or from acids similar to cyclopropanecarboxylic acid were found to be inactive (LD_{50} >0.1%) as mite ovicides. Thus, in cyclopropylmethyl dodecanote (**6**) or in the hexadecanoate (**10**), replacement of the cyclopropylmethyl group by isopropyl, isobutyl, 3-methylbutyl, 2-butenyl, 3-butenyl, cyclopropyl (**158**), cyclobutyl, cyclobutylmethyl, or cyclopentylmethyl gives inactive esters (LC_{50} >0.1%). In the terephthalate **60** (Table III), replacement of both of the cyclopropylmethyl groups by isobutyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-methyl-2-propenyl, 3-methyl-2-butenyl, or 2,3-epoxypropyl groups gives inactive diesters. Similarly, in hexadecyl cyclopropanecarboxylate (**31**), replacement of the cyclopropanecarboxylate group by 2-methyl-2-propenoate, 4-pentenoate, 3-methyl-2-butenoate, 4-methylpentanoate, cyclobutanecarboxylate, or cyclopentanecarboxylate gives inactive compounds. Also in the diester **117** (Table V) from 1,4-benzenedimethanol, replacing both cyclopropanecarboxylates by 2-methylpropanoate, 2-propenoate, 2-butenoate, 2-methyl-2-propenoate, or 3-methyl-2-butenoate groups gives inactive diesters (LC_{50} values >0.1%).

The ovicidal activity of the esters **10** and **31** (cf. Tables I and VI) is probably not related to their *shape* since the compounds **125–128** (Table VI), which are structurally similar to cyclopropylmethyl hexadecanoate (**10**), are inactive and the ketone **129**, which is structurally similar to hexadecyl cyclopropanecarboxylate (**31**), is inactive. The ether **138**, the sulfide **139**, the amine **140**, the amides **131** and **137**, the carbamate **135**, the *S,S*-dialkyl dithiocarbonate **133**, and the *S*-cyclopropylmethyl thioate **130** are also inactive. Only the carbonates (e.g., **132**) show high ovicidal activity with the sulfite **134** and the *S*-alkyl cyclopropanecarbothioate **136** showing moderate activity (Table VI). Thus, the ovicidal activity appears to depend on the ability of the compounds to readily deliver cyclopropanecarboxylic acid or cyclopropylmethanol (or some compound derived from these) from an ester (or carbonate) group.

Table VI. Ovicidal Activity of Some Cyclopropyl Compounds Related to Esters, against *T. urticae*

No.	Compd (C_3H_5 = cyclopropyl)	LC_{50}, % concn
10	$CH_3(CH_2)_{14}C(O)OCH_2C_3H_5$	0.0074[a]
31	$CH_3(CH_2)_{15}OC(O)C_3H_5$	0.0021[a]
125	$CH_3(CH_2)_{14}CH(OH)CH_2CH_2C_3H_5$	>0.10
126	$CH_3(CH_2)_{14}C(O)CH_2CH_2C_3H_5$	>0.10
127	$CH_3(CH_2)_{14}C(=CH_2)CH_2CH_2C_3H_5$	>0.10
128	$CH_3(CH_2)_{14}CH(CH_3)CH_2CH_2C_3H_5$	>0.10
129	$CH_3(CH_2)_{16}C(O)C_3H_5$	>0.10
130	$CH_3(CH_2)_{14}C(O)SCH_2C_3H_5$	>0.10
131	$CH_3(CH_2)_{14}C(O)NHCH_2C_3H_5$	>0.10
132[b]	$CH_3(CH_2)_{11}OC(O)OCH_2C_3H_5$	0.0063
133	$CH_3(CH_2)_{15}SC(O)SCH_2C_3H_5$	>0.10
134	$CH_3(CH_2)_{11}OS(O)OCH_2C_3H_5$	0.040
135	$CH_3(CH_2)_{14}NHC(O)OCH_2C_3H_5$	>0.10
136[c]	$CH_3(CH_2)_{15}SC(O)C_3H_5$	0.013
137	$CH_3(CH_2)_{17}NHC(O)C_3H_5$	>0.10
138	$CH_3(CH_2)_{11}OCH_2C_3H_5$	>0.10
139	$CH_3(CH_2)_{11}SCH_2C_3H_5$	>0.10
140	$CH_3(CH_2)_{11}NHCH_2C_3H_5$	>0.10

[a] Data refined by probit analysis. [b] Henrick and Staal, 1975b. [c] Henrick and Staal, 1974.

