toxicity (see also mosquito LC_{50} values in Tables I and II). The substantial synergism shown by pretreatment of the fly with piperonyl butoxide, especially for the unsubstituted compounds I and IV, indicates that the multifunction oxidases of the housefly play an important role in detoxication of these compounds and suggests that detoxication is hindered by 2-methyl substitution.

In summary, the results shown in Tables I and II suggest that there is little significant difference in the way in which the benzofuranyl and benzopyranyl *N*-methylcarbamates react with both mammalian and insect AChE. Toxicity for this series of carbamates to both mammal and insect is predominantly a function of the affinity or binding constant K_a for the AChE of the species and selective detoxication plays a lesser role. Improvement in the mammalian selectivity ratio for this type of compound would seem to result most logically from introduction of substituent groups which are more readily metabolized by the mammalian liver than in the insect.

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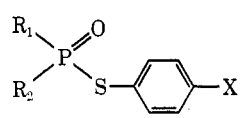
Insecticidal, Anticholinesterase, and Hydrolytic Properties of *S*-Aryl Phosphoramidothioates

James R. Sanborn and T. R. Fukuto*

The insecticidal, anticholinesterase, and hydrolytic properties for a series of *S*-phenyl phosphoramidothioates and *S*-phenyl phosphonamidothioates were examined. The compounds were moderately toxic to the housefly and were effective inhibitors of cholinesterase. Attempts to correlate cholinesterase inhibition of housefly toxicity with physical organic parameters were unsuccessful. However, an excellent linear relationship was obtained between Hammett's σ constant and alkaline hydrolysis rates of the *O*-ethyl substituted *S*-phenyl phosphoramidothioates. In addition, a kinetic study of the alkaline hydrolysis of these esters was carried out for the purpose of examining the mechanism of reaction. The results indicate that hydrolysis takes place by a direct nucleophilic attack on the phosphoryl center by hydroxide ion and the increase in hydrolytic stability with progressive nitrogen substitution can be accounted for by less favorable polar and steric effects.

Previous studies (Quistad *et al.*, 1970) in this laboratory concerning the relationship between structure, reactivity, and insecticidal activity of *O*-alkyl *S*-alkyl phosphoramidothioates revealed that several of the compounds were exceptionally toxic to the housefly, *Musca domestica*, although they were relatively weak inhibitors of fly-head acetylcholinesterase (AChE). These esters, however, produced typically cholinergic symptoms of intoxication. One of these compounds, Monitor or *O,S*-dimethyl phosphoramidothioate (Chevron Research Corp., 1967; Lorenz *et al.*, 1965), currently is undergoing evaluation as a potential insecticide.

The outstanding insecticidal properties of compounds of this type, combined with the limited amount of information available on the chemistry and mode of action of phosphoramidothioate esters, prompted us to extend our investigations to include phosphoramidothioates containing aryl moieties. This paper is concerned with the chemical, biochemical, and



A

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Table I. Physical Constants of *S*-Phenyl Phosphoramidothioates and *S*-Phenyl Phosphonamidothioates of General Structure A

	R_1	R_2	X	mp, °C	Analysis	
					Theory	Found
1	NH_2	OC_2H_5	H	81–82.5	C, 44.25 H, 5.53	C, 44.48 H, 5.61
2	NH_2	OC_2H_5	F	66	C, 40.85 H, 4.73	C, 40.93 H, 4.96
3	NH_2	OC_2H_5	Cl	88–89	C, 38.21 H, 4.81	C, 38.60 H, 4.97
4	NH_2	OC_2H_5	Br	88–90.5	C, 32.40 H, 3.74	C, 32.73 H, 3.83
5	NH_2	OC_2H_5	CH_3	65–66	C, 46.75 H, 6.06	C, 46.50 H, 6.04
6	NH_2	OC_2H_5	C_2H_5	91.5	C, 49.00 H, 6.53	C, 49.50 H, 6.44
7	NH_2	OC_2H_5	$(CH_3)_2CH$	74.5–76	C, 50.97 H, 6.95	C, 51.33 H, 7.28
8	NH_2	OC_2H_5	$(CH_3)_3C$	78–79	C, 52.70 H, 7.34	C, 52.58 H, 6.80
9	$NHCH_3$	OC_2H_5	Cl	70–71.5	C, 40.68 H, 4.90	C, 41.05 H, 5.44
10	$N(CH_3)_2$	OC_2H_5	Cl	131.5–135 (0.15 mm)	C, 42.94 H, 5.36	C, 43.53 H, 5.98
11	$NHCH_3$	CH_2CH_3	Cl	106	C, 43.29 H, 5.21	C, 43.49 H, 5.52
12	$N(CH_3)_2$	CH_2CH_3	Cl	142 (0.10 mm)	C, 45.54 H, 5.70	C, 45.11 H, 5.69

