

Synthesis and Insecticidal Properties of *O*-Alkyl *S*-Aryl Chloromethylphosphonodithioates

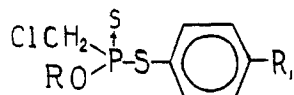
Ralph B. Fearing,¹ Edward N. Walsh,¹ Julius J. Menn,² and Ashley H. Freiberg²

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 = C₂H₅, C₃H₇, iso C₃H₇

R₁ = OCH₃, CH₃, F, Br, Cl, C(CH₃)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 chloromethylphosphonochloridodithionate (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 pesti- cidal 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*-nonyl- phenyl) 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 sus- ceptible strain (*S*-Stauffer) reared continuously in the labora- tory at the Agricultural Research Center of the Stauffer Chem- ical Co. A dry film contact bioassay method was used to de- termine LD₅₀ 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 contain- ing 0.2% peanut oil, on glass petri dishes (18.8 cm²). LD₅₀ values were determined from log concentration-probit curves by estimation or, where data fitted, by the method of Litch- field and Wilcoxon (1949). Fourth nymphal instar of the large milkweed bug, *Oncopeltus fasciatus* (Dallas), and fifth nymphal instar of the American cockroach, *Periplaneta*

¹ Stauffer Chemical Co., Eastern Research Center, Dobbs Ferry, N. Y.

² Stauffer Chemical Co., Agricultural Research Center, Mountain View, Calif.

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

$p\text{-R}_1\text{—C}_6\text{H}_4\text{—S—}\overset{\text{S}}{\underset{\uparrow}{\text{P}}}(\text{CH}_2\text{Cl})\text{—OR}$											
Code	R Group	R ₁ Group	<i>n</i> _D ²⁵	M.P., °C or B.P., °C/ mm Hg	P, %		S, %		Cl, %		Other Data or Characterization
					Calcd	Found	Calcd	Found	Calcd	Found	
1	C ₂ H ₅	Intermediate	1.5170	48 to 52/1.	16.05	15.9	16.6	16.5	36.8	36.6	Dens. ^{26°} = 1.337
2	C ₂ H ₅	<i>p</i> -OCH ₃	1.595		10.4	10.2	21.6	20.9	11.97	12.1	
3	C ₂ H ₅	<i>p</i> -CH ₃	1.5980*	36*	11.03	11.0*	22.8	22.7*	12.63	12.6*	Dens. ^{26°} = 1.240
4	C ₂ H ₅	<i>p</i> -F	1.579	47*	10.9	10.8*	22.5	22.4*	12.4	12.5*	
	C ₂ H ₅	<i>p</i> -Br	1.6252*	50-1*	8.96	9.0*	18.5	18.0			Total halogen: Calcd 5.79 meq./g, Found: 5.7*
5	C ₂ H ₅	<i>p</i> -Cl	1.612		10.3	10.4	21.2	21.8	23.5	22.8	
6	C ₂ H ₅	3,4-Cl ₂	1.614		9.23	9.4	19.1	18.7	31.7	31.4	
7	C ₂ H ₅	<i>o</i> -CH ₃	1.594		11.0	11.3	22.8	22.5	12.6	12.8	
8	C ₂ H ₅	<i>p</i> -C(CH ₃) ₃	1.577		9.6	9.7	19.8	20.0	11.0	11.0	
	CH(CH ₃) 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(CH ₃) ₂	<i>p</i> -OCH ₃	1.587		10.0	9.8	20.6	20.0	11.4	11.3	
10	CH(CH ₃) ₂	<i>p</i> -CH ₃	1.5845*	20*	10.5	10.2	21.7	21.5	12.04	11.7	
11	CH(CH ₃) ₂	<i>p</i> -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(CH ₃) ₂	<i>p</i> -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(CH ₃) ₂	<i>p</i> -Cl	1.5945*	30*	9.83	9.9	20.4	20.7	22.5	22.2	
14	CH(CH ₃) ₂	3,4-diCl	1.600	73.4*	8.86	8.8*	18.34	18.2*	30.5	29.9*	
15	CH(CH ₃) ₂	<i>o</i> -CH ₃	1.583		10.5	10.5	21.7	22.4	12.04	12.4	
16	CH(CH ₃) ₂	<i>p</i> -C(CH ₃) ₃	1.564		9.2	9.6	19.0	18.7	10.5	10.5	
	<i>n</i> -C ₃ H ₇	Intermediate	1.5100	57/0.3	14.97	14.9	15.48	15.1	34.3	33.6	Dens. ^{26°} = 1.294
17	<i>n</i> -C ₃ H ₇	<i>p</i> -OCH ₃	1.590		10.0	10.3	20.6	20.0	11.4	11.2	
18	<i>n</i> -C ₃ H ₇	<i>p</i> -CH ₃	1.585		10.5	10.7	21.7	22.2	12.04	12.5	
19	<i>n</i> -C ₃ H ₇	<i>p</i> -F	1.573		10.36	10.4	21.4	20.9	11.9	11.7	% F: Calcd 6.4 Found: 6.6
20	<i>n</i> -C ₃ H ₇	<i>p</i> -Br	1.613		8.62	8.75	17.8	18.1			Total halogen: Calcd 5.56 meq./g, Found: 5.33
21	<i>n</i> -C ₃ H ₇	<i>p</i> -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

