Insecticidal Properties of Some Diethyl Nitronaphthyl Phosphates

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The complete series of diethyl mononitro-1-naphthyl and mononitro-2-naphthyl phosphates, and a number of diethyl dinitronaphthyl phosphates, were synthesized and examined for hydrolysis rates, fly-brain cholinesterase inhibition, and toxicity to houseflies. The effect of the nitro group in the various available positions in the naphthalene nucleus on the general reactivity of the phosphorus atom was assessed, and a correlation between hydrolysis constants and σ-constants derived from three different sources was made. Some of the compounds are exceptionally strong inhibitors of fly-brain cholinesterase. Toxicity to houseflies did not parallel anticholinesterase activity, indicating wide variability in the rates of in vivo detoxification of these compounds. Diethyl 6-nitro-2-naphthyl phosphate showed the highest toxicity to houseflies and is comparable in activity to paraoxon.

INHIBITION of the cholinesterase enzymes by certain organophosphorus compounds is the result of a chemical reaction between the enzyme and phosphorus compound. This reaction has been shown to be bimolecular (*1*), the rate of reaction being dependent on the reactivity of the phosphorus atom. An earlier report from this laboratory pointed out the relationship between fly-head cholinesterase inactivation by a series of diethyl-substituted phenyl phosphates and the lability of the P–O–phenyl bond as estimated by Hammett's σ-constants, shifts in P–O-phenyl stretching frequencies, and hydrolysis rates (*8*). The effect of different substituents in the meta and para positions of the phenyl nucleus on the general reactivity of the molecule was assessed.

Recently, the complete series of mononitro-1-naphthols and mononitro-2-naphthols were made available to the authors. Aside from a brief statement by Schrader (*13*) that he had examined the naphthalene analog of parathion, the authors could find no published information on the biological and chemical properties of phosphorus esters of substituted naphthols. The examination of the properties of the mononitro-1-naphthyl and mononitro-2-naphthyl diethyl phosphates was of interest for several reasons. Since the nitro substituent was the strongest activating group in the diethyl-substituted phenyl phosphate series, it was of interest to see if phosphorus esters prepared from nitronaphthols would show similar biochemical and toxicological properties. Also, since the various nitronaphthoxide ions absorb in the visible region, the hydrolysis rates of the nitronaphthyl phosphates can be readily determined spectrophotometrically. Thus, from this study it should be possible to assess the effect of the nitro group in the various available positions

Table I. Physical Constants of Diethyl Mono- and Dinitronaphthyl Phosphates

	Diethyl Phosphate of Nitronaphthol	M.P. of Nitronaphthol, °C.	M. P., °C.	Analyses, % Calcd.	Found
I	2-NO_2-1-OH	126–127	22–23	C 51.68[a] H 4.89	C 51.62 H 4.89
II	3-NO_2-1-OH	165–166	82–85	...	C 52.09 H 5.39
III	4-NO_2-1-OH	162–163	37–40	...	C 51.67 H 5.18
IV	5-NO_2-1-OH	165–167	36–37	...	C 51.73 H 5.12
V	6-NO_2-1-OH	173–176	66–68	...	C 52.00 H 5.31
VI	7-NO_2-1-OH	205–210	57–59	...	C 51.28 H 4.98
VII	8-NO_2-1-OH	125–128	42–45	...	C 51.49 H 4.96
VIII	1-NO_2-2-OH	95–100	150° (0.2mm.)[b]	...	C 50.54 H 5.41
IX	3-NO_2-2-OH	100–102	160° (0.2mm.)[b]	...	C 50.66 H 5.06
X	4-NO_2-2-OH[c]	114–117	37–39	...	
XI	5-NO_2-2-OH	141–143	180–184 (0.1mm.)	...	C 51.70 H 5.58
XII	6-NO_2-2-OH	152–154	81–82	...	C 51.25 H 5.79
XIII	7-NO_2-2-OH[c]	155–159	40–41	...	
XIV	8-NO_2-2-OH	135–139	57–59	...	C 52.03 H 5.80
XV	2,4-NO_2-1-OH	129–132	88–92	C 45.37[d] H 4.08	C 45.03 H 4.08
XVI	4,5-NO_2-1-OH	183–185	90–94	...	C 45.39 H 4.07
XVII	4,6-NO_2-1-OH	207–210	84–85	...	C 45.12 H 4.59
XVIII	4,8 NO_2-1-OH	214–216	69–71	...	C 45.40 H 4.44
XIX	1,3-NO_2-2-OH	186–187	118–120	...	C 45.63 H 4.80
XX	1,6-NO_2-2-OH	188–189	110–113	...	C 45.65 H 4.34
XXI	1,8-NO_2-2-OH	175–178	104–105	...	C 45.07 H 4.17
XXII	3,8-NO_2-2-OH	182–183	72–75	...	C 45.62 H 4.81

