Synthesis and Insecticidal Properties of

O-Alkyl S-Aryl Chloromethylphosphonodithioates

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A new series of substituted S-aryl esters of chloromethylphosphonodithioic acid was synthesized and evaluated for toxicity to insects, spider mites, and rats. The considerable variation in bioactivity encountered appeared to depend partly on the balance of electron donation or withdrawal by the ester groups. Optimum activity was found in the following two compounds: O-isopropyl S-p-chlorophenyl chloromethylphosphonodithioate and O-isopropyl S-p-tolyl chloromethylphosphonodithioate. These compounds were obtained by known methods in fairly high yield and purity. A number of compounds in this series were moderately toxic to mammals.

In recent years a number of reports have appeared in the literature which have described the synthesis and insecticidal properties of phosphonic acid esters. This subject was reviewed by Fukuto (1961) and Schrader (1965).

This paper reports the synthesis and bioactivity of a series of new phosphonodithioate esters represented by the following structural formula:
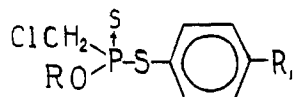
R = C_2H_5, C_3H_7, iso C_3H_7

R_1 = OCH_3, CH_3, F, Br, Cl, $C(CH_3)_3$

Where possible, relationships between structure and bioactivity have been presented and discussed.

Very little has been reported in the literature concerning the insecticidal activity of phosphonic esters of this type. Fukuto and coworkers (1959) described the weak insecticidal activity of O-ethyl-O-p-nitrophenyl chloromethylphosphonate. The thiono analog (i.e., the chloromethyl analog of parathion) has been patented (Fairchild, 1959). Schrader (1962) described the simpler S-phenyl and S-p-chlorophenyl dithio esters; others were described by Fearing et al. (1964, 1965, 1968, 1969).

EXPERIMENTAL

Reagents. The insecticide preparations began with chloromethylphosphonothioic dichloride, the preparation of which was described by Rattenbury (1961).

O-ALKYL CHLOROMETHYLPHOSPHONOCHLORIDOTHIONATES. These were prepared from the dichloride in a reaction similar to that used by Hoffman (1958). Temperatures ranged from 10° to 20 °C for the O-methyl to 50° to 60 °C for the O-isopropyl. Following water washing and preliminary rapid distillation, the pure ester chlorides were then obtained in 60 to 76% yields by careful fractionation. The ethyl ester was described by Toy (1961). Further improvements on this reaction have recently been patented by Price (1968) using hindered amines. These intermediates are included with the S-aryl esters in Table I.

ARYL THIOLS. These intermediates were mostly either commercial materials or were prepared from sulfonyl chlorides by a modification of Marvel and Adams' method (1921) due to Fancher (1961). The yields ranged from 40 to 75%.

O-ETHYL S-p-TOLYL CHLOROMETHYLPHOSPHONODITHIOATE. This preparation illustrates the Hoffman method used for the active pesticides. O-Ethyl chloromethylphosphonochloridothionate (1640 grams, 8.5 moles) and p-toluenethiol (1053 grams, 8.5 moles) were combined in 700 ml. of benzene. With strong agitation, 875 grams of triethylamine was slowly added at 45–50 °C, this temperature being maintained for an extra hour.

After overnight standing, the amine salt was removed by two water extractions. The product was further washed with 5% sodium carbonate solution and with water. After complete benzene removal, the residual product weighed 2300 grams (96.5% of theory). Although water insoluble, it is soluble in all common organic solvents with polarities ranging from methanol to kerosene.

All compounds at this stage of purity were used for pesticidal research. Eleven different preparations of compounds 2, 10, 13, and 18 were assayed with an Aerograph HYFI model 600-D gas chromatograph. The stationary phase was 10% DC 200 on Gas-Chrom Q (80–100 mesh) at 218 °C. Six of these eleven samples were > 99% pure by area %; all except one (93 + %) were over 95.5% pure.

The absence of strongly bioactive trace contaminants (in particular, pyrophosphonates) was supported also by the complete inactivity of a number of esters (such as S-p-nonylphenyl) not included in the tables.

