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Some Phosphorothionate Imported Fire Ant Toxicants with Delayed Kill

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Twenty-one diethyl aryl phosphorothionates (2), $(EtO)_2P(=S)OC_6H_3XY$, were prepared and tested as imported fire ant (IFA) toxicants. The substituents placed on the aryl ring include bromo esters, ketones, imines, an aldehyde, an oxime, a semicarbazone, a phenylhydrazone, a trifluoromethyl, an acylhydrazone, and a benzylidene malonitrile substituent. The phosphorothionates with both a bromo and a CO_2R substituent on the phenyl ring were poorer toxicants than the corresponding phosphorothionates with a single Br or CO_2R substituent on it. Phosphorothionates 2 [X = 4-C(=O)CH₂Ph, Y = H; X = 4-C(=O)NHNH₂, Y = H] were both found to give delayed kill at 0.1% toxicant in soybean oil, while 2 (X = CF₃, Y = H) was found to be nearly as good an IFA toxicant. A QSAR study found the toxicity of 2 to be correlated with the steric parameter MR and to a lesser extent with Π and σ .

Much effort has recently been directed to finding a nonpersistent replacement for the now-banned insecticide mirex, for use in bait formulations to control the imported fire ants (IFA), *Solenopsis richteri* Forel and *Solenopsis invicta* Buren. Both traditional insecticides and other types of toxicants such as insect growth regulators (Vinson and Robeau, 1974; Banks et al., 1978), the dye Phloxin B (David and Heitz, 1978), fluoroacetyl derivatives of sterols and fatty acids (Kochansky et al., 1979), and some amidohydrazone (Williams et al., 1980) have been examined.

Of the many organophosphorus insecticides studied, most do not have the delayed action (less than 15% kill after 1 day) necessary for a bait toxicant. Several dialkyl halophenyl phosphorothionates showed good delayed kill in laboratory tests but were not effective in the field (Banks et al., 1977); some analogous alkoxy-carbonylphenyl compounds, especially those of low hydrophobicity, showed promise, but delay was inadequate (Fisher et al., 1980).

In the present study, a further range of substituents on the phenyl ring is examined, as well as disubstituted compounds, with sufficient variation in electronic, lipophilic, and steric properties to allow a quantitative structure-activity analysis.

EXPERIMENTAL SECTION

Materials and Instrumentation. Diethyl phosphorochloridothionate (Aldrich) and refined soybean oil were used as obtained commercially. Acetone was distilled over phosphorus pentoxide prior to use. IR and NMR spectra were run on a Perkin-Elmer Model 283B and a Varian A-60 spectrophotometer, respectively.

Phenols (1). The following phenols were commercially available and were used without further purification: *p*-hydroxyacetophenone; *p*-hydroxypropiofenone; *p*-hydroxybenzophenone; 4-hydroxybenzaldehyde; benzyl 4-hydroxyphenyl ketone; α,α,α -trifluoro-*p*-cresol; *p*-hydroxybenzoic acid hydrazine; *p*-hydroxybenzylidene malonitrile.

Salicylic acid and *p*-hydroxybenzoic acid were brominated by the procedure of Hewitt et al. (1904) and *m*-hydroxybenzoic acid was brominated by the method of Buchler et al. (1946) to give 5-bromosalicylic acid, 3-bromo-4-hydroxybenzoic acid, and 4-bromo-3-hydroxybenzoic acid, respectively. These three bromohydroxybenzoic acids were esterified with methanol or isopropyl alcohol in ethylene dichloride solvent and a sulfuric acid

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catalyst by the method of de Leon et al. (1966) to give isopropyl 3-bromo-4-hydroxybenzoate, methyl 3-bromo-4-hydroxybenzoate, isopropyl 5-bromo-2-hydroxybenzoate, methyl 5-bromo-2-hydroxybenzoate, and methyl 4-bromo-3-hydroxybenzoate.

p-Hydroxycaprylophenone was made by the acylation of phenol according to the procedure of Ralston et al. (1940). *p*-Hydroxyisobutyrophenone was prepared from phenyl isobutyrate by the Fries rearrangement using the procedure of Ralston et al. (1940).

p-Hydroxyacetophenone was converted into its oxime, phenylhydrazone, and semicarbazone by using a sodium acetate trihydrate catalyst in ethanol-water by a traditional procedure (Vogel, 1957).

