STUDIES IN ORGANOPHOSPHORUS CHEMISTRY

A Thesis

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Doctor of Philosophy

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University of St. Andrews

by

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St. Salvator's College,
St. Andrews.
I declare that this thesis is my own composition, that the work of which it is a record has been carried out by myself, and that it has not been submitted in any previous application for a Higher Degree.

The thesis describes results of research carried out at the Chemistry Department, St. Salvator's College, University of St. Andrews under the supervision of Professor J.I.G. Cadogan since the 17th September 1963, the date of my admission as a research student.
I hereby certify that Miss Judith Ann Maynard, has spent twelve terms at research work under my supervision, has fulfilled the conditions of Ordinance No. 16 (St. Andrews) and is qualified to submit the accompanying thesis in application for the degree of Doctor of Philosophy.

Director of Research.
Various methods of alkylation of the \( \text{PO}_3^- \), \( \text{PS}_2^- \) and \( \text{PO}_3^- \) ions have been investigated. Ethyl methylphosphonate reacted with 2-methyloxiran to give ethyl 2-hydroxypropyl methylphosphonate and with \( p \)-nitrobenzonitrile oxide to give ethyl \( \alpha \)-hydroxyimino-\( 4 \)-nitrobenzyl methylphosphonate, a new type of organophosphorus ester, which was shown to hydrolyse in acid solution about 10^7 times faster than a simple phosphonate ester. A kinetic study of this remarkably fast hydrolysis suggests a mechanism involving neighboring group participation of the hydroxyimino-moiety. Alkylation of ethyl methylphosphonate was not achieved by reaction with oxaziridines. Reaction of dihexylphosphinic acid with \( p \)-nitrobenzonitrile oxide gave \( \alpha \)-hydroxyimino-\( 4 \)-nitrobenzyl dihexylphosphinate. This ester was stable in acid solution but both the \( \alpha \)-hydroxyimino-\( 4 \)-nitrobenzyl phosphonate and phosphinate esters decomposed at pH5 to give \( p \)-nitroaniline. A possible route of decomposition involving a L"ossen rearrangement is suggested.

Alkylation products were not isolated when \( \text{CO}- \)diethyl phosphoro-thioate and -dithioate reacted with \( p \)-nitrobenzonitrile oxide; the products obtained indicate that an alkylation,
similar to that of the \( \overset{\equiv}{PO_2}^- \) ion, had occurred but subsequent facile decomposition of the neutral anhydrous esters had taken place.

A possible application of the realkylation and subsequent decomposition of the \( \overset{\equiv}{PO_2}^- \) ion, brought about by reaction with nitrile oxide, in the reactivation of "aged" phosphonylated cholinesterase is discussed.

The reaction of propyl iodide with dialkyl phosphoramidates has been shown to cause an alkyl exchange process on both oxygen and nitrogen atoms, together with P-N bond fission. The phosphorylation of phenol to give triphenyl phosphate was accomplished by heating with diphenyl N-propylphosphoramidate in the presence of propyl iodide.
I should like to thank Professor J.I.G. Cadogan, who suggested this topic of research, for his constant advice and encouragement throughout the investigation.

In addition, I am indebted to Dr. B.C. Challis for frequent discussions on reaction mechanisms and for his advice on kinetic methods.

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# CONTENTS

**INTRODUCTION**

1. Nucleophilicity of Neutral Pentavalent Organophosphorus Compounds.
   1.1 Nucleophilicity of Phosphoryl Oxygen
   1.2 Nucleophilicity of Phosphorothonio and Thiolo Sulphur
   1.3 Nucleophilicity of Nitrogen in Imides, Imidates and Amidates
   1.4 Relative Nucleophilicities of Sulphur and Nitrogen in Amidothionates

2. Nucleophilicity of Pentavalent Organophosphorus Compounds Bearing a Formal Negative Charge
   2.1 Nucleophilicity of the Phosphate and Phosphonate Anions.
   2.2 Nucleophilicity of the Dithioate Anion
   2.3 Nucleophilicity of the Amidimidate Anion
   2.4 Nucleophilicity of the Monothioate Anion
   2.5 Nucleophilicity of the Amidate Anion
   2.6 Nucleophilicity of the Amidothionate Anion

**PROGRAMME OF RESEARCH**

**EXPERIMENTAL**

1. Miscellaneous Preparations
   1.1 Tripropyl Phosphate
   1.2 Triethyl Phosphorothonionate
1.3 Potassium $\text{O}_2\text{O}$-Diethyl Phosphorothioate 40
1.4 $\text{O}_2\text{O}$-Diethyl Phosphorothioate 40
1.5 Diethyl Phosphate 41
1.6 Dihexylphosphinic Acid 41
1.7 $p$-Nitrobenzhydroxamic Acid 42
1.8 $p$-Nitrobenzamidine 42