toxicological properties of *O*-ethyl *S*-aryl phosphoramidothioates and related esters of the general structure indicated (A) where R_1 is NH_2, $NHCH_3$ or $N(CH_3)_2$, and R_2 is C_2H_5 or OC_2H_5.

MATERIALS AND METHODS

O,O-Diethyl substituted *S*-phenyl phosphorothioates were prepared by established procedures from the condensation of the substituted sodium benzenethiolate with diethyl phosphorochloridate or by the reaction of triethyl phosphite with the appropriate benzenesulfonyl chloride (Morrison, 1955). The *O*-ethyl *S*-phenyl phosphorochloridothioates were prepared from the corresponding *O,O*-diethyl *S*-phenyl phosphorothioates by the action of phosphorus pentachloride according to the procedure used to convert phosphonates to phosphonochloridates (Kabachnik and Rossiiskaya, 1946). Evidently, this procedure has not been applied to phosphate or phosphonate esters containing an *S*-phenyl moiety but the reaction was quite successful, as yields up to 64% were obtained.

The *O*-ethyl *S*-phenyl phosphoramidothioates were prepared from the corresponding chloridothioates by reaction with ammonia or the appropriate amine. Typically, to 2.4 g (0.01 mol) of *O*-ethyl *S*-phenyl phosphorochloridothioate in 25 ml of dry ether was bubbled ammonia until ammonium chloride ceased to precipitate. The reaction mixture was immediately washed with water, dried, and concentrated to give the crude product, which was purified by repeated crystallization from ether–hexane. In this manner, 0.33 g of purified *O*-ethyl *S*-phenyl phosphoramidothioate, mp 81–82.5°, was obtained. Elemental analyses for the various phosphor- and phosphonamidothioates are given in Table I. Support for the indicated structures also was obtained by infrared analysis using a Perkin-Elmer Model 221 spectrophotometer and pmr analysis using a Varian Model A-60 spectrometer (TMS in deuterochloroform). Microanalyses were by C. F. Geiger, Ontario, Calif.

Bimolecular rate constants (k_i) for the inhibition of housefly-head acetylcholinesterase were determined at 37.5° by previously established procedures (Aldridge, 1950; Fukuto and Metcalf, 1956) using acetylthiocholine as the substrate (Ellman *et al.*, 1961). Triton X-100 (1%) was added to the enzyme brei after preliminary work indicated that linear pseudo-first-order plots could not be obtained with brei not containing the surfactant. Insecticidal activity was determined against a 3-day-old susceptible strain of houseflies (*Musca domestica*, S_{NAIDM} strain) according to March and Metcalf (1949) and 4th instar mosquito larvae according to Mulla *et al.* (1966).