4-Hydroxybenzaldehyde was converted to its aryl imine with *p*-fluoroaniline and *p*-toluidine by using benzene solvent in a water separator. In a like manner, *p*-hydroxyacetophenone and *p*-toluidine were converted into their corresponding imine.

All of the above phenols are either known compounds or common derivatives of known compounds. In each case, the physical properties matched those reported in the literature. The IR and NMR spectra of each phenol were consistent with its assigned structure.

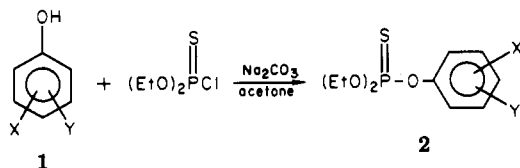
Phosphorothionates (2). The mono- and disubstituted phenols (1) were then reacted with sodium carbonate in acetone followed by overnight reflux with diethyl phosphorochloridothionate and worked up by a previously reported procedure (Fisher et al., 1980). The IR and NMR spectra of each phosphorothionate 2 were consistent with its assigned structure. Each compound 2 was obtained with less than 10% impurities as judged by the NMR spectra except for 2o, 2q, 2r, and 2u (see Table I for structures) which were obtained as more complicated mixtures that were tested as toxicants without further purification.

Toxicity Studies. The method used to determine the toxicity data of phosphorothionates 2 to the red imported fire ant was described in detail by Williams et al. (1980). Each toxicity test consisted of three replications at three concentrations, and the results of these tests are given in Table I. The method used to determine I_{50} values was given by Fisher et al. (1980).

The LD_{50} data were obtained by the following procedure. Major worker ants were strapped on their dorsal surface to clay beds, and 0.1 μ L of the toxicant in soybean oil solution was applied individually to the mandibles of each ant by using a 1- μ L Hamilton syringe. Each ant was observed under a Zeiss dissecting microscope to ensure that the solution was ingested. Following dosing, the ants were maintained at 24 °C and 70% humidity. At least 20 ants were dosed for each concentration and the kill rate was monitored daily for 10 days. Linear regression analysis (percent dose vs. probit) of the data was used to determine the LD_{50} values. Kill data of <5% and >95% were not used in these calculations.

RESULTS AND DISCUSSION

The 21 phosphorothionates (2) reported in this study were prepared from their corresponding phenols (1) by reactions with diethyl phosphorochloridothionate:



The phenols 1 include a series of 16 different substituents in the para position composed mainly of carbonyl compounds and their derivatives. The remaining phenols are disubstituted with a bromo at the 2- or 4-position and ester at the 2-, 4-, or 5-position. The ring substituents are all medium-strength electron-withdrawing groups which cause the phosphorothionates 2 to be fairly active cholinesterase inhibitors.

The phosphorothionates 2a-e each contain both a bromine atom and a $-CO_2Me$ or $-CO_2-i-Pr$ group. These compounds were prepared because both monobromo (Lofgren et al., 1967; Wojcik et al. 1973) and monoalkoxycarbonyl (Fisher et al., 1980) substituents on phosphorothionates showed good promise as IFA toxicants. Three of these compounds showed 100% kill after 14 days at 1%, but none of them showed delay. There was very little toxicity at 0.1% as expected.