$p\text{-R}_1\text{-C}_6\text{H}_4\text{-S-P(CH}_2\text{Cl)-OR}$									
Code	R	R ₁	Rat (mg/kg) Acute Oral LD ₅₀	LD ₅₀ For Test Organism				Two-Spotted Mites	
				Housefly μg/25 ♀	American cockroach in %	Milkweed bug in %	Salt-marsh caterpillar in %	P.E. ^a in %	Eggs in %
1	C ₂ H ₅	<i>p</i> -OCH ₃		6.2	0.1	>0.1	0.1	0.01	0.1
2	C ₂ H ₅	<i>p</i> -CH ₃	336	5.4	0.03	0.1	0.05	0.01	0.03
3	C ₂ H ₅	<i>p</i> -F		7.6	0.01	>0.1	>0.1	0.08	>0.1
4	C ₂ H ₅	<i>p</i> -Br		7	0.1	>0.1	0.08	>0.1	>0.1
5	C ₂ H ₅	<i>p</i> -Cl		8	>0.1	>0.1	0.1	0.1	0.1
6	C ₂ H ₅	3,4-diCl		10	>0.1	>0.1	0.1	0.05	0.08
7	C ₂ H ₅	<i>o</i> -CH ₃		39	>0.1	>0.1	>0.1	0.01	>0.1
8	C ₂ H ₅	<i>p</i> -C(CH ₃) ₃		13	>0.1	>0.1	>0.1	>0.1	>0.1
9	<i>i</i> -C ₃ H ₇	<i>p</i> -OCH ₃	108	10	0.07	0.03	0.01	0.01	0.1
10	<i>i</i> -C ₃ H ₇	<i>p</i> -CH ₃	204	5.7 ± 0.7	0.03	0.01	0.003	>0.1	>0.1
11	<i>i</i> -C ₃ H ₇	<i>p</i> -F	39.4	6.6	0.01	>0.1	0.001	0.008	0.1
12	<i>i</i> -C ₃ H ₇	<i>p</i> -Br	23	8	0.03	0.1	0.003	0.008	>0.05
13	<i>i</i> -C ₃ H ₇	<i>p</i> -Cl	26	5.5 ± 0.6	0.01	0.03	0.0003	0.005	0.03
14	<i>i</i> -C ₃ H ₇	3,4-diCl		10	0.1	>0.1	0.01	>0.1	>0.1
15	<i>i</i> -C ₃ H ₇	<i>o</i> -CH ₃		10	>0.1	>0.1	0.08	0.1	>0.1
16	<i>i</i> -C ₃ H ₇	<i>p</i> -C(CH ₃) ₃		12	>0.1	>0.1	0.05	0.03	0.08
17	<i>n</i> -C ₃ H ₇	<i>p</i> (OCH ₃)		10	>0.1	>0.1	0.03	0.01	0.1
18	<i>n</i> -C ₃ H ₇	<i>p</i> -CH ₃		12	0.1	0.1	0.01	>0.1	>0.1
19	<i>n</i> -C ₃ H ₇	<i>p</i> -F		6	0.1	>0.1	0.01	0.01	0.1
20	<i>n</i> -C ₃ H ₇	<i>p</i> -Br		8.2	0.1	0.1	0.05	>0.1	>0.1
21	<i>n</i> -C ₃ H ₇	<i>p</i> -Cl	191	7.8	0.1	0.1	0.003	>0.1	>0.1
Parathion			13 ^b	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

Code	Compound	LD ₅₀ For Test Organism		
		Housefly μg/25 ♀	Salt-marsh caterpillar, %	Rat acute oral LD ₅₀ (mg./kg.)
22	$p\text{-CH}_3\text{C}_6\text{H}_4\text{SP}(\text{OC}_2\text{H}_5)_2^a$	330	>0.1	316
23	$p\text{-CH}_3\text{C}_6\text{H}_4\text{SP}(\text{C}_2\text{H}_5)\text{OC}_2\text{H}_5^a$ (from Table II)	4.3	0.01	123
10	$p\text{-CH}_3\text{C}_6\text{H}_4\text{SP}(\text{CH}_2\text{Cl})\text{OCH}(\text{CH}_3)_2$	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 LC₅₀ 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 (R₁) 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 lepidopterocidal 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.

ACKNOWLEDGMENT

The authors thank Donald Bernhart and Melvin Singer for elementary analyses, G. D. Meyding for rat toxicity determinations, and M. E. Brokke and C. O. Persing for valuable suggestions.

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Received for review September 12, 1968. Accepted July 23, 1969.