2. Alkylation of the Phosphonate, Phosphinate, Phosphorodithioate and Phosphorothioate Anions 43

2.1 Reaction of 2-Methyloxiran with Ethyl Methylphosphonate 43

2.2 Preparation of Oxaziridines 45

2.2.1 Preparation of anils 45
2.2.2 Oxidation of anils 46

2.3 Attempted Reaction of Oxaziridines with Ethyl Methylphosphonate 47

2.3.1 Reaction of 2-t-butyl-3-phenyl-oxaziridine with ethyl methylphosphonate 47
2.3.2 Reaction of 2-t-butyl-3-$p$-nitrophenyl-oxaziridine with ethyl methylphosphonate 48

2.4 Preparation of Nitrile Oxides 49

2.4.1 Preparation of aldoximes 49
2.4.2 Chlorination of aldoximes 50
2.4.3 Preparation of nitrile oxides 51
2.5 Reaction of Nitrile Oxides with Ethyl Methylphosphonate
2.5.1 Reaction of acetonitrile oxide
2.5.2 Reaction of 2,4,6-trimethylbenzonitrile oxide
2.5.3 Reaction of p-nitrobenzonitrile oxide
2.6 Reaction of p-Nitrobenzhydroxamoyl Chloride with Sodium Ethyl Methylphosphonate
2.7 Reaction of p-Nitrobenzonitrile Oxide with Diethyl Phosphate
2.8 Reaction of Dihexylphosphinic Acid with p-Nitrobenzonitrile Oxide
2.9 Reaction of p-Nitrobenzhydroxamoyl Chloride with Salts of CO-Diethyl Phosphorodithioate
2.9.1 Reaction with potassium CO-diethyl phosphorodithioate
2.9.2 Reaction with nickel bis(CO-diethyl phosphorodithioate)
2.10 Reaction of p-Nitrobenzhydroxamoyl Chloride with Potassium CO-Diethyl Phosphorothionate
2.11 Aqueous Decomposition of α-Hydroxyimino-4-nitrobenzyl Phosphonate and Phosphinate Esters
2.11.1 Acidic decomposition of ethyl α-hydroxyimino-4-nitrobenzyl methylphosphonate
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.11.2</td>
<td>Decomposition of ethyl (\alpha)-hydroxyimino-4-nitrobenzyl methylphosphonate at pH5</td>
<td>66</td>
</tr>
<tr>
<td>2.11.3</td>
<td>Decomposition of (\alpha)-hydroxyimino-4-nitrobenzyl dithiophosphinate at pH5</td>
<td>67</td>
</tr>
<tr>
<td>2.12</td>
<td>Kinetic Measurements on the Aqueous Decomposition of Ethyl (\alpha)-Hydroxyimino-4-nitrobenzyl Methylphosphonate</td>
<td>68</td>
</tr>
<tr>
<td>3.1</td>
<td>Preparation of Phosphono- and Phosphorochloridates</td>
<td>70</td>
</tr>
<tr>
<td>3.1.1</td>
<td>Diethyl phosphorochloridate</td>
<td>70</td>
</tr>
<tr>
<td>3.1.2</td>
<td>Ethyl propyl phosphorochloridate</td>
<td>70</td>
</tr>
<tr>
<td>3.1.3</td>
<td>Dipropyl phosphorochloridate</td>
<td>71</td>
</tr>
<tr>
<td>3.1.4</td>
<td>1-Methyl-2,2-dimethylpropyl methylphosphonochloridate</td>
<td>71</td>
</tr>
<tr>
<td>3.1.5</td>
<td>Ethyl methylphosphonochloridate</td>
<td>72</td>
</tr>
<tr>
<td>3.2</td>
<td>Preparation of Phosphoramidates</td>
<td>72</td>
</tr>
<tr>
<td>3.3</td>
<td>Reaction of Propyl Iodide with Phosphono- and Phosphoramidates</td>
<td>77</td>
</tr>
<tr>
<td>3.3.1</td>
<td>Reaction with diethyl phosphoramidate</td>
<td>77</td>
</tr>
<tr>
<td>3.3.2</td>
<td>Reaction with ethyl propyl (NN)-dipropylphosphoramidate</td>
<td>78</td>
</tr>
<tr>
<td>3.3.3</td>
<td>Reaction with methyl-2,2-dimethylpropyl (N)-cyclohexyl-(P)-methylphosphonamidate</td>
<td>80</td>
</tr>
<tr>
<td>3.3.4</td>
<td>Equilibration of propylamine with propyl iodide</td>
<td>82</td>
</tr>
</tbody>
</table>
3.4 Reaction of Propyl Iodide with Phosphoramidates in the Presence of Hydroxylic Compounds