Further purification was accomplished by crystallizations or by molecular distillations at 80° to 90 °C at 5-micron pressure. The physical constants for these pure materials are indicated by asterisks in Table I.

Procedure. INSECTICIDE AND MITICIDE TESTING. Toxicity tests to houseflies, *Musca domestica* L., were conducted on a susceptible strain (S-Stauffer) reared continuously in the laboratory at the Agricultural Research Center of the Stauffer Chemical Co. A dry film contact bioassay method was used to determine LD_{50} values. Twenty-five 3-day old female houseflies were caged and exposed for 48 hours to fresh film residues of the toxicant, which was dissolved in an acetone solution containing 0.2% peanut oil, on glass petri dishes (18.8 cm^2). LD_{50} values were determined from log concentration-probit curves by estimation or, where data fitted, by the method of Litchfield and Wilcoxon (1949). Fourth nymphal instar of the large milkweed bug, *Oncopeltus fasciatus* (Dallas), and fifth nymphal instar of the American cockroach, *Periplaneta*

Table I. Characterization of *O*-Alkyl-*S*-Aryl Chloromethylphosphonodithioates and P-Cl Intermediates

$$p\text{-}R_1\text{—}C_6H_4\text{—}S\text{—}\overset{\overset{\textstyle S}{\uparrow}}{P}(CH_2Cl)\text{—}OR$$

Code	R Group	R₁ Group	$n_D{}^{25}$	M.P., °C or B.P., °C/ mm Hg	P, % Calcd	P, % Found	S, % Calcd	S, % Found	Cl, % Calcd	Cl, % Found	Other Data or Characterization
	C₂H₅	Intermediate	1.5170	48 to 52/1.	16.05	15.9	16.6	16.5	36.8	36.6	Dens.²⁶° = 1.337
1	C₂H₅	p-OCH₃	1.595		10.4	10.2	21.6	20.9	11.97	12.1	
2	C₂H₅	p-CH₃	1.5980*	36*	11.03	11.0*	22.8	22.7*	12.63	12.6*	Dens.²⁵° = 1.240
3	C₂H₅	p-F	1.579	47*	10.9	10.8*	22.5	22.4*	12.4	12.5*	
4	C₂H₅	p-Br	1.6252*	50-1*	8.96	9.0*	18.5	18.0			Total halogen: Calcd 5.79 m eq./g, Found: 5.7*
5	C₂H₅	p-Cl	1.612		10.3	10.4	21.2	21.8	23.5	22.8	
6	C₂H₅	3,4-Cl₂	1.614		9.23	9.4	19.1	18.7	31.7	31.4	
7	C₂H₅	o-CH₃	1.594		11.0	11.3	22.8	22.5	12.6	12.8	
8	C₂H₅	p-C(CH₃)₃	1.577		9.6	9.7	19.8	20.0	11.0	11.0	
	CH(CH₃)₂	Intermediate	1.5050	51/0.7	14.97	14.9	15.48	15.1	34.3	33.2	Dens.²⁶° = 1.262
9	CH(CH₃)₂	p-OCH₃	1.587		10.0	9.8	20.6	20.0	11.4	11.3	
10	CH(CH₃)₂	p-CH₃	1.5845*	20*	10.5	10.2	21.7	21.5	12.04	11.7	
11	CH(CH₃)₂	p-F	1.5701*	29*	10.36	10.3*	21.4	21.1*	11.9	11.9*	% F: Calcd 6.4 Found: 6.9*
12	CH(CH₃)₂	p-Br	1.6080*	27-8*	8.62	8.5*	17.8	17.5*	9.85	9.5*	% Br: Calcd 22.2 Found: 22.1*
13	CH(CH₃)₂	p-Cl	1.5945*	30*	9.83	9.9	20.4	20.7	22.5	22.2	
14	CH(CH₃)₂	3,4-diCl	1.600	73.4*	8.86	8.8*	18.34	18.2*	30.5	29.9*	
15	CH(CH₃)₂	o-CH₃	1.583		10.5	10.5	21.7	22.4	12.04	12.4	
16	CH(CH₃)₂	p-C(CH₃)₃	1.564		9.2	9.6	19.0	18.7	10.5	10.5	
	n-C₃H₇	Intermediate	1.5100	57/0.3	14.97	14.9	15.48	15.1	34.3	33.6	Dens.²⁶° = 1.294
17	n-C₃H₇	p-OCH₃	1.590		10.0	10.3	20.6	20.0	11.4	11.2	
18	n-C₃H₇	p-CH₃	1.585		10.5	10.7	21.7	22.2	12.04	12.5	
19	n-C₃H₇	p-F	1.573		10.36	10.4	21.4	20.9	11.9	11.7	% F: Calcd 6.4 Found: 6.6
20	n-C₃H₇	p-Br	1.613		8.62	8.75	17.8	18.1			Total halogen: Calcd 5.56 meq./g. Found: 5.33
21	n-C₃H₇	p-Cl	1.6020*		9.83	9.6	20.4	20.4	22.5	22.2	