Owing to the large difference in hydrolytic susceptibility of the various amidothioate esters, use of two different procedures for the determination of hydrolysis rates was necessary. With the less stable compounds the following procedure was used. Into two 1-cm cuvettes was placed 2.6 ml of standardized aqueous sodium hydroxide containing 10^{-5} *M* ethylenediamine tetraacetic acid (EDTA), the latter to complex any metals which might catalyze the oxidative coupling of the arylthiolate ion. Ionic strength (μ) was maintained at 1.9 using sodium chloride. The cells were placed in a thermostated cell holder in a Unicam SP-800 spectrophotometer, the temperature of the cells being maintained at 29.5 ± 0.1° by means of a Haake–Brinkman circulating bath. After thermal equilibration, 15 μl of 10^{-5} *M* solution of the test compound in acetonitrile was added, the contents were mixed, and the cuvette was tightly stoppered. All operations were carried out under nitrogen. The rate of hydrolysis was monitored by following the formation of arylthiolate ion at 263–273 nm.

Hydrolysis rates of the more stable esters were determined as follows. In a thermostated 200-ml flask equipped with magnetic stirrer and flushed with nitrogen was placed standardized sodium hydroxide containing EDTA (μ 1.9). After thermal equilibration 0.35 ml of 10^{-5} *M* solution of test compound in acetonitrile was added and the amount of arylthiolate ion formed was determined in the usual manner from aliquots taken at timed intervals.

The data obtained by these procedures gave excellent pseudo-first-order plots and the rate constants were calculated

Table II. Toxicological and Hydrolytic Properties of *S*-Phenyl Phosphoramidothioates of General Structure A

	R_1	R_2	X	Fly-head ChE $k_i \times 10^{-5}$ (M^{-1} min^{-1}) 37.5°	*Musca domestica*, LD_{50} (μg/g)	*Culex pipiens*, LC_{50} (ppm)	Second-order k_2 (M^{-1} min^{-1}) 29.5°	E_a (kcal/mol)	$\Delta S^{\pm}$ (eu)
1	NH_2	OC_2H_5	H	2.10	22.0	0.096	25.8		
2	NH_2	OC_2H_5	F	0.961	27.0	0.012	31.6		
3	NH_2	OC_2H_5	Cl	4.32	8.2	0.15	56.0	+14.0	−6.3
4	NH_2	OC_2H_5	Br	5.60	11.0	0.024	55.7		
5	NH_2	OC_2H_5	CH_3	5.27	12.5	0.044	17.3		
6	NH_2	OC_2H_5	C_2H_5	5.86	55.0	0.34	17.1		
7	NH_2	OC_2H_5	$(CH_3)_2CH$	4.37	32.0	>1.0	17.4		
8	NH_2	OC_2H_5	$(CH_3)_3C$	2.60	100.0	>1.0	16.9		
9	$NHCH_3$	OC_2H_5	Cl	0.262	13.0	0.92	1.10	+14.4	−12.8
10	$N(CH_3)_2$	OC_2H_5	Cl	0.0924	83.0	>1.0	0.00497	+15.6	−19.6
11	$NHCH_3$	C_2H_5	Cl	0.545	>500 (17)[a]	0.92	0.632	+15.5	−10.2
12	$N(CH_3)_2$	C_2H_5	Cl	*b*	75.0	0.93	0.0551	+15.7	−14.3

[a] With piperonyl butoxide 5:1 (w/w). [b] A linear pseudo-first-order inhibition rate could not be obtained.

by using a least-squares program and Olivetti Programma 101 computer. Second-order rate constants were obtained by dividing the first-order constant by the hydroxide ion concentration. Each rate constant was the result of two or three replicates and reproducibility varied from 0.2 to 5.5%. Activation parameters (E_a and $\Delta S^{\pm}$) were calculated in the usual manner from rate constants determined at three different temperatures (29.5, 36.3, 42.7 ± 0.1°).

RESULTS

Hydrolysis. Data for the alkaline hydrolysis and toxicological properties of the various *S*-aryl phosphoramidothioates and phosphonamidothioates are given in Table II. Alkaline hydrolysis rates were determined spectrophotometrically by estimating directly the amount of arylthiolate ion formed under pseudo-first-order conditions of excess sodium hydroxide. Excellent first-order plots were obtained in all cases; indicating that hydrolysis occurred essentially by P–S bond cleavage.