[a] Per cent carbon and hydrogen same for all mononitronaphthyl phosphates.
[b] Distilled in falling-film molecular still.
[c] This compound left a dark residue upon combustion, and a satisfactory analysis could not be obtained.
[d] Per cent carbon and hydrogen same for all dinitronaphthyl phosphates.

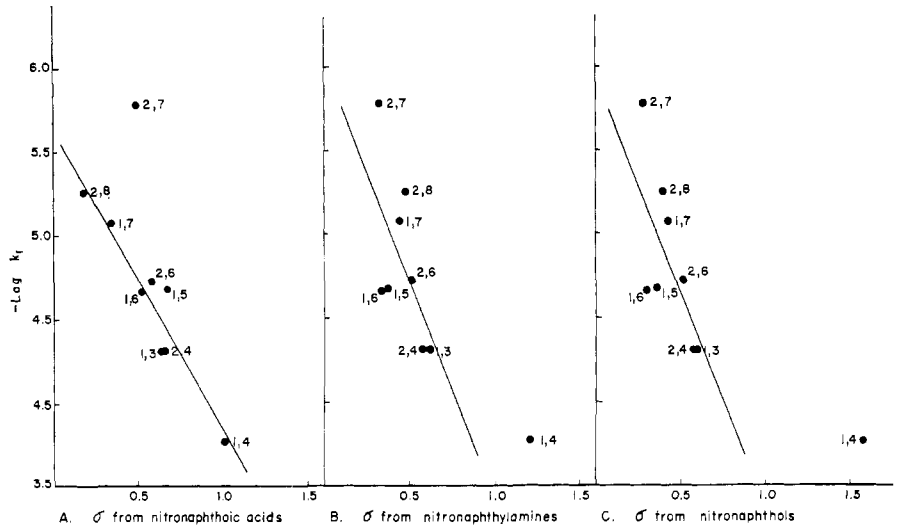


Figure 1. Relationship between logarithm of the hydrolysis constants (k_1) in 1/15M disodium hydrogen phosphate and sigma values calculated from ionization constants of nitronaphthoic acids, nitronaphthylamines, and nitronaphthols

in the naphthalene nucleus on the general reactivity of the molecule by examination of hydrolysis and cholinesterase inhibition rates, and toxicity to insects.

Materials and Methods

All nitronaphthols were provided through the kindness of Julius Hyman, Fundamental Research Corp., Berkeley, Calif., and were used without further purification.

Diethyl Nitronaphthyl Phosphates. These compounds were all prepared in the same manner. A known quantity of the nitronaphthol was converted to its sodium salt by adding an equivalent amount of sodium hydroxide from a standardized methanol solution. Excess methanol was removed, and the dry sodium salt was covered with toluene in a three-necked flask equipped with stirrer and distilling head. The toluene was distilled until the distillate was clear of moisture. To the cooled contents in the flask was added slightly less than the equivalent amount of diethyl phosphorochloridate. The reaction mixture was then stirred, heated when necessary, until the reaction was completed. The mixture was filtered through Celite, the filtrate concentrated under vacuum, and the product was crystallized from Skellysolve B or distilled in the falling-film molecular still. The physical properties of the phosphate esters and the melting points of the starting nitronaphthols are given in Table I.

***O,O*-Diethyl *O*-6-Nitro-2-naphthyl Phosphorothioate.** This compound was prepared in the usual manner from the sodium salt of 6-nitro-2-naphthol and *O,O*-diethyl phosphorothiochloridate. The compound was recrystallized from Skellysolve B, m.p. 51°–52.5° C., elemental analysis, per cent calculated for $C_{14}H_{16}NO_5PS$, C 49.27, H 4.72; found C 49.05, H 5.38.

The methods used to determine first-order rates of hydrolysis (k_1,k_2) in 1/15*M* disodium hydrogen phosphate and 1/15*M* trisodium phosphate, and second-order rates of reaction with fly-brain cholinesterase (K_e) have been described previously (*7*). All nitronaphthols and the corresponding diethyl phosphate esters were examined in the Beckman DK-2 recording spectrophotometer prior to hydrolysis rate measurements to show that overlaps in pertinent absorption peaks were not present. The hydrolysis of diethyl 5-nitro-2-naphthyl phosphate could not be followed as a result of overlap in peaks.