3.4.1 Reaction of propyl iodide with diphenyl N-propyl phosphoramidate in the presence of phenol

3.4.2 Reaction of propyl iodide with dipropyl N-propyl phosphoramidate in the presence of propanol

DISCUSSION

1. Formation and Decomposition of Alkyl Esters of the Phosphonate, Phosphinate, Phosphorodithioate and Phosphorothioate Anions

1.1 Reaction of 2-Methyloxiran with Ethyl Methylphosphonate

1.2 Attempted Reaction of Oxasiridines with Ethyl Methylphosphonate

1.3 Reaction of Nitrile Oxides with Phosphonate, Phosphinate, Phosphorodithioate and -thioate Anions

1.3.1 Preparation and reactivity of nitrile oxides

1.3.2 Reaction of ethyl methylphosphonate and dihexylphosphinic acid with nitrile oxides

1.3.3 Kinetic results and mechanism of hydrolysis of ethyl α-hydroxyimino-4-nitrobenzyl methylphosphonate

1.3.4 Reaction of p-nitrobenzhydroxamoyl chloride with the potassium and nickel salts of CO-diethyl phosphorodithioate
<table>
<thead>
<tr>
<th>Reaction</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3.5 Reaction of p-nitrobenzhydroxamoyl chloride with potassium</td>
<td>110</td>
</tr>
<tr>
<td>CO-diethyl phosphorothioate</td>
<td></td>
</tr>
<tr>
<td>2. Reactions of Phosphon- and Phosphoramidates</td>
<td>112</td>
</tr>
<tr>
<td>2.1 Reaction of Phosphon- and Phosphoramidates with Propyl Iodide</td>
<td>112</td>
</tr>
<tr>
<td>2.2 Reaction of Phosphoramidates with Propyl Iodide in the Presence of</td>
<td>117</td>
</tr>
<tr>
<td>Hydroxylic Compounds</td>
<td></td>
</tr>
<tr>
<td>APPENDIX PROTON MAGNETIC RESONANCE DATA</td>
<td>120</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>125</td>
</tr>
</tbody>
</table>
INTRODUCTION

Many illustrations of the nucleophilic nature of the hetero-atoms X and Y in organophosphorus compounds of the general type \( \overset{\text{P}}{\text{YR}} \), where X and Y are oxygen, nitrogen or sulphur, have been recorded. These compounds may be subdivided according to the nature of R. When R is an alkyl or aryl substituent the compound is neutral, but when R is hydrogen or a metal the phosphorus moiety then bears a negative charge. These two classes will be considered separately since the types of reaction which they undergo are not generally comparable.

1. NUCLEOPHILICITY OF NEUTRAL PENTAVALENT ORGANO-PHOSPHORUS COMPOUNDS.

The types of compounds to be discussed in this section are:

\[
\begin{align*}
\overset{\text{P}}{\text{O}} & \quad \overset{\text{P}}{\text{S}} & \quad \overset{\text{P}}{\text{O}} & \quad \overset{\text{P}}{\text{NR}} & \quad \overset{\text{P}}{\text{O}} & \quad \overset{\text{P}}{\text{S}} \\
\text{OR} & \quad \text{OR} & \quad \text{SR} & \quad \text{OR} & \quad \text{NR}_2 & \quad \text{NR}_2
\end{align*}
\]

and also the related compounds:

\[
\begin{align*}
\overset{\text{P}}{\text{O}} & \quad \overset{\text{P}}{\text{S}} & \quad \overset{\text{P}}{\text{NR}} \\
= & \quad = & \quad =
\end{align*}
\]

However, alkylidene phosphoranes (\( \overset{\text{P}}{\text{CR}_2} \)) which are intermediates in the Wittig reaction, will not be considered.
since they fall outside the scope of this investigation.

1.1 Nucleophilicity of Phosphoryl Oxygen.

Recently, the concept of the phosphoryl moiety reacting as a nucleophile towards many reagents has been given much attention and many illustrations of this reactivity can be cited.

The basic nature of the phosphoryl oxygen is demonstrated by the decrease of the phosphoryl infrared stretching frequency in hydrogen bonding solvents such as chloroform and also by the inflexion obtained in the titration curve when strong acid is added to a phosphine oxide.

