Continued elution, however, will eventually wash the synergist from the column. The careful following of directions will result in sharp separation and quantitative recovery of cyclethrin from the synergist. Recoveries of cyclethrin obtained, using various combinations of the insecticide with piperonyl butoxide and sulfoxide, are given in Table II.

Discussion

Specificity of Phosphoric Acid Reagent. In order to study the specificity of the cyclethrin reagent, a number of compounds were investigated. As shown in Table III, of the compounds tested, only cyclethrin, pyrethrins, and pyrethrolone reacted to produce a red color. As pyrethrolone gave a positive reaction, the alcohol portion of the cyclethrin molecule might also react positively.

The differences in the behavior of the pyrethrinlike insecticides with the phosphoric acid reagent are of interest. These insecticides are esters of chrysanthemumcarboxylic acids and cyclic ketonic alcohols. They differ only in isomerism and in the structure of a side chain. These differences in side chain structure and in reaction with the phosphoric acid reagent are illustrated in Figure 3.

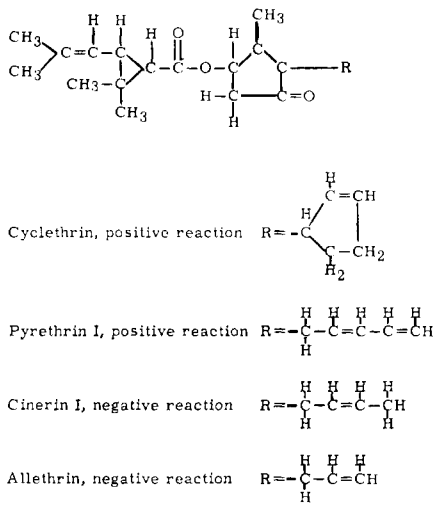

Figure 3. Side chains of pyrethrin-type insecticides and their reaction with orthophosphoric acid

The insecticides giving positive reactions—namely, pyrethrins and cyclethrin—possess side chains, five carbons in length, with at least one double bond. Therefore, a side chain of this type might be necessary for the color reaction.

Because allethrin and the cinerins yield no color when heated with orthophosphoric acid, a means for the differentiation of these insecticides from cyclethrin and from pyrethrins is available.

Also, as detailed above, the pyrethrins and cyclethrin reactions differ in respect to the composition of the color-producing reagent, the length of heating time necessary for the production of maximum color, and the stability of the color complex when heated. On the basis of these differences, a qualitative differentiation between pyrethrins and cyclethrin may be made.

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FUNGICIDAL ACTIVITY AND STRUCTURE

Fungicidal Activity of Trichloromethyl Thiolsulfonates

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A comprehensive series of trichloromethyl thiolsulfonates including several new compounds has been prepared and the effect on the germination of spores of common fungi observed. As a class, the trichloromethyl arenethiolsulfonates were found to be highly effective fungicides, and some generalizations about the effect of structural variance on fungitoxicity have been made. Several o-nitrophenyl arenethiolsulfonates were prepared and were found to lack the high order of fungitoxicity associated with the trichloromethyl analogs.

In recent years, *N*-(trichloromethylthio)tetrahydrophthalimide has been developed as a highly effective and widely used commercial fungicide. It is one of a large group of compounds containing the grouping $NSCCl_3$, which has been shown to have fungicidal properties (*3, 4, 6–9, 12, 16*). Fungicidal properties of compounds containing $CSCCl_3$ and $SSCCl_3$ linkages have also been described (*4, 5, 8*). These linkages were achieved by the addition of trichloromethanesulfenyl chloride to olefins, or by its reaction with amines, mercaptans, amides, imides, xanthates, thiocarboxylic acids, and similar compounds. Reactions such as these suggested the trichloromethyl thiosulfonates as an uninvestigated field of new fungicides. They can be made by metathesis according to the following equation:

$$ArSO_2Na + ClSCCl_3 \longrightarrow ArSO_2SCCl_3 + NaCl$$

During the extended course of synthesizing a representative series of such compounds in this laboratory, two publications appeared, which described the preparation of trichloromethyl arenethiolsulfonates (*2, 10*). Backer and Westerhuis (*2*) demonstrated the fungicidal activity of the *p*-toluenethiolsulfonate by observing its effect on the germination of beet seeds infected with *Phoma betae* Frank.