The toxicities of the bromo, alkoxycarbonyl substituted phosphorothionates (Table I) are lower than those of the bromo- and alkoxycarbonyl compounds (Fisher et al., 1980) in vivo. Similarly, in an in vitro test, the molar concentration for 50% inhibition of fire ant brain AChE (I_{50}) was 1.86×10^{-7} M for *O,O*-diethyl *O-p*-(isopropoxycarbonyl)-phenyl phosphate and 2.21×10^{-7} M for *O,O*-diethyl *O*-2-bromo-4-(isopropoxycarbonyl)phenyl phosphate, indicating that the latter compound is the less active cholinesterase inhibitor.

A series of seven phosphorothionates (2f-l) with aldehyde or ketone substituents was studied where Y = H and X = 4-C(=O)R with R = H, Me, Et, Ph, CH_2Ph , *i*-Pr, or *n*- C_7H_{15} . These compounds were all found to be very active IFA toxicants with two of them (2k,l) showing 100% 1-day kill at 0.05% toxicant in soybean oil. The phosphorothionate with the phenyl ketone substituent (2f) was the least toxic of the carbonyl series, just as the phenyl ester substituted phosphorothionate was the least toxic of the ester series. Phosphorothionate 2h [Y = H, X = 4-C(=O) CH_2Ph] showed delayed kill at 0.1%.

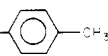
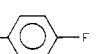
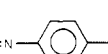
The LD_{50} values of three phosphorothionates were determined against the imported fire ant and the results are given in Table II. From the three day LD_{50} data, it is seen that the toxicant with the *p*-acetyl substituent, 2j, is approximately 5 times as toxic to the fire ant as the two toxicants with the carbalkoxy substituents. These data also show that the $-CO_2Me$ -substituted toxicant has the most delay of the three since its 7-day LD_{50} is nearly 50% smaller than its 4-day LD_{50} . The other two show much less delay.

Three phosphorothionates with imine substituents (2m-o) and three with carbonyl derivatives (2p-r) were studied. The only compound of this series with any appreciable delay (20% kill at day 1) was the one containing the semicarbazone of the acetyl group, 2p [Y = H, X = 4-C(CH_3)=NNHC(=O)NH $_2$].

Of the remaining compounds studied, the phosphorothionate with the acyl hydrazine substituent 2t [Y = H, X = 4-C(=O)NHNH $_2$] also showed delayed kill at 0.1%. The phosphorothionate 2s (Y = H, X = 4-CF $_3$) also showed delay and 85% kill after 14 days. The $-CF_3$ substituent is also present in several amidinohydrazone IFA toxicants (Williams et al., 1980) including AMDRO [tetrahydro-5,5-dimethyl-2(1*H*)-pyrimidinone, [3-[4-(trifluoromethyl)phenyl]-1-[2-[4-(trifluoromethyl)phenyl]ethenyl]-2-propenylidene]hydrazone].

In this work, 16 phosphorothionates were studied which contain only a para substituent on the aryl ring. These substituents have considerable structural variability and the toxicities of the phosphorothionates that contain them

Table I. Toxicity of Phosphorothionates 2, (EtO)₂P(=S)OC₆H₃XY, to the Imported Fire Ant (*S. invicta*)