Table VII. Ovicidal Activity of Saturated ω-Cyclopropylalkyl Esters against *T. urticae*

	$CH_3(CH_2)_mOC(=O)(CH_2)_nC_3H_5$[b]		
No.	*m*	*n*	LC_{50}, % concn
151	0	16	>0.10
152	3	16	>0.10
153	9	10	0.014
154	0	10	0.0037
155	0	8	0.0049
156	0	6	0.017
157	0	4	0.035
	$CH_3(CH_2)_{m'}C(=O)O(CH_2)_{n'}C_3H_5$[b]		
	m′	*n′*	LC_{50}, % concn
158	14	0	>0.10
10	14	1	0.0074[a]
159	14	2	>0.10
160	14	3	0.0047
161	12	4	0.037
162	10	5	0.0040
163	8	7	0.0020
164	6	9	0.0031
165	0	17	0.051

[a] Data refined by probit analysis. [b] C_3H_5 = cyclopropyl.

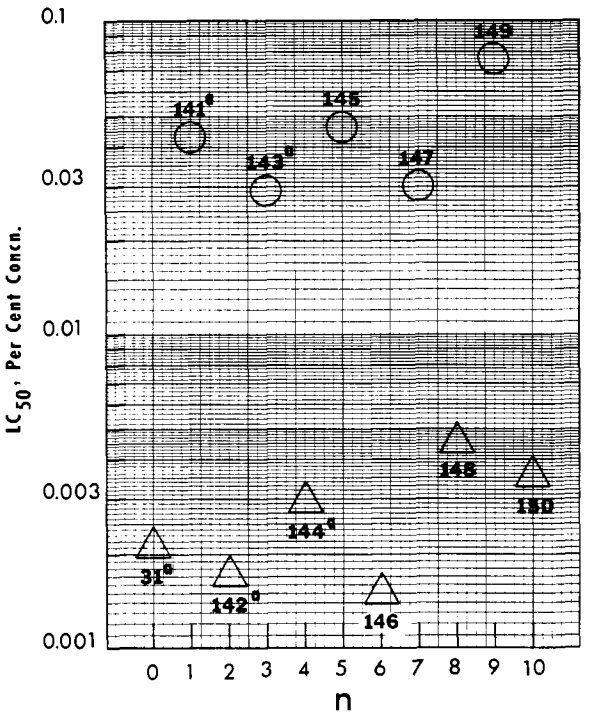
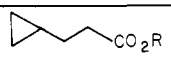
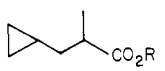
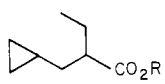
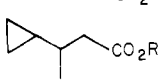
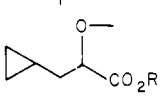
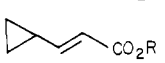
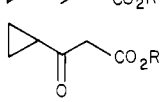
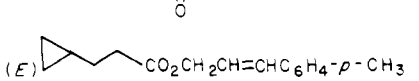


Figure 1. LC_{50} values for ovicidal activity in alkyl ω-cyclopropylalkanoates as a function of the position of the carbonyl group [$C_3H_5(CH_2)_nC(O)O(CH_2)_mCH_3$; $(n + m) = 15$]; C_3H_5 = cyclopropyl; values followed by a superscript a are from Henrick and Staal, 1975d.

ω-Cyclopropylalkyl Compounds. One of the more interesting results in this work comes from a study of saturated ω-cyclopropylalkanoates (Figure 1 and Table VII). When one examines the series of esters (of constant molecular weight) **31** and **141** to **150** (Figure 1) it is found that high ovicidal activity is exhibited for all esters containing an even number of methylenes between the ring and the carboxylate group (i.e., n = even, Figure 1). The corresponding esters prepared from ω-cyclopropylalkanoic acids with n = odd (Figure 1) consistently show only one-tenth of this activity. This regular even–odd activity pattern suggests that the esters when n = even are hydrolyzed by the mite eggs to their corresponding acids which are in turn either degraded by the well-established (cf. Wakil, 1970; Weete, 1974) β-oxidation sequence of fatty acid metabolism, or are elongated biosynthetically by the mite eggs, to a toxic material or materials (cf. Oshima and Ariga, 1975). The acids for the esters in Figure 1, where n = odd are presumably degraded (or built up) less efficiently to the same toxicant or toxicants, or the metabolic products in these cases are less toxic. In this context, Dear and Pattison (1963) previously observed that in a series of ω-fluorocarboxylic acids, only those acids with an even number of carbon atoms were toxic to mice, presumably due to their degradation (by β oxidation) to fluoroacetic acid (toxicant). Activity in this group of alkyl ω-cyclopropylalkanoates (cf. Figure 1 and Table VII) is governed by the actual chain length of the acid portion of the ester, in addition to the even–odd factor, since the esters **151** and **152** which are derived from the *odd-carbon acid* 17-cyclopropylheptadecanoic acid are inactive (LC_{50} >0.1%). Activity also depends upon the total chain length of the esters (cf. **150** with **153**, **146** with **156**, and **144** with **157**).