The trichloromethyl thiolsulfonates, RSO_2SCCl_3, in which R represents a substituted or nonsubstituted aliphatic or aromatic group, were described by Uhlenbroek at the XIVth International Congress of Pure and Applied Chemistry (Zurich, 1955), as a new class of organic fungicides (*15*). It was claimed that the fungitoxicity appeared to be fairly independent of the nature of R. Diminished phytotoxicity was claimed for the only specific structure, trichloromethyl *p*-carboxybenzenethiosulfonate, revealed in an abstract of this paper (*15*).

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Table I. Trichloromethyl Alkane- and Arenethiolsulfonates

Arene or Alkane[a]	Crude Yield, %[b]	Solvent[c]	M.P., °C.[d]	Formula	Analyses Calcd. %S	Calcd. %Cl	Found %S	Found %Cl
Methane	(83.3)	A	56–58	$C_2H_3Cl_3O_2S_2$	27.9	46.3	27.8	46.3
1,4-Butanebis	55[e]	B	159–160[d]	$C_6H_8Cl_6O_4S_4$	26.4	43.9	26.4	43.7
1,3-Benzenebis	68.5[e]	A	120–123	$C_8H_4Cl_6O_4S_4$	25.4	42.1	25.7	41.8
Phenylmethane	50	A, C	83–85	$C_8H_7Cl_3O_2S_2$	21.0	34.8	21.2	34.3
o-Toluene	(73.2)	A	51–52	$C_8H_7Cl_3O_2S_2$	21.0	34.8	20.7	34.8
p-Toluene	(76)	A	66–67.5[f]	$C_8H_7Cl_3O_2S_2$	21.0	34.8	20.9	34.7
2-Phenylethylene	...	D, E	95–97.5	$C_9H_7Cl_3O_2S_2$	20.2	33.5	20.1	33.2
o-Ethylbenzene	(55)	D	29.5–31	$C_9H_9Cl_3O_2S_2$	20.1	33.4	20.3	33.3
p-*tert*-Butylbenzene	(65.3)	A	80–82	$C_{11}H_{13}Cl_3O_2S_2$	18.4	30.6	18.5	30.0
p-Fluorobenzene	(83)	D	37–38.5	$C_7H_4Cl_3FO_2S_2$	20.7	34.0	20.6	34.2
o-Chlorobenzene	(70.5)	A	71–71.5	$C_7H_4Cl_4O_2S_2$	19.7	43.5	19.9	43.2
p-Chlorobenzene	94.2[e]	C	60–61[g]	$C_7H_4Cl_4O_2S_2$	19.7	43.5	19.7	43.1
3,4-Dichlorobenzene	(72)	C	57–58[h]	$C_7H_3Cl_5O_2S_2$	17.8	49.2	17.6	49.2
o-Methoxybenzene	92	A	112–113	$C_8H_7Cl_3O_3S_2$	19.9	33.1	20.1	33.4
p-Methoxybenzene	93.2	A, F	55–56.5[i]	$C_8H_7Cl_3O_3S_2$	19.9	33.1	19.8	33.1
5-Chloro-2-methoxybenzene	98	A	104–105	$C_8H_6Cl_4O_3S_2$	18.0	39.8	18.5	39.6
m-Nitrobenzene	(81.5)	A	65–66[j]	$C_7H_4Cl_3NO_4S_2$	19.1	31.6	19.1	31.6
m-Carboxybenzene	89.5[k]	G	158[dl]	$C_8H_5Cl_3O_4S_2$	19.1	31.7	19.0	31.6
3,5-Dicarboxybenzene	78[m]	H	200[dn]	$C_9H_5Cl_3O_6S_2$	16.9	28.0	17.0	28.0
p-Acetamidobenzene	58.5	D, G	146–148[d]	$C_9H_8Cl_3NO_3S_2$	18.4	[o]	18.5	
2-Naphthalene	96	A	56–57[p]	$C_{11}H_7Cl_3O_2S_2$	18.8	31.1	18.7	31.5
p-Phenoxybenzene	87.7[q]	...	[q]	$C_{13}H_9Cl_3O_3S_2$	16.7	27.7	16.7	27.9
3,3′-Diphenylsulfonebis	51[e]	I, J	151–156[d]	$C_{14}H_8Cl_6O_6S_5$	24.8		24.8	