2	X	Y	% in soybean oil	% kill after day						
				1	2	3	6	8	10	14
a	2-Br	4-CO ₂ -i-Pr	1.0	62	70	73	73	73	75	77
			0.5	67	75	75	75	77	77	78
			0.1	0	0	0	2	2	2	7
b	2-Br	4-CO ₂ Me	1.0	75	100					
			0.5	65	68	68	70	73	73	73
			0.1	0	2	2	3	5	7	10
c	4-Br	2-CO ₂ Me	1.0	100						
			0.5	68	83	88	88	88	88	88
			0.1	3	7	10	12	17	17	20
d	4-Br	2-CO ₂ -i-Pr	1.0	47	100					
			0.5	28	35	35	35	35	35	35
			0.1	0	3	3	5	7	7	8
e	2-Br	5-CO ₂ Me	1.0	17	43	45	45	47	47	47
			0.5	22	38	40	40	43	43	47
			0.1	0	0	0	0	0	5	5
f	4-C(=O)Ph	H	1.0	57	82	82	85	85	87	92
			0.1	0	0	0	2	2	5	10
			0.01	0	0	0	2	2	2	10
g	4-CHO	H	1.0	100						
			0.1	27	55	58	60	60	62	62
			0.01	0	3	3	3	3	3	5
h	4-C(=O)CH ₂ Ph	H	1.0	100						
			0.1	5	43	62	92	97	98	98
			0.01	2	3	5	7	7	8	10
i	4-C(=O)Et	H	1.0	100						
			0.1	97	100					
			0.05	68	95	97	97	97	98	98
j	4-C(=O)Me	H	1.0	100						
			0.1	100						
			0.01	0	0	0	7	17	20	30
k	4-C(=O)-i-Pr	H	1.0	100						
			0.1	78	100					
			0.05	100						
l	4-C(=O)-n-C ₇ H ₁₅	H	1.0	100						
			0.1	90	100					
			0.05	98	100					
m		H	1.0	2	2	2	2	5	5	15
			0.1	0	2	3	3	7	7	18
			0.05	0	3	5	7	12	12	17
n		H	1.0	73	97	97	97	97	97	97
			0.1	45	55	55	55	58	58	63
			0.05	0	0	0	2	3	5	5
o		H	1.0	100						
			0.1	43	62	62	67	67	67	67
			0.05	18	30	33	38	43	45	45
p	4-C(CH ₃)=NNHC(=O)NH ₂	H	1.0	100						
			0.1	20	100					
			0.01	0	0	3	5	5	5	12
q	4-C(CH ₃)=NOH	H	1.0	100						
			0.1	47	72	72	73	75	77	80
			0.01	2	2	2	3	3	7	20
r	4-C(CH ₃)=NNHPh	H	1.0	100						
			0.1	95	100					
			0.01	2	2	5	10	18	20	48
s	4-CF ₃	H	1.0	100						
			0.1	8	53	72	80	83	83	85
			0.01	0	0	0	5	5	5	5
t	4-C(=O)NHNH ₂	H	1.0	100						
			0.1	8	85	93	93	93	95	97
			0.01	2	3	3	5	7	7	7
u	4-CH=C(CN) ₂	H	1.0	100						
			0.1	52	95	95	95	97	97	97
			0.01	2	2	2	2	3	3	3
mirex (standard)			1.0	0	41	64	92	99	100	100
			0.1	0	6	21	66	78	86	97
			0.01	1	1	1	6	21	28	53
soybean oil (check)			1.0	0	0	0	0	2	3	5
			0.01	0	0	0	0	0	0	0

also show wide variability. Table III is a summary comparison of substituent and IFA mortality data at 0.1% toxicant in soybean oil. Also included in this table are the eight para-substituted esters studied earlier (Fisher et al., 1980). Enough structural variation is present in these compounds to warrant a quantitative structure-activity

relationship (QSAR) study.

STRUCTURE-ACTIVITY CORRELATIONS

Correlations of the cholinesterase-inhibitory effect of organophosphorus insecticides using the Hansch approach (Hansch and Fugita, 1964) is usually strongest with the

Table II. Fire Ant LD₅₀ Values for (EtO)₂P(=S)OPhY

Y	LD ₅₀ (4 day), mg/ant	LD ₅₀ (7 day), mg/ant
-CO ₂ Me	396	209
-CO ₂ -i-Pr	396	341
-C(=O)Me	84	62

Table III. Summary of Substituent Influences on IFA Toxicity of 0.1% (EtO)₂P(=S)OPhY in Soybean Oil