The technique for determination of contact toxicity (LD_{50}) to the common housefly has been described previously (*11*).

Elemental analyses were carried out by C. F. Geiger, Ontario, Calif.

Results and Discussion

Hydrolysis rates of the diethyl nitronaphthyl phosphates were determined in two buffer systems—1/15*M* disodium hydrogen phosphate (pH 8.5) and 1/15*M* trisodium phosphate (pH 11.8). The calculated first-order hydrolysis constants in disodium hydrogen phosphate (k_1) and in trisodium phosphate (k_2) are given in Table II. In both the nitro-1-naphthyl and nitro-2-naphthyl series, k_1 and k_2 were greater for the homonuclear (nitro group in same ring as diethyl phosphoryloxy group) than the heteronuclear compounds. The effect of the homonuclear nitro group on hydrolytic cleavage of P—O—naphthyl bond is similar in magnitude as found with diethyl nitrophenyl phosphates where both mesomeric and inductive effects are operating. The activating effect by the heteronuclear nitro group is much smaller and is probably mainly inductive. Compounds in which quinonoid contributions between the two groups are possible are generally more reactive.

In general, the effect of the group on hydrolysis rates were consistent with expected values predicted from the ionization constants of nitronaphthols (*15*), nitronaphthylamines (*5*), and nitronaphthoic acids (*3*). Several recent reports have dealt with the effect of substituents in substituted naphthalenes, and σ-constants of nitro groups on naphthalene have been reported for nitronaphthols (*15*), nitronaphthylamines (*5, 6*), and nitronaphthoic acids (*3, 6*). σ-Constants obtained from these three sources show that a number of discrepancies exist in the σ-values. Because of contributions from mutual conjugation between the nitro group and the hydroxyl or amino group, σ-constants obtained from nitronaphthols and nitronaphthylamines are expected to be similar but different from σ-constants obtained from nitronaphthoic acids. This is indeed the case since the only serious discrepancy in the σ-constants for nitro in nitronaphthylamines and nitronaphthols is in the value obtained from the 1,4-isomer. On the other hand, σ-constants obtained from nitronaphthoic acids differ markedly from those obtained from the corresponding naphthylamine and naphthols in several instances. The discrepancies in σ-values are shown graphically in Figure 1, in which plots of the negative logarithm of the hydrolysis constant in disodium hydrogen phosphate (k_1) against σ-constants obtained from the ionization of nitronaphthoic acids (*A*), nitronaphthylamines (*B*), and nitronaphthols (*C*) are presented. In each plot, there is a single serious deviation from a linear relationship—for 7-nitro-2-naphthyl phosphate in *A*, and 4-nitro-1-naphthyl phosphate in *B* and *C*. It is difficult to decide which set of σ-constants better fits these hydrolysis data. The σ-values obtained from the ionization constants of 4-nitronaphthol and 4-nitronaphthylamine may be abnormally high due to mutual conjugation—an effect which should not be as strong in the 4-nitronaphthyl diethyl phosphate. Since the deviation of the 7-nitro-2-naphthyl phosphate in *A* cannot be reasonably explained, σ-constants from either nitronaphthylamines or nitronaphthols may be preferred. The straight lines presented in *A*, *B*, and *C* were determined by the method of least squares in which the 2,7-point was omitted in *A*, and 1,4-point omitted in *B* and *C*. The calculated ρ values are 1.81 for *A*, 2.86 for *B*, and 2.92 for *C*.

Of some interest are the greater values of k_1 and k_2 of diethyl 1-nitro-2-naphthyl phosphate (VIII) compared to diethyl

