New Insecticidal Cyclopropanecarboxylic Esters. Part V. 4-Aryl-2-buten-1-yl Chrysanthemates and Related Esters (2)* Kaoru SOTA[*1], Takehiro AMANO, Akifumi HAYASHI, Ichiro TANAKA, and Katsura MUNAKATA[*2] ([*1]Research Laboratory, Taisho Pharmaceutical Co., Ltd., Toshima, Tokyo and [*2]Laboratory of Pesticide Chemistry, Faculty of Agriculture, Nagoya University, Chikusa, Nagoya) Received April 25, 1973. *Botyu-Kagaku*, 38, 191, 1973.

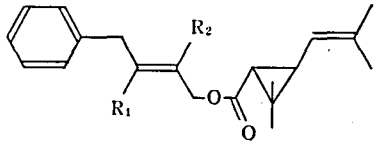
26. 新殺虫性シクロプロパンカルボン酸エステル（第5報）4-アリル-2-ブテン-1-イル第一菊酸エステル類および関連エステル (2)

曽田 馨[*1], 天野武宏, 林 晃史, 田中一郎, 宗像桂[*2] ([*1]大正製薬株式会社研究部. 東京都豊島区 [*2]名古屋大学農学部農薬化学教室, 名古屋市千種区) 48. 4. 25 受理.

4-Aryl-halosubstituted-*trans*-2-buten-1-yl *dl-cis, trans*-第一菊酸エステルおよび 2,2,3,3-テトラメチルシクロプロパンカルボン酸エステル類を合成し，家バエに対する殺虫作用を検討した．両系列において，ハロゲンの導入，ことに，3位への導入により殺虫作用の大巾な増加が認められた．これらの中で，4-phenyl-3-chloro-*trans*-2-buten-1-yl *dl-cis, trans*- 第一菊酸エステル (Va) が最も有効で，アレスリンの12倍の殺虫力を示した．Va に関連する異性体5種—*dl-trans*-Va, *dl-cis*-Va, *d-trans*-Va, 4-phenyl-2-chloro-*trans*-2-buten-1-yl *dl-trans*- 酸エステル，および，その *dl-cis*-酸エステルーを合成し，殺虫作用と異性の関係を検討した．

また，ベンゼン環上の置換は，置換位置および置換基の種類にかかわらず，殺虫力を低下させた．

We have recently reported the synthesis of a number of chrysanthemic acid esters of 4-aryl-*trans*-2-buten-1-ols and their insecticidal activities against houseflies.[1] Some of the esters were more active than allethrin in activity by topical application method and four of them (I, II, III, and IV) were shown to possess a great potency enough to carry out further modification of this 2-buten-1-yl series.



I, $R_1=R_2=H$ Va, $R_1=Cl$, $R_2=H$
II, $R_1=CH_3$, $R_2=H$ VIa, $R_1=H$, $R_2=Cl$
III, $R_1=H$, $R_2=CH_3$ VIIa, $R_1=Br$, $R_2=H$
IV, $R_1=R_2=CH_3$ VIIIa, $R_1=R_2=Cl$

Chart 1

In this paper, we would like to report the synthesis and the insecticidal activities of the chrysanthemic acid esters (Va, VIa, VIIa, and VIIIa) of 4-phenyl-halo-*trans*-2-buten-1-ols and the related esters (series of V～XIII).

* A part of this paper was presented at Annual Meeting of Agricultural Chemical Society of Japan, Fukuoka, April 4, 1970.

The chrysanthemic or 2,2,3,3-tetramethylcyclopropanecarboxylic acid esters of 4-aryl-2 and /or 3-substituted-*trans*-2-buten-1-ols were, in general, prepared by the esterification of the corresponding 4-aryl-1-chloro-2 and/or 3-substituted-2-butenes (XIV XVI, XVIII, and XIX) with potassium chrysanthemate or 2,2,3,3-tetramethylcyclopropanecarboxylate. The synthesis of 4-aryl-1-chloro-2 and/or 3-substituted-2-butenes was readily carried out by the Meerwein arylation reaction[2] of the appropriately substituted-1,3-butadiene with aryldiazonium chloride as shown in Chart 2. However, in the case of the reaction of 2-chloro- or 2-bromo-butadiene, 4-aryl-1-chloro-2-halo-2-butene (XV or XVII), 4,1-adduct as a minor product, was confirmed by the NMR and GLC analysis. For example, in the reaction of benzenediazonium chloride with 2-chloro-1, 3-butadiene, the ratio of 4,1-adduct to 1,4-adduct in the reaction product was about 1 : 3. When the mixture was esterified with potassium salt of the appropriate cyclopropanecarboxylic acid, only a small amount of the ester from 4,1-adduct was formed together with the ester from 1,4-adduct, and the purity of the latter was above 90%. Thus, there is a great difference in the esterification rate between 1,4- and 4,1-adducts. The Meerwein arylation product of 2-methoxy-

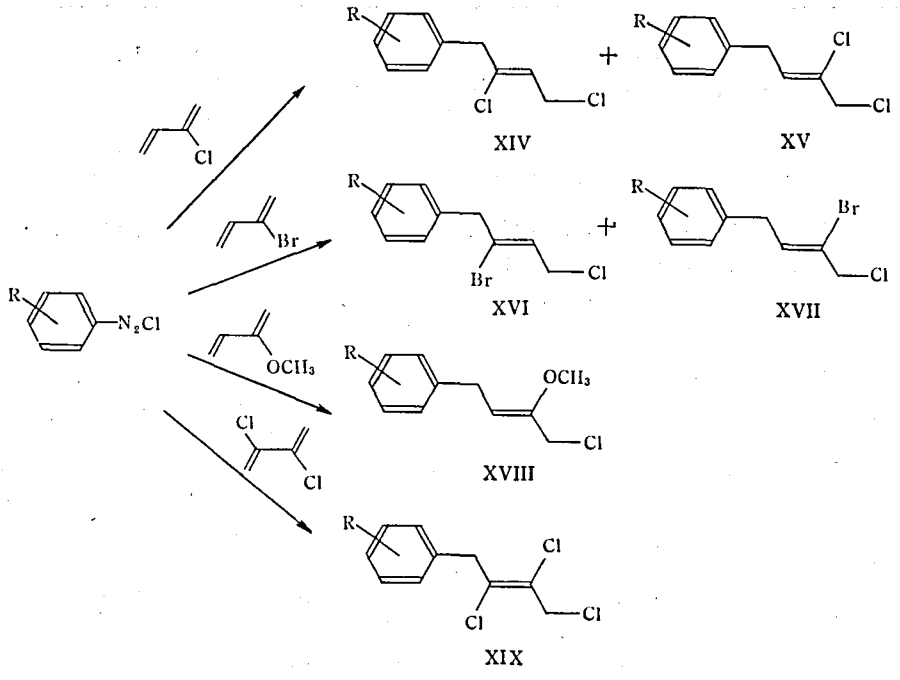


Chart 2

1,3-butadiene was not 4-aryl-1-chloro-3-methoxy-2-butene, 1,4-adduct, but 4-aryl-1-chloro-2-methoxy-2-butene, 4,1-adduct.