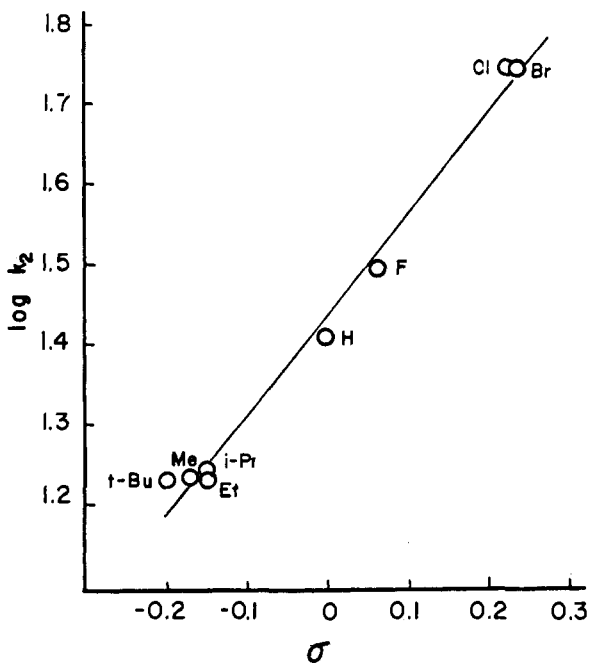


Figure 1. A plot showing the relation between Hammett's σ constant and the logarithm of the second-order constant (log k_2) for the alkaline hydrolysis of *O*-ethyl substituted *S*-phenyl phosphoramidothioates

For the various *O*-ethyl substituted *S*-phenyl phosphoramidothioates in Table II (**1**–**8**), a linear relationship was observed between the logarithm of the calculated second-order hydrolysis constants, k_2, and Hammett's σ constants derived from substituted benzoic acids. The relationship is shown in Figure 1 and, from the line fitting the data (correlation coefficient $r = 0.99$), the value of 1.27 for the reaction constant, ρ, was calculated. This value is very similar to the ρ values of 1.03 and 1.32 calculated for the hydrolysis of *O*,*O*-diethyl substituted *S*-phenyl phosphorothioates (Murdock and Hopkins, 1968) and diethyl substituted phenyl phosphates (Fukuto and Metcalf, 1956), respectively. The close similarity of ρ values in these cases suggests that the hydrolytic reaction in these three cases takes place by a common mechanism.

Comparison of **3**, **9**, and **10**, compounds of identical structure except for the number of methyl groups on the amido nitrogen, shows that sequential replacement of hydrogen by a methyl group results in marked increase in hydrolytic stability, *e.g.*, k_2 (M^{-1} min^{-1}) is 56.0 for **3**, 1.1 for **9**, and 4.97 × 10^{-3} for **10**. Similarly, the k_2 value of 0.63 for the *N*-methylphosphonamidothioate, **11**, is approximately 11-fold greater than k_2 of 0.050 for the *N*,*N*-dimethyl analog, **12**. The difference in this case, however, is much smaller than the 200-fold difference between the analogous phosphoramidothioates, **9** and **10**.

Values for the energy (E_a) and entropy ($\Delta S^{\pm}$) of activation for **3**, **9**, **10**, **11**, and **12** are given in Table II. The data show that the range in E_a for the five compounds is small (14.0–15.7 kcal/mol). In comparison, the change in $\Delta S^{\pm}$ is much more substantial, becoming uniformly more negative with each replacement of hydrogen by a methyl group. On this basis it appears that the decrease in k_2 with nitrogen substitution is caused more by steric restraints than by electronic effects.

The rate constant, k_2, for the hydrolysis of **9**, a phosphoramidothioate, is almost twofold larger than k_2 for the corresponding phosphonamidothioate, **11**. The significant but faster rate of hydrolysis of **9** compared to **11** was unexpected, since phosphonate esters generally are less stable to alkali than phosphate esters (Kirby and Warren, 1967). From the values of E_a and $\Delta S^{\pm}$ for **9** and **11**, the free energy of activation $\Delta F^{\pm}$ was calculated to be 17.8 and 18.1 kcal/mol, respectively, values which are consistent with the second-order hydrolysis constants (k_2).