Y	% kill at 0.1%
-COPh, -CO ₂ Ph	0
-CH=NPhMe	20
-CO ₂ Oct	
-CO ₂ Et	40
-CO ₂ -i-Bu, -CO ₂ Am	
-CO ₂ Bu	60
-CHO, -CH=NPhF	
-C(Me)=NPhMe, -CO ₂ -i-Pr	80
-CO ₂ Me, -C(Me)=NOH, -CF ₃	
-C(=O)NHNH ₂ , -CH=C(CN) ₂ , -C(=O)CH ₂ Ph	100
-C(Me)=NNHC(=O)NH ₂ , -COEt, -C(Me)=NNHPh	
-C(=O)Me, -C(=O)-i-Pr, -C(=O)C ₆ H ₁₃	

electron-withdrawing power, σ , of the substituent(s) (Fukuto and Metcalf, 1956; Fukuto, 1976), but steric effects can also be important (Hansch and Deutsch, 1966; Hansch, 1970; Zerba and Fukuto, 1978).

Hydrophobic effects are not normally important for organophosphorus cholinesterase inhibitors, in contrast to carbamate esters where such effects are important. The LD₅₀ values of some phoxin-type phosphoramidates (Zerba and Fukuto, 1978) and the toxicities of a series of diethyl alkoxy carbonyl phenyl phosphorothionates (Fisher et al., 1980) have been found to be correlated with Π , the oil-water partition constant.

The substituent constants for all of the substituents used in this study were not available, but enough were known to allow a QSAR study. The parameters used in this study are given in Table IV. A good variety of substituents are included in this table including aldehyde, ketone, ester, imine, and CF₃ substituents. Molar refraction was the parameter chosen to represent the substituent steric effects because of its ready availability.

A QSAR study of the seven phosphorothionates in Table IV was done and the following two equations were found:

$$\log \% \text{ kill} = -0.032 \text{ MR} + 2.21 \quad (1)$$

$$r = 0.887 \quad s = 0.188 \quad n = 9 \quad F = 25.9$$

$$\log \% \text{ kill} = -0.019 \text{ MR} - 0.18 \Pi + 3.37 \sigma + 0.48 \quad (2)$$

$$r = 0.941 \quad s = 0.164 \quad n = 9 \quad F = 12.8$$

Each of these equations is statistically significant at the $\alpha = 0.01$ level as measured by the F values obtained from the backward elimination procedure of Draper and Smith (1966). In this study, the most important influence on the percent kill was found to be the steric parameter MR. Equation 2 is a three-parameter equation that is also statistically significant. In it, the coefficients of MR and Π are both negative while the coefficient of σ is positive, indicating that small, hydrophilic, electron-withdrawing substituents cause phosphorothionates **2** to be the most toxic imported fire ant toxicants.

Table IV. Mortality Data for 0.1% Soybean Oil Solution of (EtO)₂P(=S)OPhY and Some Substituent Parameters^a of Y

Y	log % kill	σ	Π	MR
-COPh	1.000	0.43	1.05	30.33
-CO ₂ Ph	1.230	0.44	1.46	30.14
-C(=NPhMe)H	1.255	0.42	-0.29	33.01
-CO ₂ Et	1.580	0.45	0.51	17.47
-CHO	1.792	0.42	-0.65	6.88
-CO ₂ Me	1.903	0.45	-0.01	12.87
-CF ₃	1.929	0.54	0.88	5.02
-COCH ₃	2.000	0.50	-0.55	11.18
-COCH ₂ CH ₃	2.000	0.48	0.06	15.83

^a Values of σ , Π , and MR taken from Hansch et al. (1973) and Hansch and Leo (1979).

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Registry No. **2a**, 85480-12-2; **2b**, 85506-86-1; **2c**, 85480-13-3; **2d**, 85480-14-4; **2e**, 85480-15-5; **2f**, 85480-16-6; **2g**, 85480-17-7; **2h**, 85480-26-8; **2i**, 85480-18-8; **2j**, 17027-75-7; **2k**, 85480-19-9; **2l**, 85480-20-2; **2m**, 85480-21-3; **2n**, 85480-22-4; **2o**, 85480-23-5; **2p**, 85480-24-6; **2q**, 22941-82-8; **2r**, 85480-25-7; **2s**, 41083-04-9; **2t**, 85480-27-9; **2u**, 20871-50-5.

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