* Data with asterisks were obtained on molecularly redistilled, or recrystallized samples. All preparations supercooled easily, making it possible to read refractive indices on normally solid compounds.

Table II. Effect of Alkyl (R) and Ring (R₁) Substitution on Biological Activity of Chloromethylphosphonodithioate Esters

$$p\text{-}R_1\text{—}C_6H_4\text{—}S\text{—}\overset{\overset{\textstyle S}{\uparrow}}{P}(CH_2Cl)\text{—}OR$$

| | | | | LD₅₀ For Test Organism | | | | Two-Spotted Mites | |
Code	R	R₁	Rat (mg/kg) Acute Oral LD₅₀	Housefly µg/25 ♀	American cockroach in %	Milkweed bug in %	Salt-marsh caterpillar in %	P.E.ᵃ in %	Eggs in %
1	C₂H₅	p-OCH₃		6.2	0.1	>0.1	0.1	0.01	0.1
2	C₂H₅	p-CH₃	336	5.4	0.03	0.1	0.05	0.01	0.03
3	C₂H₅	p-F		7.6	0.01	>0.1	>0.1	0.08	>0.1
4	C₂H₅	p-Br		7	0.1	>0.1	0.08	>0.1	>0.1
5	C₂H₅	p-Cl		8	>0.1	>0.1	0.1	0.1	0.1
6	C₂H₅	3,4-diCl		10	>0.1	>0.1	0.1	0.05	0.08
7	C₂H₅	o-CH₃		39	>0.1	>0.1	>0.1	0.01	>0.1
8	C₂H₅	p-C(CH₃)₃		13	>0.1	>0.1	>0.1	>0.1	>0.1
9	i-C₃H₇	p-OCH₃	108	10	0.07	0.03	0.01	0.01	0.1
10	i-C₃H₇	p-CH₃	204	5.7 ± 0.7	0.03	0.01	0.003	>0.1	>0.1
11	i-C₃H₇	p-F	39.4	6.6	0.01	>0.1	0.001	0.008	0.1
12	i-C₃H₇	p-Br	23	8	0.03	0.1	0.003	0.008	>0.05
13	i-C₃H₇	p-Cl	26	5.5 ± 0.6	0.01	0.03	0.0003	0.005	0.03
14	i-C₃H₇	3,4-diCl		10	0.1	>0.1	0.01	>0.1	>0.1
15	i-C₃H₇	o-CH₃		10	>0.1	>0.1	0.08	0.1	>0.1
16	i-C₃H₇	p-C(CH₃)₃		12	>0.1	>0.1	0.05	0.03	0.08
17	n-C₃H₇	p(OCH₃)		10	>0.1	>0.1	0.03	0.01	0.1
18	n-C₃H₇	p-CH₃		12	0.1	0.1	0.01	>0.1	>0.1
19	n-C₃H₇	p-F		6	0.1	>0.1	0.01	0.01	0.1
20	n-C₃H₇	p-Br		8.2	0.1	0.1	0.05	>0.1	>0.1
21	n-C₃H₇	p-Cl	191	7.8	0.1	0.1	0.003	>0.1	>0.1
Parathion			13ᵇ	1	0.001	0.003	0.01	0.03	>0.1

ᵃ P.E. = post-embryonic.
ᵇ Hayes, W. J., Public Health Service Publication No. 476. U.S. Govt. Printing Office, Washington, D.C., 1963.