Cholinesterase Inhibition and Toxicity. The data in Table II for anticholinesterase activity show that all of the primary phosphoramidothioates (**1**–**8**) are moderately strong inhibitors

of fly-head cholinesterase with k_i values (M^{-1} min^{-1}) ranging from approximately 1×10^5 to 5.9×10^5. Attempts to correlate rates of cholinesterase inhibition with k_2 or any of the free energy parameters for ring substituents (σ, π, π^2), or combination of these parameters, proved to be unfruitful. The failure to obtain a suitable relationship between k_i and the various parameters was disappointing, since an excellent correlation between k_i and a combination of π and hydrolysis rates previously was demonstrated (Neely and Whitney, 1968) for a series of methyl substituted phenyl *N*-methylphosphoramidates.

Progressive substitution of the hydrogens on the amido nitrogen by a methyl group resulted in expected decrease in anticholinesterase activity (compare **3**, **9**, and **10**). Within this limited series of compounds a reasonably good linear relationship was obtained between log k_i and log k_2, indicating that anticholinesterase activity is primarily a function of the reactivity of the ester. A similar relationship was demonstrated earlier with a larger series of 2,4,5-trichlorophenyl *O*-methyl phosphoramidates (Fukuto *et al.*, 1963; Hansch and Deutsch, 1966).

A k_i value for *S*-*p*-chlorophenyl *N*,*N*-dimethyl-*P*-ethylphosphonamidothioate (**12**) could not be obtained since the first-order plot of log $[A_0]/[A_t]$ *vs.* time t, where A_0 and A_t represent the activity of the enzyme at time zero and t, was curvalinear, *i.e.*, the rate of inhibition did not increase in a logarithmic manner with time. A curved relationship was not attributable to impurities since the same curve also was obtained after allowing **12** to stand for 24 hr in phosphate buffer (pH 7.6) prior to measurement of inhibition rates. This procedure has been used to destroy small amounts of anticholinesterase impurities which may be present in preparations of organophosphorus esters (Aldridge and Davison, 1952).

The primary phosphoramidothioates (**1**–**8**) in Table II showed wide variability in their toxicity to houseflies compared to their activity as anticholinesterases. In general, these esters were substantially less toxic than the primary *O*,*S*-dialkyl phosphoramidothioates reported earlier (Quistad *et al.*, 1970). For example, *O*,*S*-dimethyl phosphoramidothioate (Monitor) with an LD_{50} to houseflies of 1.3 μg/g is approximately sixfold more effective than *O*-ethyl *S*-*p*-chlorophenyl phosphoramidothioate (**3**), the most toxic compound in this series. Compared to Monitor ($k_i = 9.2 \times 10^2$ M^{-1} min^{-1}), however, **3** is about 450-fold more effective in inhibiting fly-head cholinesterase. It appears that anticholinesterase activity is not a useful guide for the prediction of the insecticidal activity of phosphoramidothioates.

As in the case of cholinesterase inhibition, progressive replacement of hydrogens on the amido nitrogen by methyl groups resulted in a decrease in housefly toxicity. For example, the housefly LD_{50} (μg/g) of the primary amidate (**3**) was 8.2, the monomethylamidate (**9**) was 13, and dimethylamidate was 83. The effect of sequential methyl substitution on the reduction of toxicity, however, is much less in comparison to the *O*,*S*-dialkyl phosphoramidothioate analogs, *e.g.*, the toxicity of the *N*-methyl derivative of Monitor to houseflies (LD_{50}, μg/g) was 49 and of *N*,*N*-dimethyl was >500.