A demonstration of the nucleophilic nature of the phosphoryl oxygen towards carbon has been provided by Horner and Winkler, who showed that optically active phosphine oxides were racemized in boiling acetic anhydride. These workers invoked a five-co-ordinate phosphorus intermediate formed by attack of the phosphoryl oxygen on the acyl carbon:

\[
\begin{align*}
R_1 \quad & R_3 \quad \cdots \quad PO + (\text{MeCO})_2C \\
\text{R}_2 \quad & \leftrightarrow \quad R_1 \quad \cdots \quad \text{P} \quad \cdots \quad \text{R}_3
\end{align*}
\]
A further example is afforded by catalysis of the Arbuzov rearrangement of trimethyl phosphite to dimethyl methylphosphonate by a phosphine oxide, probably by alkylation of the phosphoryl group as follows:

\[ R_3PO + (\text{MeO})_3P \rightarrow R_3P\text{OMe}[(\text{MeO})_2P]^+ \]

\[ \rightarrow R_3PO + (\text{MeO})_2P(\text{O})\text{Me} \]

The three major types of reagents undergoing reaction with phosphoryl oxygen are alkyl halides, acyl halides and carbonyl chloride. In such reactions it is not possible to determine whether the nucleophilic site is the phosphoryl or the alkoxy oxygen by simple product analysis, since both routes lead to the same product e.g.

\[ (\text{EtO})_3PO + RI \]

phosphoryl attack

\[ (\text{EtO})_3P(\text{OR}) \quad \text{I}^- \]

\[ \rightarrow (\text{EtO})_2P(\text{O})(\text{OR}) + \text{EtI} \]

However Green and Hudson have elegantly demonstrated by \(^{18}\text{O}\) tracer methods that, for the reaction of a phosphinate with carbonyl chloride, attack by phosphoryl rather than
alkoxyl oxygen was the initial step. They labelled the phosphinate ester with $^{18}$O at the alkoxyl oxygen and showed that the activity was retained as follows:

$$R_2^+P(O)O^{18}R_1 + COCl_2 \xrightarrow{O^0} R_2^P(O^{18})Cl + CO_2 + R^1Cl$$

This confirmed that the intermediate involved was

$$R_2^+P\leftarrow O\cdot CO\cdot Cl^-$$

and not $$R_2^P\rightarrow O^{18}\rightarrow R^1\rightarrow Cl^-$$

The analogous reaction between phosphonates, and carbonyl chloride was reported by Coe, Perry and Brown:

$$R^1P(O)(OR)_2 + COCl_2 \xrightarrow{25^0} R^1P(O)(OR)Cl + CO_2 + RCl$$

Phosphonates, however, were found by Cadogan to be unreactive towards carbonyl chloride. Green and Hudson thus concluded that the order of reactivity

$$R_2^P(O)OR \gg RP(O)(OR)_2 \gg (RO)_3PO$$

towards carbonyl chloride reflected the greater degree of electron release to phosphoryl oxygen by alkyl compared with alkoxyl. The same order of electron release was observed by Cadogan who showed that while O$_3$-diethyl methyl-phosphonothiolate reacted with carbonyl chloride in the above way, triethyl phosphorothiolate was unreactive.
Several reactions of phosphoryl oxygen with acyl halides have also been investigated. Green and Hudson studied the reaction of phosphinates, Pudovik and co-workers that of phosphonates and Whetstone investigated that of phosphates with acyl chlorides. Most reactions yielded a mixture of a carboxylic anhydride and a pyrophosphate, pyrophosphonate or pyrophosphinate. However, in certain cases, for example in the reaction of triethyl phosphate with benzoyl chloride, the intermediate mixed carboxylic-phosphoric anhydride was obtained. The overall reaction may be exemplified by:

\[(BuO)_3PO + Ph.CO.Cl \rightarrow (BuO)_2P(0)O.CO Ph + BuCl \]

\[\rightarrow [(BuO)_2P(0)]_2O + (PhCO)_2O\]

In contrast to the above findings Yakubovich and co-workers showed that acetyl fluoride reacted with phosphonates to form phosphonofluoridates:

\[\text{e.g. } EtP(O)(OEt)_2 + MeCO.F \rightarrow EtP(O)(OEt)F + MeCO_2Et\]

This may be explained by the increased nucleophilicity of fluoride ion, with respect to chloride ion, towards phosphorus.