Table II. Hydrolysis Constants

Compound	K_1, 37.5° C. (Min.$^{-1}$)	K_2, 37.5° C. (Min.$^{-1}$)	$K_e \times 10^{-6}$ 37.5° C. L.Mole^{-1} (Min.$^{-1}$)	LD_{50}, ♀ Fly, μg. per Gram
I	2.43×10^{-4}	1.02×10^{-1}	0.024	>500
II	4.92×10^{-5}	4.48×10^{-2}	0.71	>500
III	1.68×10^{-4}	6.00×10^{-2}	5.8	20
IV	2.15×10^{-5}	4.01×10^{-2}	0.48	>500
V	2.20×10^{-5}	2.36×10^{-2}	0.25	250
VI	8.73×10^{-6}	8.67×10^{-3}	0.16	325
VII	2.18×10^{-5}	1.67×10^{-2}	0.34	>500
VIII	4.73×10^{-4}	1.83×10^{-1}	82	22.5
IX	8.68×10^{-5}	3.16×10^{-2}	3.2	85
X	5.20×10^{-5}	2.96×10^{-2}	10	55
XI	...	...	1.7	42.5
XII	1.89×10^{-5}	1.22×10^{-2}	1.4	2.5
XIII	1.65×10^{-6}	3.61×10^{-3}	0.41	15.5
XIV	5.45×10^{-6}	6.05×10^{-3}	2.7	500
XV	1.83×10^{-2}	...	1.3	>500
XVI	1.02×10^{-3}	...	5.2	>500
XVII	1.09×10^{-3}	...	11	>500
XVIII	1.35×10^{-3}	...	0.46	>500
XIX	1.85×10^{-2}	...	0.52	>500
XX	2.49×10^{-3}	...	11	>500
XXI	4.09×10^{-3}	...	34	>500
XXII	6.25×10^{-4}	...	25	>500

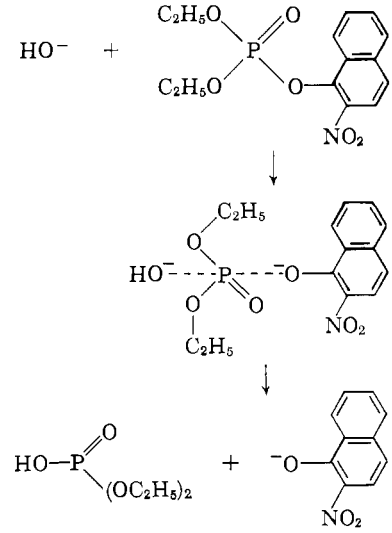
Table III. Rate Constants and Energies and Entropies of Activation

Compound	Temp., °C.	K_1 (Min^{-1})	K_2 (Min.$^{-1}$)	K_e (L. Mole^{-1} Min.$^{-1}$)
I	47.7	6.72×10^{-4}	2.39×10^{-1}	...
	37.5	2.43×10^{-4}	1.02×10^{-1}	3.3×10^{4}
	30.0	1.13×10^{-4}	5.90×10^{-2}	3.2×10^{4}
	23.0	...	...	1.3×10^{4}
	ΔEa 24.0 kcal./mole		ΔEa 16.3 kcal./mole	ΔEa 17 kcal./mole
	$\Delta S^{\ddagger}$ −8.0 e.u.		$\Delta S^{\ddagger}$ −20.9 e.u.	$\Delta S^{\ddagger}$ 5.4 e.u.
III	47.7	4.42×10^{-4}	1.07×10^{-1}	...
	37.5	1.68×10^{-4}	6.00×10^{-2}	2.8×10^{6}
	30.0	7.45×10^{-5}	3.47×10^{-2}	1.4×10^{6}
	23.0	...	...	7.1×10^{5}
	ΔEa 25.3 kcal./mole		ΔEa 13.2 kcal./mole	ΔEa 18 kcal./mole
	$\Delta S^{\ddagger}$ −4.6 e.u.		$\Delta S^{\ddagger}$ −31.9 e.u.	$\Delta S^{\ddagger}$ 18 e.u.
VIII	47.7	1.34×10^{-3}	3.59×10^{-1}	...
	37.5	4.73×10^{-4}	1.83×10^{-1}	4.2×10^{7}
	30.0	2.18×10^{-4}	1.09×10^{-1}	2.4×10^{7}
	23.0	...	...	1.2×10^{7}
	ΔEa 19.9 kcal./mole		ΔEa 13.7 kcal./mole	ΔEa 16 kcal./mole
	$\Delta S^{\ddagger}$ −19.9 e.u.		$\Delta S^{\ddagger}$ −29.0 e.u.	$\Delta S^{\ddagger}$ 18 e.u.
X	47.7	1.42×10^{-4}	5.91×10^{-2}	...
	37.5	5.20×10^{-5}	2.73×10^{-2}	1.0×10^{7}
	30.0	2.36×10^{-5}	1.45×10^{-2}	1.9×10^{6}
	23.0	...	...	5.4×10^{5}
	ΔEa 19.8 kcal./mole		ΔEa 14.5 kcal./mole	ΔEa 37 kcal./mole
	$\Delta S^{\ddagger}$ −24.7 e.u.		$\Delta S^{\ddagger}$ −34.5 e.u.	$\Delta S^{\ddagger}$ 82 e.u.
XII	47.7	5.55×10^{-5}	2.91×10^{-2}	...
	37.5	1.89×10^{-5}	1.22×10^{-2}	1.4×10^{6}
	30.0	6.72×10^{-6}	7.06×10^{-3}	6.7×10^{5}
	23.0	...	...	2.9×10^{5}
	ΔEa 22.5 kcal./mole		ΔEa 13.7 kcal./mole	ΔEa 20 kcal./mole
	$\Delta S^{\ddagger}$ −18.0 e.u.		$\Delta S^{\ddagger}$ −34.9 e.u.	$\Delta S^{\ddagger}$ 24 e.u.