These ω-esters were prepared, in general, by the reaction of lithium dicyclopropylcuprate with the appropriate ω-bromoester. For example, 0.88 mol of decyl 7-bromoheptanoate was added, dropwise at −25 °C, to a 0.5 M solution of lithium dicyclopropylcuprate in 1:1 ether–tetrahydrofuran. After 2.5 h decyl 7-cyclopropylheptanoate was isolated in 85% yield.

Table VIII. Ovicidal Activity of 3-Cyclopropylpropanoate Derivatives against *T. urticae*

No.	Compound [R = $(CH_2)_{13}CH_3$]	LC_{50}, % concn
142[a]		0.0016[b]
166		0.0013[b]
167		>0.10
168		0.0042
169		>0.10
170[a]		0.0051[b]
171		0.030
172[a]		0.0046[b]

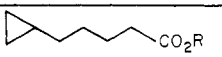
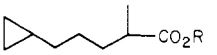
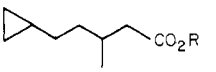
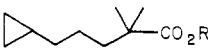
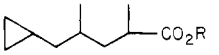
[a] Henrick and Staal, 1975d. [b] Data refined by probit analysis.

In the ω-cyclopropylalkyl alkanoates **10** and **158–165** (Table VII) a similar pattern of activity vs. the number of methylenes between the cyclopropyl group and the oxygen atom is observed. When n' is 0, 2, or 4 the esters have low activity (LC_{50} >0.1%) and when n' is odd the esters show much higher activity. The actual chain length of the alcohol portion of the molecule also appears to be important since **165** exhibits only moderate activity compared to **10**, **160**, and **162–164**.

The activities of the alkyl and aryl 3-cyclopropylpropanoates (e.g., **142** and **172**, Table VIII) show similar patterns to those previously described for the cyclopropanecarboxylates, with the activities often being higher for the 3-cyclopropylpropanoate analogues. The alcohol portion of the ester (or diester) apparently functions as a carrier for the toxicant (in this case 3-cyclopropylpropanoic acid or its metabolite). The 2-methyl substituted analogue **166** and the 3-methyl analogue **168** retain high activity but the corresponding 2-ethyl (**167**) and 2-methoxy (**169**) analogues show low activity. The 3-cyclopropyl-2-propenoic acid analogue **170** also shows high activity whereas the β-keto ester **171** has much lower activity. If a β-oxidation process (cf. Wakil, 1970; Weete, 1974) operates for metabolism of **142**, **170**, and **171**, then the coenzyme A thioesters derived from the acid portions of **170** and **171** could be intermediates in the β-oxidation degradation of **142** to cyclopropanecarboxylic acid.

Several of the ω-cyclopropylalkanoic *acids* also show high ovicidal activity. These acids exhibit the same overall activity pattern as their esters (cf. Figure 1) although the high activity range is quite narrow [only the heptanoic (**178**), nonanoic (**180**), and undecanoic (**182**) acids exhibit high activity] and may possibly be related to their ability to penetrate mite eggs. In some cases both the acids and their corresponding esters exhibit nearly identical activities [cf. **178** and **146**, **180** and **148**, **182** and **150**, **179** and its n-decyl ester]. For the ω-cyclopropylalkanols (Table IX)

Table IX. Ovicidal Activity of Some Cyclopropylalkyl Esters, Acids, and Alcohols against *T. urticae*