[a] Where arene is benzene, *p*-xylene, *p*-ethylbenzene, *p*-cumene, and *p*-(1-methylbutyl)benzene, analytically impure oils were obtained; vacuum distillation of these oils was not attempted.
[b] Parentheses indicate the yield from $ClSCCl_3$ based on two or three crops of product from the solvent given in adjacent column; otherwise yield of crude dried product isolated from reaction mixture is given.
[c] Solvent for recrystallization: A, methanol; B, 2-propanol added to hot acetone solution; C, petroleum ether; D, water added to cold methanol solution; E, benzene added to petroleum ether solution; F, petroleum ether added to benzene solution; G, chlorobenzene; H, *o*-dichlorobenzene; I, 3 to 1 2-propanol–benzene; J, petroleum ether added to tetrahydrofuran solution.
[d] Uncorrected. Melting with decomposition is indicated by d following melting point.
[e] Crude washed with cold methanol and dried.
[f] Backer (*2*) reported 65.5–66.5°; Lo (*10*) reported 67–68.5°.
[g,h,i,j] Lo (*10*) reported, respectively, 56–57.5°, 53–54.5°, 52.5–54°, and 65.5–66°.
[k] Yield was obtained from disodium salt, but monosodium salt can be used.
[l] Decomposition point depends on rate of heating—e.g., slow, 158°; fast, 170°.
[m] From trisodium salt.
[n] Decomposition point depends on rate of heating.
[o] Per cent N: calculated 4.0; found, 4.3.
[p] Lo (*10*) reported an oil.
[q] Crude extracted with ether, washed with water and aqueous sodium bicarbonate, and ether removed by evaporation to give an oil, which on long standing solidified. The crude solid melted at 43.5–50°.

The series of trichloromethyl thiolsulfonates prepared for this work (Table I) included two strictly aliphatic derivatives (trichloromethyl methanethiolsulfonate and trichloromethyl 1,4-butanebisthiolsulfonate), which exhibited no fungicidal activity in contrast to the high order of activity in the arene derivatives and in the phenylmethane and phenylethylene analogs. Comparison of the data in Table II shows the influence of structure on fungicidal activity toward *Curvularia lunata* and in some cases toward *Monilinia fructicola*. The former fungus causes gladiolus leaf spot and corm rot, root rot of grasses and other plants, and is an active textile-rotting organism; the latter causes brown rot of peaches. *Curvularia lunata* was apparently the more resistant organism to the arenethiolsulfonates and therefore became the basis for screening. More consistent results were obtained by testing a solution of the candidate fungicide in an organic solvent—usually 2-propanol—rather than in an aqueous suspension.

For comparative purposes, several *o*-nitrophenyl arenethiolsulfonates were prepared by reaction of *o*-nitrobenzenesulfenyl chloride with a sodium arenesulfinate (Table III). These lacked the high order of fungicidal activity shown by the corresponding trichloromethyl derivatives (Table IV).

The generalizations that can be derived from the data of Tables II and IV are:

1. The trichloromethyl arenethiolsulfonates, as a class, effectively inhibit the germination of spores of two common fungi.
2. Strictly aliphatic derivatives may be fungicidally inactive.
3. Two trichloromethylthiolsulfonyl groups per nucleus appear to reduce fungitoxicity.
4. There appears to be little difference in fungitoxicity between *o*- and the corresponding *p*-substituted arene derivatives.
5. An increase in the size of the alkyl group beyond propyl in the alkylarene series decreases fungitoxicity.
6. The fungitoxicity associated with the group —$SCCl_3$ is reduced markedly by replacing the trichloromethyl group with an *o*-nitrophenyl group.

Experimental

Fungicide Screening Technique. The fungitoxic activity of the candidate compounds was determined by measuring the inhibition of germination of fungus spores in the presence of different concentrations of the compounds. The procedure represents a modification of a general procedure already described (*7*). For these tests, two fungi were selected: *Curvularia lunata* (Wakker) Boed and *Monilinia fructicola* (Wint.) Honey. To obtain varying concentrations of the compounds, weighed amounts were dissolved in 2-propanol or some other organic solvent. These solutions were then diluted to the desired concentrations with the same solvent and sampled by placing 0.1 ml. of each concentration in a cavity slide and permitting the solvent to evaporate. The spores, suspended in a 1% orange juice medium, were then added to the cavity slides—0.1 ml. was added to each cavity. Duplicate slides were made for each organism with each compound. After 24 hours in an incubation chamber at