In order to clarify the isomerism-activity relationship of the esters, five isomeric esters consisting of the geometrical isomers of chrysanthemic acid and the positional isomers of the 4-phenyl-2 or 3-chloro-2-buten-1-ol were prepared. The isomeric alcohols, 4-phenyl-3-chloro- and 4-phenyl-2-chloro-*trans*-2-buten-1-ols were prepared by the 4-nitrobenzoylation of the mixture of 4-phenyl-1, 2-dichloro- and 4-phenyl-1,3-dichloro-2-butenes (XIV and XV, R=H) followed by repeated recrystallization. The esters of *dl-trans*-chrysanthemic acid were obtained by the acid chloride method. Since the *cis*-chrysanthemoyl chloride might be isomerized to the *trans* isomer under the condition of the acid chloride method[3], the esters of *dl-cis*-chrysanthemic acid were prepared by treatment of *dl-cis*-chrysanthemic acid with an appropriate alcohol in the presence of N, N′-dicyclohexylcarbodiimide.

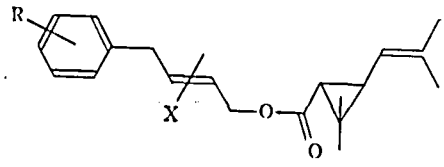
The insecticidal activities by topical application method[4] and spray method[5] were given in Tables 5, 6, 7, 8, and 9.

Esters having unsubstituted phenyl group.

The replacement of the methyl group of the 2-buten-1-yl moiety in the chrysanthemates II, III, and IV chlorine atom exerted, in general, a great influence on insect toxicity; that is, the chloro-substituted chrysanthemates Va, VIa, and VIIIa were, respectively, about 5, 1, and 3 times as active as the corresponding methyl-substituted esters II, III, and IV. Of these chloro-substituted chrysanthemates, the 3-chloro-substituted compound (Va) was the most active and it was shown to be about 12 times as active as allethrin in insect toxicity. This compound (Va) is proposed to be designated as "butethrin"[6].

The 3-bromo- (VIIa) and 2,3-dichloro- (VIIIa) substituted chrysanthemates were slightly less active than the 3-chloro-substituted ester (Va), but introduction of a chlorine atom at the 2-position of the 2-buten-1-yl moiety of the chrysanthemate was found to be not so effective. A chlorine substitution on the 3-position of the 2-buten-1-yl moiety of esters was found to be more effective than that on the 2-position. The structure-activity relationship of these chloro-substituted chrysanthemate series (Va, VIa, and

Table 1. 4-Aryl-monosubstituted-*trans*-2-buten-1-yl *dl-cis, trans*-Chrysanthemates



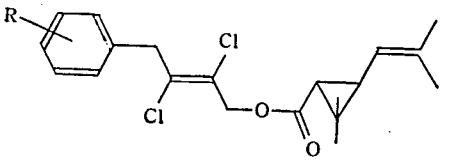
No.	R	X	bp°C(mmHg)	n_D^{20}	Formula	*Anal.* (%) Calcd. C	Calcd. H	Found C	Found H
Va	H[a)]	3-Cl	142~5 (0.12)	1.5300	$C_{20}H_{25}ClO_2$	72.16	7.57	71.95	7.31
Vb	2-CH_3	3-Cl	155~7 (0.07)	1.5336	$C_{21}H_{27}ClO_2$	72.71	7.85	72.84	7.88
Vc	3-CH_3	3-Cl	150~1 (0.08)	1.5308	$C_{21}H_{27}ClO_2$	72.71	7.85	72.48	7.86
Vd	4-CH_3	3-Cl	150~1 (0.15)	1.5291	$C_{21}H_{27}ClO_2$	72.71	7.85	72.65	7.69
Ve	2-Cl	3-Cl	155~6 (0.08)	1.5405	$C_{20}H_{24}Cl_2O_2$	65.40	6.59	65.33	6.42
Vf	3-Cl	3-Cl	167~8 (0.16)	1.5372	$C_{20}H_{24}Cl_2O_2$	65.40	6.59	65.27	6.51
Vg	4-Cl	3-Cl	165~6 (0.15)	1.5376	$C_{20}H_{24}Cl_2O_2$	65.40	6.59	65.46	6.55
Vh	2-F	3-Cl	152~4 (0.20)	1.5223	$C_{20}H_{24}ClFO_2$	68.46	6.89	68.63	6.84
Vi	3-F	3-Cl	160~2 (0.35)	1.5197	$C_{20}H_{24}ClFO_2$	68.46	6.89	68.57	6.72
Vj	4-F	3-Cl	154 (0.28)	1.5181	$C_{20}H_{24}ClFO_2$	68.46	6.89	68.42	6.83
Vk	2-CH_3O	3-Cl	157~8 (0.07)	1.5338	$C_{21}H_{27}ClO_3$	69.50	7.50	69.37	7.49
Vl	3-CH_3O	3-Cl	162~5 (0.06)	1.5345	$C_{21}H_{27}ClO_3$	69.50	7.50	69.56	7.45
Vm	4-CH_3O	3-Cl	167~9 (0.20)	1.5348	$C_{21}H_{27}ClO_3$	69.50	7.50	69.41	7.58
Vn	4-C_2H_5	3-Cl	158~62 (0.08)	1.5276	$C_{22}H_{29}ClO_2$	73.21	8.10	73.19	8.03
Vo	4-NO_2	3-Cl	203 (0.30)	1.5493	$C_{20}H_{24}ClNO_4$[e)]	63.57	6.40	63.35	6.47
Vp	2-CH_3O, 5-CH_3	3-Cl	165~6 (0.06)	1.5322	$C_{22}H_{29}ClO_3$	70.10	7.76	69.89	7.66
Vq	2,4-di-CH_3	3-Cl	157~9 (0.10)	1.5308	$C_{22}H_{29}ClO_2$	73.21	8.10	73.37	8.05
VIa[b)]	H	2-Cl	164~6 (0.65)	1.5295	$C_{20}H_{25}ClO_2$	72.14	7.57	72.26	7.51
VId	4-CH_3	2-Cl	149~51 (0.13)	1.5283	$C_{21}H_{27}ClO_2$	72.71	7.85	72.62	7.84
VIIa[c)]	H	3-Br	156~8 (0.20)	1.5406	$C_{20}H_{25}BrO_2$	63.66	6.68	63.40	6.57
IXa[d)]	H	2-CH_3O	152~4 (0.10)	1.5263	$C_{21}H_{28}O_3$	76.79	8.59	76.52	8.44
IXd	4-CH_3	2-CH_3O	152~5 (0.10)	1.5240	$C_{22}H_{30}O_3$	77.15	8.83	77.04	8.77