No.	Compound [R = $(CH_2)_{11}CH_3$]	LC_{50}, % concn
144[a]		0.0029
173		0.0035
174		0.0060
175		>0.10
176		0.035
177	$HO_2C(CH_2)_4C_3H_5$[b]	0.043
178	$HO_2C(CH_2)_6C_3H_5$	0.0056
179	$HO_2CCH(CH_3)(CH_2)_5C_3H_5$	0.031
180	$HO_2C(CH_2)_8C_3H_5$	0.0034
181	$HO_2C(CH_2)_9C_3H_5$	0.090
182	$HO_2C(CH_2)_{10}C_3H_5$	0.0038
183	$HO_2C(CH_2)_{12}C_3H_5$	0.028
184	$HO_2C(CH_2)_{14}C_3H_5$	>0.10
185	$HO_2C(CH_2)_{16}C_3H_5$	>0.10
186	$HO(CH_2)_5C_3H_5$	>0.10
187	$HO(CH_2)_7C_3H_5$	0.034
188	$HO(CH_2)_9C_3H_5$	0.012
189	$HO(CH_2)_{11}C_3H_5$	0.0086
190	$HO(CH_2)_{15}C_3H_5$	0.021
191	$HO(CH_2)_{17}C_3H_5$	>0.10

[a] Henrick and Staal, 1975d. [b] C_3H_5 = cyclopropyl.

the range of ovicidal activity is much less than that of the other series (esters and acids) of the present study although 11-cyclopropylundecanol (**189**) exhibits high activity.

In dodecyl 5-cyclopropylpentanoate (**144**), substituting the 2 position or the 3 position of the carboxylate group with a methyl group (**173** and **174**, respectively, Table IX) does not affect the ovicidal activity (however, substituting the 2 position of the 7-cyclopropylheptanoate **146** (Figure 1) with a methyl group does considerably lower the activity). The 2,4-dimethyl analogue **176** has much lower activity and the 2,2-dimethyl analogue **175** is inactive (LC_{50} > 0.1%). Presumably in the last compound the 2,2-disubstitution completely prevents the degradation (to cyclopropanecarboxylic acid or a toxic metabolite) by β oxidation and hence the compound is inactive (the 2,2-disubstitution might not, however, affect chain extension). The 3-methyl analogues **168** and **174** are almost as active as the corresponding unsubstituted analogues, **142** and **144**, respectively. Such 3-methyl substitution would be expected to hinder degradation by β-oxidation. If **168** and **174** are being degraded to cyclopropanecarboxylic acid by the mite egg, processes other than β oxidation may be involved (cf. Wakil, 1970; Weete, 1974).