Table II. Inhibition of Spore Germination by Trichloromethyl Thiolsulfonates

Alkane or Arene	Concentration (P.P.M.) for 50% Inhibition: Curvularia lunata	Monilinia fructicola
Methane	>1000	>1000
1,4-Butanebis	>1000	>1000
Benzene	2	...
1,3-Benzenebis	89	...
Phenylmethane	<1	...
o-Toluene	2	...
p-Toluene	2	...
p-Xylene	5	...
2-Phenylethylene	5	2
o-Ethylbenzene	2	...
p-Ethylbenzene	2	...
p-Cumene	5	...
p-*tert*-Butylbenzene	59	4
p-(1-Methylbutyl)-benzene	100	...
p-Fluorobenzene	8	...
o-Chlorobenzene	2	...
p-Chlorobenzene	7	1
3,4-Dichlorobenzene	2	...
o-Methoxybenzene	2	...
p-Methoxybenzene	4	1
5-Chloro-2-methoxybenzene	2	...
m-Nitrobenzene	<1	...
m-Carboxybenzene	4	...
3,5-Dicarboxybenzene	94	15
p-Acetamidobenzene	2	...
2-Naphthalene	7	...
p-Phenoxybenzene	8	6
3,3′-Diphenylsulfonebis	96	...

25° C., the slides were examined under the microscope and the percentage germination was recorded after observing and counting 100 spores in each slide. The concentration in parts per million, at which there is 50% inhibition of spore germination, is determined from a plot of these data on logarithm-probability graph paper.

Preparations of Thiolsulfonates. The intermediate sulfinates were prepared by the application of conventional techniques—i.e., primarily by the reduction of sulfonyl chlorides with zinc or sodium sulfite; the ortho-substituted arenesulfinates were prepared by treatment of the diazotized *o*-amino compound with sulfur dioxide in the presence of copper powder. The preparation of sulfinic acids has been reviewed by Truce and Murphy (*14*).

Trichloromethanesulfenyl chloride was obtained from Distillation Products Industries and from Stauffer Chemical Co.; *o*-nitrobenzenesulfenyl chloride, from Monsanto Chemical Co.

A general procedure for the preparation of most of the trichloromethyl arenethiolsulfonates listed in Table I is as follows:

Trichloromethanesulfenyl chloride was added in increments to a cold aqueous solution—usually 10%—of the appropriate sodium arenesulfinate—usually in slight excess because of an inadvertent inorganic salt content—with intermittent shaking. Occasional shaking in the cold was continued for a short period—usually 0.5 to 1 hour. When a solid product was obtained, it was collected by suction filtration, washed with cold water, and dried either in air or in a vacuum desiccator over sulfuric acid. The crude solid was then recrystallized from an appropriate solvent, usually methanol. A liquid product was washed by decantation, dissolved in methanol, and reprecipitated by the addition of water in the cold. It was then dried in vacuo over sulfuric acid. The addition of a solution of the sulfenyl chloride in an appropriate solvent (chloroform) might improve both the yield and purity of the crude product. Chloroform was used to dissolve the solid *o*-nitrobenzenesulfenyl chloride in preparing the *o*-nitrophenyl analogs, and an inert solvent has been used to advantage in preparing the tetrahydrophthalimido analog (*7*).

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Table IV. Inhibition of Spore Germination by o-Nitrophenyl Arenethiolsulfonates

Arene	Concentration (P.P.M.) for 50% Inhibition: Curvularia lunata	Monilinia fructicola
Benzene	126	103
p-Chlorobenzene	>1000	124
p-Ethylbenzene	270	160
o-Methoxybenzene	>1000	71
m-Nitrobenzene	>1000	83

Table III. o-Nitrophenyl Arenethiolsulfonates

Arene	Crude Yield, %	M.P., ° C.[a]	Formula	Analyses: Calcd. %S	Calcd. %N	Found %S	Found %N
Benzene	85.5	81–82[b]	$C_{12}H_9NO_4S_2$	21.7	4.74	21.4	4.76
p-Chlorobenzene	97	122.5–123.5[c]	$C_{12}H_8ClNO_4S_2$	19.4[d]		19.6	
p-Ethylbenzene	50	53–54	$C_{14}H_{13}NO_4S_2$	19.8	4.33	19.7	4.40
o-Methoxybenzene	100	109.5–110.5	$C_{13}H_{11}NO_5S_2$	19.7	4.31	19.6	4.36
m-Nitrobenzene	96	112–113	$C_{12}H_8N_2O_6S_2$	18.8	8.23	19.0	8.27

[a] Each crude product recrystallized from methanol, then precipitated from benzene with petroleum ether, and recrystallized again from methanol. Melting points uncorrected.
[b] Loudon (*11*) reported melting point 87 °.
[c] Miller (*13*) reported melting point 123 °.
[d] Per cent Cl: calculated, 10.75; found, 10.73.