3-nitro-2-naphthyl phosphate (IX), the former hydrolyzing approximately six times faster. These values provide further evidence of the notable difference between the C_1—C_2 and the C_2—C_3 bonds in naphthalene and indicate that the C_1—C_2 bond has considerably more double bond character than the C_2—C_3 bond, permitting mesomeric effects to operate (*12*).

Hydrolysis rates for 2-nitro-1-naphthyl (I), 4-nitro-1-naphthyl (III), 1-nitro-2-naphthyl (VIII), 4-nitro-2-naphthyl (X), and 6-nitro-2-naphthyl (XII) diethyl phosphates were determined at different temperatures. The values of the rate constants and energies and entropies of activation are given in Table III. The activation energies calculated from hydrolysis constants determined in disodium hydrogen phosphate (k_1) and trisodium phosphate (k_2) are consistently different enough to conclude that the k_1 values actually represent solvolysis or noncatalyzed hydrolysis constants, while k_2 values are constants for hydroxide ion hydrolysis. Similar differences in activation energies have been reported by Bruice and Schmir (*4*) for the aqueous hydrolysis (phosphate buffer pH 8.0) and hydroxide ion catalyzed hydrolysis of *p*-nitrophenyl acetate.

The entropies of activation indicate that hydrolysis rates are not greatly influenced by steric factors. In fact, diethyl 2-nitro-1-naphthyl phosphate (I) in which the nitro group and second aromatic ring are just adjacent to the phosphate moiety had a greater $\Delta S^{\ddagger}$ value than all compounds in trisodium phosphate and all except diethyl 4-nitronaphthyl phosphate (III) in disodium hydrogen phosphate. That ortho substituents do not interfere with hydrolysis is not surprising if one considers that P—O—naphthyl bond split occurs by nucleophilic attack of hydroxide ion or a water molecule on the phosphorus atom as depicted below.



Interference by substituents in the naphthalene ring should not be expected if the nucleophile approaches the phosphorus atom from the side opposite the nitronaphthyl moiety. Work with optically active phosphorus compounds has indicated that the phosphorus atom undergoes inversion in reactions of this type (*9*), and the data here add support to a concerted mechanism.

Most of the compounds listed in Table II strongly inhibited fly-brain cholinesterase as shown by the second-order inhibition constants (K_e). Diethyl 1-nitro-2-naphthyl phosphate (VIII) was, by far, the most potent inhibitor. Among the mononitronaphthyl phosphates, the homonuclear-substituted compounds were generally better inhibitors than the heteronuclear compounds, and the 2-naphthyl phosphates were generally better than the 1-naphthyl phosphates. Unlike the hydrolysis reaction, the inhibition of the cholinesterase enzyme appears to be influenced by steric factors. The very low K_e value for diethyl 2-nitro-1-naphthyl phosphate (I) must be due to steric interference by the ortho nitro and second aromatic ring. The activation energy for cholinesterase inhibition by I (Table III) is comparable to diethyl 4-nitro-1-naphthyl (III) or 1-nitro-2-naphthyl (VIII) phosphate and its low rate of reaction with cholinesterase must be attributed to its low $\Delta S^{\ddagger}$ value. Although enzyme inhibition occurs by nucleophilic attack of a functional group in the enzyme (serine hydroxyl or imidazole nitrogen) on the phosphorus atom resulting in a phosphorylated enzyme,

steric inhibition may be due to the bulkiness of the enzyme molecule. Electric eel cholinesterase is reported to have a molecular weight of approximately three million (*10*). Since VIII with a nitro group ortho to the phosphorus moiety showed the highest anticholinesterase activity, and since the 1-naphthyl series was generally lower in activity than the 2-naphthyl series, the bulk of the interference may be due to the adjacent second aromatic ring.