a) NMR (CCl_4) δ: 3.56 (s, $PhCH_2$), 4.63 (d, J=6.0 cps, CH_2Cl)
b) NMR (CCl_4) δ: 3.49 (d, J=7.2 cps, $PhCH_2$), 4.58 (s, CH_2Cl)
c) NMR (CCl_4) δ: 3.68 (s, $PhCH_2$), 4.58 (d, J=6.0 cps, CH_2Cl)
d) NMR (CCl_4) δ: 3.36 (d, J=7.2 cps, $PhCH_2$), 4.56 (s, CH_2Cl)
e) *Anal.* N(%): Found, 3.85; Calcd., 3.71

VIIIa) is very similar to that of the methyl-substituted chrysanthemate series (II, III, and IV) as observed previously.[1)] A halogen substitution at the 6-position of the alcohol moiety of piperonyl chrysanthemate doubled the insecticidal activity of the ester,[7)] and also in our 4-phenyl-*trans*-2-buten-1-yl ester series, introduction of chlorine to the 3-position of the 2-buten-1-yl moiety was found to play an important part for high activity. Since the chlorine in the molecule of Va corresponds sterically to the ortho chlorine of barthrin and to the carbonyl of cyclopentenones in pyrethrins and allethrin, the presence of an electron-attracting group at this position seems to be of deep significance for high activity of pyrethroids. The chrysanthemate (IXa) having a methoxy group at the 2-position of the 2-buten-1-yl moiety of the ester was also considerably effective.

The 2, 2, 3, 3-tetramethylcyclopropanecarboxylic acid esters having 3-chloro (Xa), 2-chloro (XIa), 3-bromo (XIIa), and 2, 3-dichloro (XIIIa) groups were about 6, 1, 5.5, and 3.5 times as active as allethrin, respectively. Although the activity of Xa was about a half that of the corresponding chrysanthemates (Va), XIa, XIIa, and XIIIa exhibited the activities almost equal to those of the corresponding chrysanthemates VIa, VIIa,

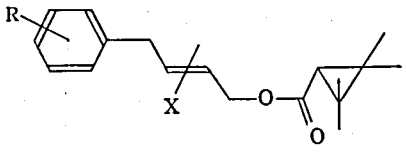
Table 2. 4-Aryl-2, 3-dichloro-*trans*-2-buten-1-yl *dl-cis, trans*-Chrysanthemates



No.	R	bp°C(mmHg)	n_D^{20}	Formula	*Anal.* (%) Calcd. C	Calcd. H	Found C	Found H
VIIIa[a)]	H	157~9 (0.10)	1.5404	$C_{20}H_{24}Cl_2O_2$	65.40	6.59	65.17	6.55
VIIIb	2-CH_3	175~6 (0.20)	1.5390	$C_{21}H_{26}Cl_2O_2$	66.14	6.87	66.34	6.86
VIIIc	3-CH_3	165~7 (0.10)	1.5352	$C_{21}H_{26}Cl_2O_2$	66.14	6.87	66.01	6.64
VIIId	4-CH_3	164~5 (0.10)	1.5360	$C_{21}H_{26}Cl_2O_2$	66.14	6.87	66.23	6.79
VIIIe	2-Cl	165~7 (0.13)	1.5449	$C_{20}H_{23}Cl_3O_2$	59.79	5.77	59.74	5.72
VIIIf	3-Cl	177~80 (0.13)	1.5452	$C_{20}H_{23}Cl_3O_2$	59.79	5.77	59.90	5.85
VIIIg	4-Cl	182~3 (0.15)	1.5435	$C_{20}H_{23}Cl_3O_2$	59.79	5.77	59.66	5.69
VIIIj	4-F	155~6 (0.15)	1.5269	$C_{20}H_{23}Cl_2FO_2$	62.34	6.02	62.16	5.98
VIIIk	2-CH_3O	175~6 (0.13)	1.5412	$C_{21}H_{26}Cl_2O_3$	63.48	6.60	63.40	6.59
VIIIl	3-CH_3O	175~8 (0.13)	1.5391	$C_{21}H_{26}Cl_2O_3$	63.48	6.60	63.32	6.68
VIIIm	4-CH_3O	177~8 (0.10)	1.5396	$C_{21}H_{26}Cl_2O_3$	63.48	6.60	63.51	6.54

a) NMR (CCl_4) δ: 3.83 (s, $PhCH_2$), 4.85 (s, CH_2Cl)

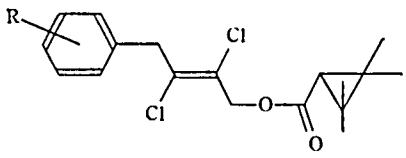
Table 3. 4-Aryl-monosubstituted-*trans*-2-buten-1-yl 2, 2, 3, 3-Tetramethylcyclopropanecarboxylates