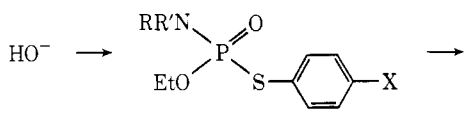
The virtual absence of toxicity demonstrated by *S*-*p*-chlorophenyl *N*-methyl-*P*-ethylphosphonamidothioate (**11**) toward houseflies (LD_{50} >500 μg/g) was surprising since measurable toxicity was found for the corresponding *N*,*N*-dimethyl analog (LD_{50} 75 μg/g). Unfortunately, comparison with the primary phosphonamidothioate was not possible since all attempts to synthesize this compound were unsuccessful. Further, the corresponding *N*-methylphosphoramidothioate analog (**9**) with k_i and k_2 values similar to those of **11** also was quite toxic to flies. The toxicity of **11**, however, was pronouncedly synergized when applied together with 5:1 parts piperonyl butoxide (LD_{50} 17 μg/g). The level of synergism of this magnitude, although quite common for methylcarbamate esters (Metcalf, 1967), is unusual for organophosphorus esters and suggests that **11**, for some reason, is peculiarly susceptible to oxidative detoxication.

In limited studies using the white mouse, an LD_{50} value of 5–8 mg/kg was obtained for **3**. This compound, therefore, is approximately of equal toxicity to houseflies and mice.

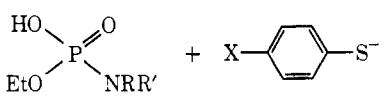
DISCUSSION

Considerable effort has been given to the study of the alkaline hydrolysis of phosphoramidate esters (Heath, 1956; Traylor and Westheimer, 1965; Gerrard and Hamer, 1967, 1968, 1969). In past studies major emphasis has been placed on the effect of alkyl substitution on the amido nitrogen and relatively little has been done on the influence of ring substituents on reactivity. The hydrolysis of a limited number of ring-substituted methyl phenyl *N*-methylphosphoramidates has been examined (Neely and Whitney, 1969) but attempts to assess substituent effects were unsatisfactory owing to poor correlation between hydrolysis rates and reactivity parameters.

The excellent correlation obtained between σ and log k_2 for the primary phosphoramidothioates (**1**–**8**), combined with the similarity in the magnitude of ρ calculated for this series and for substituted phenyl diethyl phosphates and phosphorothioates, indicates that substituent effects are transmitted from the ring to the phosphorus atom with equal facility through sulfur and oxygen. The alkaline hydrolysis of diethyl phenyl phosphates and diethyl *S*-phenyl phosphorothioates undoubtedly takes place by nucleophilic attack of hydroxide ion on the phosphoryl center (Cox and Ramsay, 1964). In light of the similarity in ρ values for the three series of esters, it appears that *S*-phenyl phosphoramidothioates also hydrolyze by a direct displacement reaction on phosphorus, as shown below.



R, R′ = methyl or hydrogen



The values for E_a and $\Delta S^{\pm}$ for **3**, **9**, and **10**, and for **11** and **12** also are consistent with a direct displacement mechanism. As indicated earlier, there is a small but significant increase in E_a, accompanied by a larger but uniform decrease in $\Delta S^{\pm}$ with each replacement of hydrogen by a methyl group. The decrease in k_2, therefore, can be accounted for primarily on the basis of polar and steric effects created by each succeeding methyl group. Support for this contention is found in Figure 2, where the relation between log k_2 for **3**, **9**, and **10** and the sum of Taft's (1956) polar (σ^*) and steric (E_s) substituent constants for NH_2, $NHCH_3$ and $N(CH_3)_2$ is given. The very good linear relationship observed provides evidence that **3**, **9**, and **10** all hydrolyze by the same mechanism and that the rate of hydrolysis is altered mainly by polar and steric effects created by the additional methyl groups.