Table III. Comparative Toxicity of Phosphoric and Phosphonic Acid Esters to Insects and the Rat

| | | LD$_{50}$ For Test Organism | | |
Code	Compound	Housefly μg/25 ♀	Salt-marsh caterpillar, %	Rat acute oral LD$_{50}$ (mg./kg.)
22	$\overset{\text{S}}{\underset{\uparrow}{}}$ p-CH$_3$C$_6$H$_4$SP(OC$_2$H$_5$)$_2$[a]	330	>0.1	316
23	$\overset{\text{S}}{\underset{\uparrow}{}}$ p-CH$_3$C$_6$H$_4$SP(C$_2$H$_5$)OC$_2$H$_5$[a] (from Table II)	4.3	0.01	123
10	$\overset{\text{S}}{\underset{\uparrow}{}}$ p-CH$_3$C$_6$H$_4$SP(CH$_2$Cl)OCH(CH$_3$)$_2$	5.7	0.003	204

[a] From Menn and Szabo (1965).

americana (L.), were sprayed with aqueous suspensions containing the candidate compounds. Third instar larvae of the salt-marsh caterpillar, *Estigmene acrea* (Drury), were exposed to leaves of sour dock, *Rumex crispus* L., which had been dipped in aqueous suspensions of the test compounds. Mortality counts were made 72 hours post treatment.

To determine the miticidal properties of these compounds, young pinto bean plants in the primary leaf stage were infested with several hundred two-spotted spider mites, *Tetranychus urticae* (Koch). Dispersions of test compounds were prepared by dissolving them in acetone and further diluting with water containing 0.175% v/v of Sponto 221 (Retzloff Chemical Co., Houston, Tex.) an emulsifier. The test suspensions were sprayed on the infested plants with a spray gun (De Vilbiss, type EGA, ser. 502, with No. 390 nozzle) at 10 p.s.i. Treated plants were held in the greenhouse, and ovicidal and miticidal action was determined after seven days (Menn and Stoffey, 1963). Per cent mortality was determined by visual inspection of treated plants, and the LC$_{50}$ values were calculated from log concentration-probit plots. Acute oral mammalian toxicity determinations were carried out on male, albino rats using standardized procedures.

HYDROLYTIC STABILITY. Compounds 2, 10, and 13, highly purified and free of acid chloride, were mixed as 3% slurries in aqueous buffers of pH 5, 7, and 9. After 50 days' agitation at room temperature, no thiophenols nor thiophosphonic acid species could be detected by differential titrations (runs *vs.* buffer blanks).

RESULTS AND DISCUSSION

The bioactivity of the *O*-alkyl-*S*-aryl chloromethylphosphonodithioates listed in Table II is presented in terms of the effects of *O*-alkyl (R) and ring (R$_1$) substitutions on insecticidal and acaricidal activity, and on mammalian toxicity of certain members. Although many other chloromethylphosphonodithioate esters were studied only the most active ones are included in the tables.

EFFECT OF *O*-ALKYL GROUP. Nearly all the data in the last four columns of Table II show a striking superiority of *O*-isopropyl over *O*-ethyl esters, sometimes by a factor of 100. *O*-Methyl and *O*-isoamyl homologs, as well as *S*-aryl *P*-dimethylamides displayed very weak or no activity.

EFFECT OF RING SUBSTITUENT. Compounds 1 to 6 and 9 to 14 are listed in order of increasing electron withdrawal by the para substituent. For the *O*-ethyl group, peak activity is obtained with the *S*-*p*-tolyl ester (compound 2). In the *O*-isopropyl group, optimum electron density is evidently in the *S*-*p*-chlorophenyl compound 13. With too strong electron withdrawal, the nearly inactive *S*-*p*-nitrophenyl

ester can be likened to *O*-ethyl-*O*-*p*-nitrophenyl chloromethylphosphonate (Fukuto, 1959).