No.	R	X	bp°C(mmHg)	n_D^{20}	Formula	*Anal.* (%) Calcd. C	Calcd. H	Found C	Found H
Xa	H[a)]	3-Cl	124 (0.10)	1.5252	$C_{18}H_{23}ClO_2$	70.46	7.55	70.21	7.37
Xb	2-CH_3	3-Cl	134~5 (0.12)	1.5264	$C_{19}H_{25}ClO_2$	71.12	7.85	70.98	7.59
Xc	3-CH_3	3-Cl	134 (0.12)	1.5237	$C_{19}H_{25}ClO_2$	71.12	7.85	70.84	7.66
Xd	4-CH_3	3-Cl	132~3 (0.13)	1.5235	$C_{19}H_{25}ClO_2$	71.12	7.85	71.16	7.73
Xe	2-Cl	3-Cl	146~8 (0.13)	1.5342	$C_{18}H_{22}Cl_2O_2$	63.35	6.50	63.17	6.44
Xf	3-Cl	3-Cl	149~51 (0.15)	1.5383	$C_{18}H_{22}Cl_2O_2$	63.35	6.50	63.50	6.38
Xg	4-Cl	3-Cl	154~5 (0.19)	1.5332	$C_{18}H_{22}Cl_2O_2$	63.35	6.50	63.52	6.33
Xh	2-F	3-Cl	129~31 (0.14)	1.5162	$C_{18}H_{22}ClFO_2$	66.55	6.83	66.46	6.75
Xi	3-F	3-Cl	134~5 (0.20)	1.5153	$C_{18}H_{22}ClFO_2$	66.55	6.83	66.58	6.64
Xj	4-F	3-Cl	129~30 (0.12)	1.5147	$C_{18}H_{22}ClFO_2$	66.55	6.83	66.31	6.67
Xk	2-CH_3O	3-Cl	145~6 (0.10)	1.5280	$C_{19}H_{25}ClO_3$	67.74	7.48	67.93	7.40
Xl	3-CH_3O	3-Cl	150~2 (0.10)	1.5282	$C_{19}H_{25}ClO_3$	67.74	7.48	67.85	7.54
Xm	4-CH_3O	3-Cl	151~3 (0.15)	1.5290	$C_{19}H_{25}ClO_3$	67.74	7.48	67.66	7.52
Xn	4-C_2H_5	3-Cl	155~6 (0.28)	1.5223	$C_{20}H_{27}ClO_2$	71.10	8.13	70.91	8.24
XIa[b)]	H	2-Cl	128~30 (0.20)	1.5265	$C_{18}H_{23}ClO_2$	70.46	7.55	70.34	7.59
XIIa[c)]	H	3-Br	143~4 (0.23)	1.5363	$C_{18}H_{23}BrO_2$	61.54	6.60	61.59	6.44

a) NMR (CCl_4) δ: 3.53 (s, $PhCH_2$), 4.55 (d, J=6.0 cps, CH_2Cl)
b) NMR (CCl_4) δ: 3.47 (d, J=7.2 cps, $PhCH_2$), 4.53 (s, CH_2Cl)
c) NMR (CCl_4) δ: 3.69 (s, $PhCH_2$), 4.55 (d, J=6.0 cps, CH_2Cl)

Table 4. 4-Aryl-2,3-dihloro-*trans*-2-buten-1-yl 2,2,3,3-Tetramethylcyclopropanecarboxylates



No.	R	bp°C(mmHg)	n_D^{20}	Formula	*Anal.* (%) Calcd. C	Calcd. H	Found C	Found H
XIIIa[a)]	H	144~6 (0.13)	1.5338	$C_{18}H_{22}Cl_2O_2$	63.35	6.50	63.29	6.41
XIIIb	2-CH_3	150~2 (0.18)	1.5369	$C_{19}H_{24}Cl_2O_2$	64.23	6.81	64.07	6.79
XIIIc	3-CH_3	143~5 (0.13)	1.5310	$C_{19}H_{24}Cl_2O_2$	64.23	6.81	63.99	6.75
XIIId	4-CH_3	147~9 (0.15)	1.5319	$C_{19}H_{24}Cl_2O_2$	64.23	6.81	64.41	6.57
XIIIe	2-Cl	152~4 (0.10)	1.5428	$C_{18}H_{21}Cl_3O_2$	57.54	5.63	57.33	5.72
XIIIf	3-Cl	158~60 (0.07)	1.5458	$C_{18}H_{21}Cl_2O_2$	57.54	5.63	57.45	5.56
XIIIg	4-Cl	155~7 (0.10)	s[b)]	$C_{18}H_{21}Cl_2O_2$	57.54	5.63	57.29	5.41
XIIIk	2-CH_3O	165~6 (0.16)	1.5418	$C_{19}H_{24}Cl_2O_3$	61.46	6.56	61.20	6.38
XIIIl	3-CH_3O	156~7 (0.15)	1.5361	$C_{19}H_{24}Cl_2O_3$	61.46	6.56	61.57	6.41
XIIIm	4-CH_3O	160~2 (0.10)	s[b)]	$C_{19}H_{24}Cl_2O_3$	61.46	6.56	61.25	6.50

a) NMR (CCl_4) δ: 3.89 (s, $PhCH_2$), 4.88 (s, CH_2Cl)
b) s=partly solidified

and VIIIa, respectively. These halogen substituted compounds Xa, XIa, XIIa and XIIIa are 23, 4, 20, and 13 times as active as the parent compound, 4-phenyl-*trans*-2-buten-1-yl 2,2,3,3-tetramethylcyclopropanecarboxylate.[1)]

Introduction of a halogen group to the 2-buten-1-yl moiety of the 2,2,3,3-tetramethylcyclopropanecarboxylate series gives more pronounced effect than in the case of the chrysanthemate series.

3-Chloro-substitution in the 2-buten-1-yl moiety of esters exhibited the most active knockdown effect in both the chrysanthemate and 2,2,3,3-tetramethylcyclopropanecarboxylate series. The KT_{50} values of the esters (Va and Xa) were about 6 and 3 minutes. As observed by Matsui *et al.*, recently,[8)] replacement of chrysanthemic acid with 2,2,3,3-tetramethylcyclopropanecarboxylic acid resulted generally in a considerable increase of the knockdown effect.

Substitution on benzene ring.

In 4-aryl-3-chloro-*trans*-2-buten-1-yl chrysanthemate series, the substitution on the benzene ring resulted in a decrease on potency. The substitution at the *ortho*- or *meta*-position resulted in a greater decrease of the activity than the *para*-substitution except for fluorine substitution.

For example, the activities of the *ortho*-, *meta*, and *para*-methyl compounds (Vb, Vc, and Vd) were about 1/2, 1/4, and 1/4 of that of the unsubstituted compound (Va), respectively.

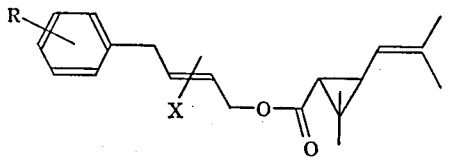
For the *para*-substituted analogs, the insecticidal activity was in the following order ; $H > CH_3 > F \fallingdotseq OCH_3 > Cl > C_2H_5 \gg NO_2$. The topical LD_{50} values varied over 50-fold, but no linear relationship exists between the LD_{50} values and Hammett σ values. However, the activity appears to be governed mainly by the steric effect of substituents.

The activities of the *ortho*- or the *meta*-substituted compounds in a series of esters V varied in the following order ; $H > F > CH_3 > Cl > CH_3O$. In the *ortho*- and *meta*-substituted compounds, the activity also seems to decrease with increasing in the size of substituents.