Evidence for the enhancement of cholinesterase inhibition by steric effects is also evident in the high activity of diethyl 4-nitro-2-naphthyl phosphate (X). Table III shows that this compound has an unusually high energy of activation and, therefore, less reactive ester linkage. Its high K_t value at 37.5° C. must then be attributed to steric attraction as is evident by high $\Delta S^{\ddagger}$ value. It is possible that the nitro group meta to the diethyl phosphoryloxy moiety facilitates inhibition by binding to the enzyme surface prior to phosphorylation.

Hydrolysis and biological data for a number of diethyl dinitronaphthyl phosphates are also included in Table I. These were considerably less stable to aqueous hydrolysis than the mononitro compounds. The higher reactivity of the P—O—naphthyl bond here is also reflected in their higher rates of cholinesterase inhibition. The data in Table I showed no obvious correlation between hydrolysis and inhibition rates, however. None of the dinitro compounds showed any toxicity to the female housefly. This is to be expected in view of the instability of these compounds in water, and they are probably hydrolyzed before reaching any vital center.

The extremely wide variability in toxicity of the diethyl mononitronaphthyl phosphates was surprising and unexpected. The LD_{50} values in μg. per gram to the female housefly ranged from 2.5 to >500. The data in Table II show that there is no direct correlation between toxicity and anticholinesterase activity. The most toxic compound in the series is the 6-nitro-2-naphthyl phosphate (XII), a moderate cholinesterase inhibitor. The 2-naphthyl phosphates were generally more toxic than the 1-naphthyl phosphates. Although compounds in the 2-naphthyl series were generally better cholinesterase inhibitors than those in the 1-naphthyl series, it is unlikely that the large differences in toxicity can be accounted for by differences in anticholinesterase activity alone. Because of the consistently higher toxicity of compounds in the 2-naphthyl series, these are apparently detoxified at a slower rate than those in the 1-naphthyl series. Terriere *et al.* (*2, 14*) have shown that both naphthalene and 1-naphthol rapidly converted via hydroxylation to a number of metabolites in house flies.

The outstanding toxicity of XII warranted further investigation, and the corresponding phosphorothionate analog was synthesized and examined for toxicity since in many instances the thionate esters show superior insecticidal properties than the corresponding phosphates. *O,O*-Diethyl 6-nitro-2-naphthyl phosphorothioate was slightly less toxic to houseflies than XII with an LD_{50} of 4.5 μg. per gram, but is toxic enough to deserve further attention as a potential insecticide.

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INSECTICIDE ACTIVITY AND STRUCTURE

Para-Substituted *Meta*-Xylenyl Diethyl Phosphates and *N*-Methylcarbamates as Anticholinesterases and Insecticides

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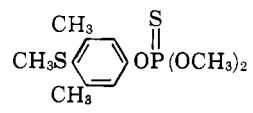
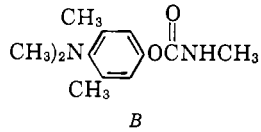
Previous studies from this laboratory have sought to account quantitatively for the wide variation in insecticidal activity exhibited by a variety of monosubstituted phenyl diethyl phosphates. This has been related to the electron density about the reactive phosphorus atom which undergoes a bimolecular reaction with cholinesterase enzyme (*7, 14*). The insecticidal and anticholinesterase activity of the monosubstituted phenyl *N*-methylcarbamates has also been investigated (*12, 13, 16*). However, these carbamates are competitive rather than irreversible inhibitors of cholinesterase, and steric factors play a dominant role in determining their activity. Nevertheless, the electronic properties of the molecule as influenced by various substituent groups have an important effect on activity by influencing the electron density around the carbonyl carbon and thus affecting hydrolytic stability and turnover number with the enzyme.

More recently, the importance of ring alkylation in producing compounds with especially useful and unique insecticidal properties, has been demonstrated with both dialkyl phosphates and *N*-methylcarbamates of various phenols. Examples are *O,O*-dimethyl *O*-4-methylthio - 3,5 - xylenyl phosphorothionate (Compound 37342, Farbenfabriken Bayer) (*A*) and 4-dimethylamino-3,5-xylenyl *N*-methylcarbamate (Zectran, Trademark, Dow Chemical Co.) (*B*).



A



B

Therefore the anticholinesterase activity and insecticidal action of the diethyl phosphates and *N*-methylcarbamates of a series of 4-substituted xylenols were investigated. The influence of the *m*-methyl groups upon the resonance of