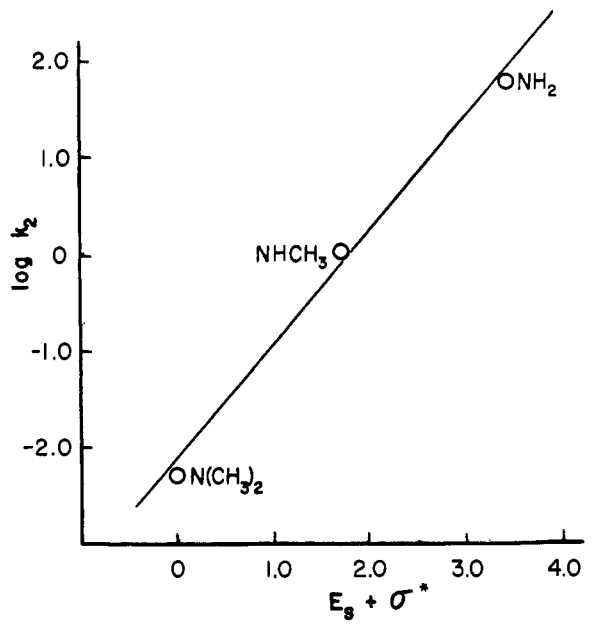
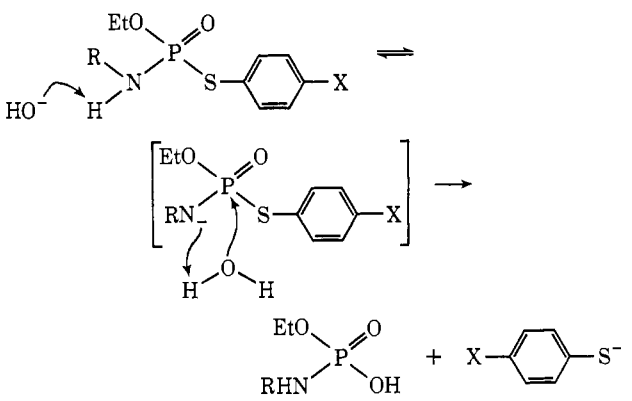


Figure 2. A plot showing the relation between the sum of Taft's polar (σ^*) + steric (E_s) substituent constant and the second-order constant (log k_2) for the alkaline hydrolysis of *O*-ethyl *S*-*p*-chlorophenyl *N*-substituted phosphoramidothioates

Another mechanism for the hydrolytic reaction may be suggested which is analogous to the one proposed by Gerrard and Hamer (1967) for the hydrolysis of *O*-methyl *O*-*p*-nitrophenyl *N*-cyclohexylphosphoramidothioate (**13**). This mechanism was suggested to explain kinetic and stereochemical results obtained from the study of **13** and may be applied to the *S*-phenyl phosphoramidothioates as shown below.



Obviously, this mechanism cannot apply to **10**, the *N,N*-dimethyl derivative, where a proton is not present on the amido nitrogen. Although this mechanism is useful in explaining the much faster rate of hydrolysis of **3** and **9** compared to **10**, it is not consistent with the linear relationship obtained for log k_2 and (σ^* + E_s) since this correlation includes the *N,N*-dimethyl derivative **10**.

k_2 for the hydrolysis of **11**, the *N*-methylphosphonamidothioate, is only 11-fold larger than k_2 for the *N,N*-dimethylphosphonamidothioate **12**. The reduction in k_2 is small compared to that found for other *N*-mono- and *N,N*-disubstituted phosphoramidates (Gerrard and Hamer, 1967; Traylor and Westheimer, 1965) and is readily explainable on the basis of a displacement reaction on phosphorus in which polar and steric effects from the second methyl group reduce the rate.

It is apparent from the toxicological data that the insecticidal activity of the various phosphoramidothioates and phosphonamidothioates in Table II can not be anticipated from the structure nor from any of the reactivity parameters. *S*-Aryl phosphoramidothioates generally are less toxic to insects than the simple *S*-alkyl phosphoramidothioates, although they are substantially more effective as anticholinesterases. However, because of the unpredictable variability in their insecticidal activity, other esters of related structure deserve to be examined.

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