With the effect of substitution on the benzene ring, the preferred position and bulkiness of substituent in the series of V are substantially contrast to those of a series of aryl N-methylcarbamate insecticides.[9)]

As seen in Table 6, in 4-aryl-2,3-dichloro-

Table 5. Insecticidal Activities of 4-Aryl-monosubstituted-*trans*-2-buten-1-yl *dl-cis, trans*-Chrysanthemates



No.	R	X	Topical application LD_{50}(μg/fly)	Relative potency	Spray method KT_{50}
Va	H	3-Cl	0.10	1200	6′12″
Vb	2-CH_3	3-Cl	0.43	280	15′14″
Vc	3-CH_3	3-Cl	0.44	270	18′00″
Vd	4-CH_3	3-Cl	0.18	670	14′00″
Ve	2-Cl	3-Cl	1.10	120	19′38″
Vf	3-Cl	3-Cl	1.19	100	20′50″
Vg	4-Cl	3-Cl	0.43	280	12′56″
Vh	2-F	3-Cl	0.18	670	6′00″
Vi	3-F	3-Cl	0.24	500	6′25″
Vj	4-F	3-Cl	0.30	400	8′32″
Vk	2-CH_3O	3-Cl	2.31	52	16′20″
Vl	3-CH_3O	3-Cl	1.46	89	7′52″
Vm	4-CH_3O	3-Cl	0.33	360	7′47″
Vn	4-C_2H_5	3-Cl	0.99	120	>30′
Vo	4-NO_2	3-Cl	>5	<24	13′20″
Vp	2-CH_3O, 5-CH_3	3-Cl	>5	<24	>30′
Vq	2, 4-di-CH_3	3-Cl	1.58	76	>30′
VIa	H	2-Cl	1.15[a]	100	7′30″
VId	4-CH_3	2-Cl	1.95	62	>30′
VIIa	H	3-Br	0.16	750	7′43″
IXa	H	2-CH_3O	0.41	290	4′10″
IXd	4-CH_3	2-CH_3O	>5	<24	>30′
	allethrin[b]		1.20		

a) The value previously reported by us (*Agr. Biol. Chem.*, 35, 968(1971)) was corrected after reexamination.
b) *dl-cis, trans*-chrysanthemate.

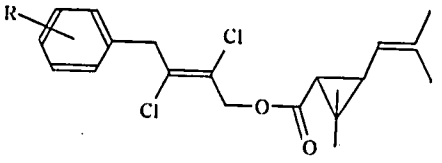
trans-2-buten-1-yl chrysanthemate series (VIII), the *para*-substitutions (methyl, chloro, methoxy, and fluoro) resulted in a greater decrease in potency than in the case of the *ortho*- or the *meta*-substitution, and the activity of these compounds is 1/15 or less compared with the parent compound (VIIIa). Such a great decrease of the activity by the *para*-substitution have been previously observed in the case of 2, 3-dimethyl-*trans*-2-buten-1-yl ester series.[1] The *ortho*- and the *meta*-substitutions (methyl, chloro, and methoxy) gave about 1/4～1/6 of the activity of the parent compound (VIIIa).

Although the fluorine substitutions at the *ortho*-, *meta*-, and *para*-position resulted in almost equal knockdown effect to the parent ester (Va), introduction of the other groups led to a decrease in the effect. In the series of esters VIII, the substitution on the benzene ring resulted in a great decrease of knockdown effect, and their KT_{50} values were all above 30 minutes.

With respect to the insecticidal activity of the 2, 2, 3, 3-tetramethylcyclopropanecarboxylate series (X and XIII), the substitution on the benzene ring resulted in a decrease of the toxicity.

Although these substituted esters in both series were slightly less active than the corresponding chrysanthemates, the structure-activity relation-

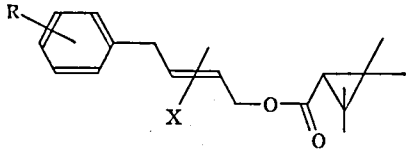
Table 6. Insecticidal Activites of 4-Aryl-2,3-dichloro-*trans*-2-buten-1-yl *dl-cis, trans*-Chrysanthemates



No.	R	Topical application LD_{50}(μg/fly)	Relative potency	Spray method KT_{50}
VIIIa	H	0.30	100	12′40″
VIIIb	2-CH_3	1.19	25	>30′
VIIIc	3-CH_3	1.23	24	>30′
VIIId	4-CH_3	>10	<3	>30′
VIIIe	2-Cl	1.25	24	>30′
VIIIf	3-Cl	1.29	23	>30′
VIIIg	4-Cl	>10	<3	>30′
VIIIj	4-F	>5	<6	>30′
VIIIk	2-CH_3O	1.94	15	>30′
VIIIl	3-CH_3O	1.49	20	>30′
VIIIm	4-CH_3O	>10	<3	>30′
allethrin[a)]		1.20	25	

a) *dl-cis, trans*-chrysanthemate

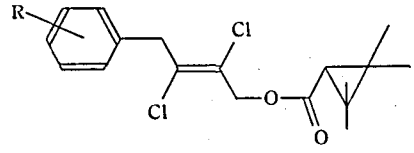
Table 7. Insecticidal Activities of 4-Aryl-monosubstituted-*trans*-2-buten-1-yl 2,2,3,3-Tetramethylcyclopropanecarboxylates



No.	R	X	Topical application LD_{50}(μg/fly)	Relative potency	Spray method KT_{50}
Xa	H	3-Cl	0.19	630	3′31″
Xb	2-CH_3	3-Cl	0.37	320	7′02″
Xc	3-CH_3	3-Cl	0.34	350	6′52″
Xd	4-CH_3	3-Cl	0.21	570	6′08″
Xe	2-Cl	3-Cl	1.08	110	12′05″
Xf	3-Cl	3-Cl	3.38	36	15′13″
Xg	4-Cl	3-Cl	0.86	140	11′25″
Xh	2-F	3-Cl	0.37	320	3′44″
Xi	3-F	3-Cl	0.28	430	4′36″
Xj	4-F	3-Cl	0.28	430	5′40″
Xk	2-CH_3O	3-Cl	1.74	70	9′23″
Xl	3-CH_3O	3-Cl	1.34	90	8′10″
Xm	4-CH_3O	3-Cl	0.31	390	6′35″
Xn	4-C_2H_5	3-Cl	0.56	210	17′52″
XIa	H	2-Cl	0.99	120	5′55″
XIIa	H	3-Br	0.22	550	4′49″
	allethrin[a)]		1.20	100	

a) *dl-cis, trans*-chrysanthemate.