CONCLUSION

This new class of cyclopropyl-containing miticides exhibits predominantly ovicidal activity against the two-spotted spider mite. Activity clearly depends upon the presence of the cyclopropane ring and the probable metabolism, in vivo, of the compounds to some toxic product or products. Activity is obtained against eggs in all stages of embryonic development following either direct application to the eggs or deposition of the eggs upon previously sprayed leaves (Staal et al., 1975). Several of these compounds exhibit ovicidal activities which match or surpass those of most currently available commercial mite ovi-larvicides. For example, by the same ovicidal bioassay technique as used in this paper, some common miticides gave the following LC_{50} values: Kelthane, 0.039%; ovex, 0.067%; Tedion, 0.0027%; Galecron, 0.0018%; Plictran, 0.0086%; and Omite, 0.17%. In general, our compounds prevent the hatching of eggs. Associated with this are morphogenetic abnormalities observable during the late stages of embryonic development (Staal et al., 1975) but the biochemical mechanisms of action of these compounds are unknown. Studies have been carried out by various workers on the metabolism and toxicology of cyclopropanecarboxylic acid, especially with respect to its inhibition of gluconeogenesis and fatty acid metabolism in vertebrate animals. The guinea pig and monkey are sensitive to the hypoglycemic action of cyclopropanecarboxylic acid whereas the rabbit, rat, mouse, and man are not very sensitive (Stewart, 1962; Duncombe and Rising, 1972b). However, this effect may not be relevant to the ovicidal action on mites since acids such as 4-pentenoic acid have hypoglycemic activity (Senior et al., 1968; Senior and Sherratt, 1968, 1969) but esters such as dodecyl 4-pentenoate (discussed above) have no mite ovicidal activity (LC_{50} >0.1%). The toxicity of cyclopropanecarboxylic acid to mice is apparently due to biochemical properties other than its hypoglycemic activity (Senior and Sherratt, 1969). Duncombe and Rising (1968) have reported that radioactivity from [^{14}C]cyclopropanecarboxylic acid is incorporated into fatty acids by various rat tissues in vitro, apparently via the addition of C_2 units, to give fatty acids postulated to contain a cyclopropyl ring in the ω position. Rats apparently cannot metabolize the cyclopropyl ring in acids such as *cis*-9,-10-methanooctadecanoic acid (Chung, 1966; Wood and Reiser, 1965). Apparently the fungus *Fusarium oxysporum* can metabolize cyclopropanecarboxylic acid to γ-hydroxybutyric acid (Schiller and Chung, 1970; Guilbert and Chung, 1974) via the carnitine ester (see also Tipton and Al-Shathir, 1974). In view of the recent work by Guilbert and Chung (1974) on the critical role of 3-cyclopropylcarbonyloxycarnitine in *F. oxysporum* and the work of Duncombe and Rising (1972a) on the effects of cyclopropanecarboxylic acid and its carnitine ester on mitochondrial processes in the rat liver, it is possible that the mite ovicidal effect is related to the disruption of fatty acid metabolism in the mite eggs. Thus, the mode of action of this new group of selective miticides is probably related to the ability to deliver cyclopropanecarboxylic acid or cyclopropylmethanol (or some compound derived metabolically from these), resulting in the blocking of some critical process in the embryonic development of the eggs. Treated eggs fail to hatch although embryonic development is visually normal throughout most of the period of egg development (Staal et al., 1975). Penetration of the chorion of the mite eggs and chemical transport within the egg is probably of critical importance for these miticides, since the activity appears to be dependent upon the physical properties and the molecular weights for otherwise similar compounds in a given series. It should be noted that a distinct larvicidal activity has been observed also for the most active compounds described in this paper (Staal et al., 1975), but since the ovicidal activity is approximately ten times more pronounced, only the latter has been investigated in detail. There is little doubt that the additional activity on motile stages and the pronounced selectivity of these compounds for target pest species have contributed greatly to the success obtained with these compounds in field applications.

Zoecon Corporation is presently developing hexadecyl cyclopropanecarboxylate (**31**; ZR 856; Zardex miticide; cycloprate) for commercial use. It has been widely field

tested and exhibits excellent activity against both overwintering eggs and all stages of actively developing eggs of phytophagous mites and also exhibits some activity against motile forms. The compound exhibits little or no activity on eggs or motile stages of insects, and field tests have thus far shown no significant adverse effects on population levels of beneficial predaceous mites (Palmer and Koslucher, 1975). Preliminary toxicology suggests that ZR 856 has low acute toxicity to mammals (the acute oral toxicity of technical ZR 856 for rats was found to be 12 200 mg/kg).

EXPERIMENTAL SECTION

All substances containing asymmetric carbon atoms described herein are racemic compounds; the prefix (±) is omitted. All compounds which could not be purified by simple short-path distillation or recrystallization were purified by preparative thin-layer chromatography on 1 m × 20 cm plates coated with 1.3 mm or (Merck (Darmstadt) silica gel PF-254. Spinning-band distillations were performed using a 100-cm helical Teflon spinning-band distillation column (Normag, W. Germany). Infrared spectra were recorded on a Unicam SP 200 G spectrophotometer. NMR spectra were recorded on a Varian T-60 spectrometer using tetramethylsilane as an internal standard. Mass spectra were measured on a Varian MAT CH-7 spectrometer. Gas–liquid chromatographic analyses were performed on Model 402 Hewlett-Packard instruments equipped with hydrogen flame ionization detectors. Elemental analyses were obtained by A. Bernhart, W. Germany. Solvents were dried over activated 4A molecular sieves (3A for methanol), and most reactions were carried out under an argon or a nitrogen atmosphere.

All compounds mentioned in Tables I–IX gave satisfactory elemental analyses (within ±0.4% of the theoretical values) *and were characterized also by their NMR, ir, and mass spectra.* Selected examples of experimental details and physical constants are given in the microfilm edition of this volume of the journal (see Supplementary Material paragraph).

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Supplementary Material Available: Synthetic experimental details and physical constants for selected compounds from Tables I–IX and Figure 1 (40 pages). Ordering information is given on any current masthead page.

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