Other factors are also important, as evidenced by poor activity in compounds with the bulky *p*-tertiary butyl group (whose sigma value is nearly the same as methyl). The weakness due to ortho substitution (compounds 7 and 15) has also been pointed out by Menn and Szabo (1965).

AREAS OF SUPERIORITY. The *O*-isopropyl *S*-*p*-chlorophenyl ester (13) is superior to all other compounds in the series against all insect species in Table II. (The activity of compound 10 on milkweed bugs is the only exception, superior to that of compound 13.) Its most noteworthy feature is the outstanding lepidoptericidal activity, which is 30-fold stronger than that of parathion on the salt-marsh caterpillar. The activity on dipterous insects is also evident by the results obtained against third instar larvae of the mosquito *Aedes aegypti* (Pass and Knapp, 1966). In these mosquito tests, compound 13 performed better than the standard treatments: parathion, malathion, and fenthion. These results are especially significant if one considers the hydrolytic stability of this compound.

The *p*-tolyl esters 2 and 10 are considerably less toxic to mammals than the chlorophenyl. According to the toxicity ratings made by Hodge and Sterner (1943), compounds 2 and 10 are classified as moderately toxic. Each of these has its area of superiority: compound 2 against mites, and compound 10 as a lepidoptericide.

Although no direct comparisons were made with precisely corresponding dialkyl phosphorodithioic and alkylphosphonic acid esters, some measure of relative activity and toxicity can be obtained by comparing the related esters shown in Table III. The phosphorodithioate (22) is less toxic to the rat; however, it is significantly less insecticidal than phosphonates (Nos. 10 and 23) shown here.

Although the alkyl phosphonate (23) appears to have a similar insecticidal action, the chloromethyl phosphonate (10) has the advantage of lessened mammalian toxicity.

LITERATURE CITED

Fairchild, H. E., (to duPont) U. S. Patent 2,910,402 (1959).
Fancher, L., Western Research Center, Stauffer Chemical Co., 1200 South 47th Street, Richmond, Calif. 94804, private communication, 1961.

Fearing, R. B., Walsh, E. N., McBain, J. B. (to Stauffer Chemical Co.), U.S. Patent 3,205,254 (Sept. 7, 1965); French Patents 1,348,126 (Nov. 25, 1964) and 1,348,127 (Nov. 25, 1964); German Patent 1,184,759 (Jan. 7, 1965); and U.S. Patent 3,400,178 (Sept. 3, 1968) and 3,442,985 (May 6, 1969).

Fukuto, T. R., *Ann. Rev. Entomol.* 6, 313–32 (1961).

Fukuto, T. R., Metcalf, R. L., Winton, M., *J. Econ. Entomol.* 52, 1121–7 (1959).

Hodge, H. C., Sterner, J. H., *Am. Ind. Hyg. Assoc. Quart.* 10 (4), 93 (1943).

Hoffman, F. W., Wadsworth, D. H., Weiss, H. D., *J. Am. Chem. Soc.* 80, 3945–8 (1958).

Litchfield, J. T., Wilcoxon, F., *J. Pharmacol. Exptl. Therap.* 96, 99–113 (1949).

Marvel, C. W., Adams, R., *Org. Syntheses* I, 71 (1921).

Menn, J. J., Stoffey, D. G., "Chemical Structure and Acaricidal Activity of Certain Carbamate Phosphate Esters" in "Advances in Acarology," Vol. I, J. A. Naegele, Ed., Comstock Publishing Associates (div. of Cornell Univ. Press, Ithaca, N. Y.) pp. 142–50 (1963).

Menn, J. J., Szabo, K., *J. Econ. Entomol.* 58, 734–9 (1965).

Pass, B. C., Knapp, F. W., *Mosquito News* 26, 35–7 (1966).

Price, G. (to Stauffer Chemical Co.), U.S. Patent 3,419,643 (Dec. 31, 1968).

Rattenbury, K. H., U.S. Patent 2,993,929 (July 25, 1961).

Schrader, G., German Patent 1,138,049 (Oct. 18, 1962).

Schrader, G., *World Rev. Pest Control* 4 (4), 140–9 (1965).

Toy, A. D. F., U.S. Patent 2,988,565 (June 13, 1961).