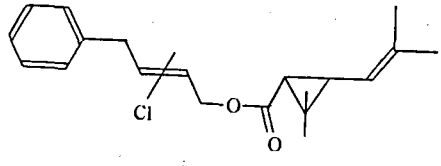
Table 8. Insecticidal Activities of 4-Aryl-2, 3-dichloro-*trans*-2-buten-1-yl 2, 2, 3, 3-Tetramethylcyclopropanecarboxylates



No.	R	Topical application LD_{50}(μg/fly)	Relative potency	Spray method KT_{50}
XIIIa	H	0.34	100	6′20″
XIIIb	2-CH_3	1.09	31	14′52″
XIIIc	3-CH_3	0.39	87	14′52″
XIIId	4-CH_3	>5	<7	>30′
XIIIe	2-Cl	0.70	49	19′09″
XIIIf	3-Cl	1.68	20	20′03″
XIIIg	4-Cl	>5	<7	>30′
XIIIk	2-CH_3O	1.29	26	13′52″
XIIIl	3-CH_3O	1.69	20	8′00″
XIIIm	4-CH_3O	>5	<7	>30′
allethrin[a)]		1.20	28	

a) *dl-cis, trans*-chrysanthemate

Table 9. Insecticidal Activity of Isomers of Butethrin (Va)



4-Phenyl-*trans*-2-buten-1-ol	Chrysanthemic acid	LD_{50}[a)] (μg/fly)	Relative potency
3-Cl	*dl-cis, trans*	0.056	100
3-Cl	*dl-trans*	0.053	106
3-Cl	*dl-cis*	0.207	27
3-Cl	*d-trans*	0.024	230
2-Cl	*dl-trans*	0.641	9
2-Cl	*dl-cis*	1.794	3
allethrin	*dl-cis, trans*	0.729	8

a) Topical application method.

ship of these series (X and XIII) were analogous to those of the corresponding chrysanthemate series.

As to the knockdown effect of the 2, 2, 3, 3-tetramethylcyclopropanecarboxylate series (X and XIII) with substituted phenyl group, introduction of substituent resulted generally in a decrease of the effect, but the fluorine substitutions in series X, regardless of whether the substitution occurs at *para*, *meta*, or *ortho* position, showed a comparable effect to the unsubstituted compound (Xa). In general, the 2, 2, 3, 3-tetramethylcyclopropanecarboxylates showed approximately half the KT_{50} values of those of the corresponding chrysanthemate.

Some isomers of butethrin (Va).

As seen in Table 9, there is a marked difference

in the activity of these isomers to houseflies. With the same alcohol component, a change from the *dl-cis* to the *dl-trans* form of the acid component resulted in 3～4-fold increase in activity of the ester. With the same acid component, moving the chlorine atom from the 2- to the 3-position of the 2-buten-1-yl moiety of the ester was accompanied by about 9～12-fold increase in potency of the ester. The position isomerism of the alcohol component exerts a great influence upon the activity than the geometrical isomerism of the acid component.

Although a planar cyclic nucleus such as cyclopentenone in pyrethrins, benzene in benzyl esters[10-12] and furan in furylmethyl esters[13,14] has been considered to be indispensable for high insecticidal activity of pyrethroids[15], our study has revealed that an acyclic *trans* double bond skeleton substituted by a halogen can play a similar role to the planar cyclic nucleus.

The structure-activity relationship which was outlined above allow us to define at least three structural requirements for the alcohol moiety which are necessary for high activity in the arylbutenyl series: (1) *trans* configuration around the double bond in the arylbutenyl moiety, (2) benzene ring with no substituent, (3) a halogen substitution (perhaps an electron-attracting group) at the position 3 of the 2-buten-1-yl moiety of the ester.

Va, which is one of the most active compounds of these series, possessed very low mammalian toxicity. The acute oral LD_{50} value was above 20 g/kg in mice, while it was 1 g/kg for allethrin. Hardly any insecticides with such low toxicity has been reported.

Experimental

IR spectra were recorded on a Hitachi IR spectrometer in film. NMR spectra was measured on a Hitachi Perkin-Elmer R-20 type (60 Mc) spectrometer in CCl_4 (unless otherwise stated) with TMS as internal standard. Gas chromatography was carried out with a Hitachi gas chromatograph 063.

4-Aryl-1-chloro-substituted-2-butenes.

General method. A solution of ArN_2Cl, prepared from 0.1 mole of $ArNH_2$, 0.1 mole of $NaNO_2$, and 0.35 mole of conc. HCl, was neutralized to pH 6～7 with $NaHCO_3$ at −5～−10°C. To this ice-cold solution was added 0.12 mole of substituted-1,3-butadiene in 50 m*l* of Me_2CO and 0.01 mole of $CuCl_2 \cdot 2H_2O$, and the mixture was vigorously stirred until N_2 evolution is complete. The resultant oily layer was then extracted with Et_2O, washed with water, and dried (Na_2SO_4). After evaporation of the solvent, the residual oil was distilled *in vacuo* to give the following 2-butenes.

4-Aryl-1, 3-dichloro-2-butenes. Phenyl, bp 78～82°C (0.3 mmHg) (lit.[16] 112～3°C (4mmHg)). This fraction revealed the presence of 1,4-adduct (XV, R=H) in a ratio of about 1 : 3 to 1,4-adduct (XIV, R=H) by the NMR and GLC analysis. NMR δ: 5.61 (t, $J=7.2$ cps, (Cl)C=CH− of 1,4-adduct), 5.93 (t, $J=7.2$ cps, −CH=C(Cl) of 4,1-adduct). GLC : 1% NPGS on Chromosorb G, 1 m, 130°C, N_2 30 m*l*/min ; 2-tolyl, bp 79～83°C (0.09 mmHg); 3-tolyl, bp 82～4°C (0.15 mmHg); 4-tolyl, bp 77～8°C (0.1 mmHg) (lit.[16] 127～9°C (4 mmHg)); 2-Cl-phenyl, bp 90～3°C (0.15 mmHg); 3-Cl-phenyl, bp 105～6°C (0.50 mmHg); 4-Cl-phenyl, bp 89～91°C (0.13 mmHg) (lit.[16] 141～2°C (4 mmHg)) ; 2-F-phenyl, bp 70～2°C (0.28 mmHg); 3-F-phenyl, bp 70～2°C (0.25 mmHg) ; 4-F-phenyl, bp 75～7°C (0.35 mmHg); 2-anisyl, bp 96～9°C (0.20 mmHg) ; 3-anisyl, bp 105～6°C (0.20 mmHg); 4-anisyl, bp 109～10°C (0.20 mmHg) ; 4-Et-phenyl, bp 90～3°C (0.18 mmHg); 4-NO_2-phenyl, bp 135～6°C (0.20mmHg) (lit.[16] 175～8°C (2 mmHg)); 2-MeO-5-Me-phenyl, bp 105～7°C (0.25 mmHg); 2,4-di-Me-phenyl, bp 90～1°C (0.10 mmHg).

4-Phenyl-3-bromo-1-chloro-2-butene. This butene was prepared from 2-bromo-1,3-butadiene and PhN_2Cl, bp 86～98°C (0.20 mmHg). This fraction revealed the presence of 4,1-adduct (XVII) in a ratio of about 1 : 3 to 1,4-adduct (XVI). NMR δ: 3.43 (d, $J=7.2$ cps, $PhCH_2$ of XVII), 3.64 (s, $PhCH_2$ of XVI), 4.01 (d, $J=7.2$ cps, CH_2Cl of XVI), 4.12 (s, CH_2Cl of XVII), 5.79 (t, $J=7.2$ cps, (Cl)C=CH of XVI), 6.15 (t, $J=7.2$ cps, CH=C(Cl) of XVII).

4-Aryl-1-chloro-2-methoxy-2-butenes. The butenes were prepared from 2-methoxy-1,3-butadiene and ArN_2Cl. Phenyl, bp 72～82°C (0.2 mm-

Hg). NMR δ: 3.33 (d, J=7.2 cps, $PhCH_2$), 3.64 (s, OCH_3), 3.95 (s, CH_2Cl), 4.91 (t, J=7.2 cps, CH=C<); 4-tolyl, bp 78～90°C (0.25 mmHg).

4-Aryl-1,2,3-trichloro-2-butenes. These butenes were prepared from 2,3-dichloro-1,3-butadiene and ArN_2Cl. Phenyl,[17] bp 76～9°C (0.15 mmHg). NMR δ: 3.82 (s, $PhCH_2$) 4.33 (s, CH_2Cl), 7.17 (s. Ph-H); 2-tolyl,[17] bp 85～8°C (0.10mmHg); 3-tolyl, bp 93～7°C (0.30 mmHg); 4-tolyl, bp 92～5°C (0.15 mmHg); 2-Cl-phenyl, bp 95～8°C (0.15 mmHg); 3-Cl-phenyl, 114～5°C (0.05 mmHg); 4-Cl-phenyl, bp 110～1°C (0.20 mmHg); 2-anisyl, bp 90～5°C (0.15 mmHg); 3-anisyl, bp 128～32°C (0.90 mmHg); 4-anisyl, bp 105～10°C (0.10 mmHg); 4-F-phenyl, bp 82～5°C (0.25 mmHg).

Esterification of 4-aryl-1-chloro-substituted-2-butenes.

General method. A mixture of 0.03 mole of 4-aryl-1-chloro-substituted-2-butene, 0.02 mole of potassium salt of the appropriate cyclopropanecarboxylic acid and 30 m*l* of iso-PrOH was refluxed for 8 hr. The solvent was removed and the residue was poured onto 50 m*l* of water. The mixture was extracted with Et_2O and the etheral solution was washed with water, dried (Na_2SO_4), and distilled *in vacuo* to afford the ester (Tables 1, 2, 3 and 4).

Iodide-acetone method. A mixture of potassium *dl-cis, trans*-chrysanthemate (from 1.7 g of *dl-cis, trans*-chrysanthemic acid and 0.7 g of KOH), and 4.4 g of 4-phenyl-3-chloro-1-iodo-2-butene in 35 m*l* of acetone was stirred for 3 hr at room temperature and allowed to stand for 15 hr at room temperature. After evaporation of the solvent, the etheral extract was washed with water and dried ($MgSO_4$). After evaporation of the solvent, the residue was distilled *in vacuo* to afford 2.8 g of the ester, bp 154～5°C (0.1 mmHg). The ratio of the ester Va to VIa of this fraction was 97 : 3 from the GLC analysis (2% NPGS on Chromosorb P, 2 m, 170°C, N_2 35 m*l*/min) of the hydrolysate. IR (cm^{-1}): 1725 (ester C=O), 1660 (C=C), 1600, 1495, 1190, 1160, 1110, 855 (>C=CH-).

4-Phenyl-3-chloro-*trans*-2-buten-1-yl p-nitrobenzoate. Treatment of potassium p-nitrobenzoate and crude 4-phenyl-1, 3-dichloro-2-butene (74%) in DMF for 6 hr at 80°C gave crude 4-phenyl-3-chloro-*trans*-2-buten-1-yl p-nitrobenzoate. Recrystallization from MeOH afforded pure material, mp 76°C. NMR ($CDCl_3$) δ: 3.68 (2H, s, $PhCH_2$), 5.02 (2H, d, J=6.5 cps, CH_2O), 5.85 (1H, d, J=6.5 cps, (Cl)C=CH-), 7.26 (5H, s, Ph-H), 8.19 (4H, s, p-NO_2-Ph-H). *Anal.* Found : C, 61.41 ; H, 4.33 ; N, 4.15. Calcd. for $C_{17}H_{14}ClNO_4$: C, 61.54; H, 4.25; N, 4.22%.

4-Phenyl-2-chloro-*trans*-2-buten-1-yl p-nitrobenzoate. Using the above filtrate of p-nitrobenzoylation, the repeated p-nitrobenzoylation and filtration afforded the crude 4-phenyl-2-chloro-*trans*-2-buten-1-yl p-nitrobenzoate. Recrystallization from MeOH gave pure material, mp 81.0°C. NMR ($CDCl_3$) δ: 3.58 (2H, d, J=7.2 cps, $PhCH_2$), 4.93 (2H, s, CH_2O), 6.11 (1H, t, J=7.2 cps, -CH=C(Cl)), 7.19 (5H, s, Ph-H), 8.18 (4H, s, p-NO_2-Ph-H). *Anal.* Found : C, 61.39 ; H, 4.40; N, 4.31. Calcd. for $C_{17}H_{14}ClNO_4$: C, 61.54; H, 4.25; N, 4.22%.

Preparation of isomers of butethrin (Va).

The above p-nitrobenzoates were hydrolysed and the alcohols obtained were used for esterification immediately without further purification. The *dl-trans*-and *d-trans*-chrysanthemates were prepared from the corresponding alcohols by the acid chloride method, respectively. The *dl-cis*-chrysanthemates were prepared by the condensation of the acid and the corresponding alcohols using N, N'-dicyclohexylcarbodiimide, respectively. With all isomers, *Anal.* Calcd. for $C_{20}H_{25}ClO_2$: C, 72.16; H, 7.57%.

4-Phenyl-3-chloro-*trans*-2-buten-1-yl *dl-trans*-chrysanthemate. bp 138～40°C (0.10 mmHg). NMR δ : 3.57 (2H, s, $PhCH_2$), 4.66 (2H, d, J=6.0 cps, CH_2O), 5.63 (1H, t, J=6.0 cps, (Cl)C=CH-)), 7.17 (5H, s, Ph-H). *Anal.* Found: C, 72.03 ; H, 7.73%.

4-Phenyl-3-chloro-*trans*-2-buten-1-yl *d-trans*-chrysanthemate. bp 140～2°C (0.11mmHg). *Anal.* Found : C, 72.10 ; H, 7.62%.

4-Phenyl-2-chloro-*trans*-2-buten-1-yl *dl-trans*-chrysanthemate. bp 153～4°C (0.25 mmHg). NMR δ : 3.48 (2H, d, J = 7.2 cps, $PhCH_2$), 4.59 (2H, s, CH_2O), 5.91 (1H, t, J=7.2 cps, -CH=C(Cl)), 7.12 (5H, s, Ph-H). *Anal.* Found: C, 72.24 ; H, 7.72%.

4-Phenyl-3-chloro-*trans*-2-buten-1-yl *dl-cis*-chrysanthemate. bp 146～8°C (0.15 mmHg). NMR δ: 3.57 (2H, s, $PhCH_2$), 4.62 (2H, d, J = 6.0 cps, CH_2O), 5.12～5.46 (1H, m, $CH{=}C(Me)_2$), 5.61 (1H, t, J=6.0 cps, $(Cl)C{=}CH$-), 7.17 (5H, s, Ph-H). *Anal.* Found: C, 72.13; H, 7.76%.

4-Phenyl-2-chloro-*trans*-2-buten-1-yl *dl-cis*-chrysanthemate. bp 143～5°C (0.12 mmHg). NMR δ: 3.50 (2H, d, J=7.2 cps, $PhCH_2$), 4.57 (2H, s, CH_2O), 5.10～5.43 (1H, m, $CH{=}C(Me)_2$), 5.91 (1H, t; J=7.2 cps, $-CH{=}C(Cl)$), 7.13 (5H, s, Ph-H). *Anal.* Found: C, 72.10; H, 7.74%.

Evaluation of insecticidal activities

Topical application method.[4] Susceptible houseflies ("Takatsuki"), *Musca domestica vicina* Macq., were tested on the dorsum of the thorax with 0.5 μl of an acetone solution of the test compound by means of a micrometer syringe, and kept at 24～27°C. Mortality accounts were made after twenty-four hours.

Spray chamber method. The knockdown test was carried out according to the method of Nagasawa[5] against houseflies by spraying 0.5 m*l* of 1% Deo-base solution of the test compound, and knockdown (%) after 30 min were assessed.

Acknowledgement. The authors wish to express their thanks to Prof. T. Saito, Nagoya University, and Prof. K. Sato, Yokohama National University, for their valuable instruction. Thanks are also due to Mr. S. Uehara, Vice President, and Dr. S. Ikawa, Executive Director, for their encouragement.

References

1) K. Sota, T. Amano, A. Hayashi and I. Tanaka, *Botyu-Kagaku*, 38, 181 (1973).
2) "Organic Reactions", Vol. 11, ed. by R. Adams *et al.*, John Wiley & Sons, Inc., New York, p. 189.
3) J. Šmejkal and J. Farkaš, *Colln Czech. Chem. commun.*, 28, 481 (1963).
4) K. Sota, M. Aida, K. Noda, and A. Hayashi, *Agr. Biol. Chem.*, 36, 2287 (1972).
5) S. Nagasawa, *Botyu-Kagaku*, 181, 138 (1953).
6) A. Hayashi, I. Tanaka, and K. Sota, *Botyu-Kagaku*, 37, 86 (1972).
7) W. A. Gersdorff and P. G. Piquett, *J. Econ. Entomol.*, 52, 85 (1959).
8) M. Matsui and T. Kitahara, *Agr. Biol. Chem.*, 31, 1143 (1967).
9) R. L. Metcalf, T. R. Fukuto, and M. Y. Winton, *J. Econ. Entomol.*, 55, 889 (1962).
10) W. F. Barthel, *Adv. Pest Control Rev.*, 4, 33 (1961).
11) M. Elliott, N. F. Janes, K. A. Jeffs, P. H. Needham, and R. M. Sawicki, *Nature*, 207, 938 (1965).
12) Y. Katsuda and H. Ogami, *Botyu-Kagaku*, 31, 30 (1965).
13) M. Elliott, A. W. Farnham, N. F. Janes, P. H. Needham, and B. C. Person, *Nature*, 213, 493 (1967).
14) Y. Katsuda, H. Ogami, T. Kunishige, and Y. Sugii, *Agr. Biol. Chem.*, 31, 259 (1967).
15) T. Kato and K. Ueda, Abstracts of Papers, Annual Meeting of Agricultural Chemical Society of Japan, Tokyo, 1969, p. 297.
16) M. I. Ganushchak and F. V. Kvasnyuk-Mudrii, *Nauk. Zap. Chernivets'k. Univ.* 53, 77 (1961) [*C. A.*, 60, 14410f (1964)].
17) V. O. Babayan, L. G. Grigoryan, and S. Toganyan, *Zh. Org. Khim.*, 5 (2), 317 (1969) [*C. A.*, 70, 106081n (1969)].

Summary

A number of 4-aryl-halosubstituted-*trans*-2-buten-1-yl *dl-cis*, *trans*-chrysanthemates and 2, 2, 3, 3-tetramethylcyclopropanecarboxylates were prepared and tested for insect toxicity against houseflies. Among them, 4-phenyl-3-chloro-*trans*-2-buten-1-yl *dl-cis*, *trans*-chrysanthemate (Va) was most active being 12 times as active as allethrin. Substitutions on the benzene ring resulted in a decrease of insect toxicity. Five isomers related to Va—*dl-trans*-, *dl-cis*-, and *d-trans*-Va and 4-phenyl-2-chloro-*trans*-2-buten-1-yl *dl-trans*-chrysanthemate and the *dl-cis* isomer—were synthesized and the relationship between isomerism and activity was investigated.