The reaction of phosphoryl oxygen with alkyl halides has been extensively studied. Ester exchange reactions of phosphates or phosphonates with the alkyl group of alkyl bromides or
iodides have been reported by Laughlin and Pudovik and co-workers. 

\[
\text{e.g. } (RO)_3PO + R'X \rightarrow (RO)_3P(OR')^+ \ X^-
\]

(\(R = \text{Me}, \text{Et}; \ R' = \text{Bu}^n, \text{Hexyl}, \text{Dodecyl}\))

\[
\rightarrow (RO)_2P(0)OR' + RX
\]

This ester exchange reaction accounts for the abnormal phosphonate product sometimes obtained in an Arbuzov reaction between a trialkyl phosphite and an alkyl halide. For example Laughlin showed that the following occurred:

\[
(\text{MeO})_3P + R'Br \rightarrow R'P(0)(\text{OME})_2 + \text{MeBr} \quad \cdots \quad (1)
\]

(normal product)

\((R' = \text{Dodecyl})\)

\[
(\text{MeO})_3P + \text{MeBr} \rightarrow \text{MeP}(0)(\text{OME})_2 \quad \cdots \quad (2)
\]

\[
\text{MeP}(0)(\text{OME})_2 + R'Br \rightarrow \text{MeP}(0)(\text{OME})(OR') + \text{MeBr} \quad \cdots \quad (3)
\]

isomeric with normal product

In a similar investigation, Harwood and Grisley showed that the abnormal product was the major one when dimethyl phenylphosphonite reacted with 2-bromoethylacetate. This was thought to be due to the much greater electrophilicity of...
methyl bromide compared with 2-bromoethylacetato i.e. the reactions analogous to (2) and (3) above were very much faster than (1).

Further evidence concerning the nucleophilicity of phosphoryl oxygen towards alkyl halides has recently been provided by Cadogan and Mackie who postulated that alkylation of the phosphoryl group to give the quasiphosphonium ion as in the following scheme, was followed by elimination of a secondary carbonium ion rather than by $S_N^2$ dealkylation,

$$\text{(Me}_3\text{C.CHMe.O)}_2\text{PO.Me} + \text{MeI} \rightarrow \text{(Me}_3\text{C.CHMe.O)}_2^+ \text{I}^-$$

Decomposition of the carbonium ion gave hydrogen iodide and a mixture of olefins. Subsequent dealkylation of the phosphorus ester led to regeneration of methyl iodide which was therefore only necessary in catalytic amounts:

$$\text{(Me}_3\text{C.CHMe.O)}(\text{Me})\text{PO.OMe} + \text{HI} \rightarrow \text{(Me}_3\text{C.CHMe.O})(\text{Me})\text{PO}_2\text{H} + \text{MeI}$$

A novel extension of the work with alkyl halides is provided by an intramolecular attack by phosphoryl oxygen as proposed in the following example. 2-Haloethyl alkylphosphonates undergo cyclisation with elimination of alkyl halide.
The reaction may be formulated as:

\[
\begin{align*}
&\text{R}_1\text{O}\text{P} \equiv \text{O} \text{CH}_2 \quad \rightarrow \quad \text{R}_1\text{O} \equiv \text{O} \text{CH}_2 \quad \rightarrow \quad \text{O} \equiv \text{P} \text{O} \text{CH}_2 + \text{R}_1\text{X} \\
\end{align*}
\]

In an analogous way, the formation of phostones in the attempted Arbuzov reaction between 1,3-dibromopropane and a phosphonite diester\(^{16}\) may be explained. The first step is presumably the formation of the Arbuzov product:

\[
\text{R}_1\text{P}(\text{OR}_1)_2 + \text{Br(\text{CH}_2)_3Br} \rightarrow \text{R}_1\text{P}(\text{OR}_1)_0(\text{CH}_2)_3\text{Br} + \text{R}_1\text{Br}
\]

An intramolecular cyclisation, as above, would then give the phostone:

\[
\begin{align*}
&\text{R}_1\text{O}\text{P} \equiv \text{O} \text{CH}_2 \quad \rightarrow \quad \text{R}_1\text{O} \equiv \text{O} \text{CH}_2 \quad \rightarrow \quad \text{O} \equiv \text{P} \text{O} \text{CH}_2 + \text{R}_1\text{Br} \\
\end{align*}
\]

Griffin,\(^{17}\) has found that the rate of hydrolysis of a benzyl bromide substituted by a dialkoxy phosphoryl group in the ortho position is much faster than when substituted in the
meta or para positions by such a group. The stereochemistry of the transition state for the ortho substituted compound is similar to that of the above two cases and thus the phosphoryl group could provide anchimeric assistance to the hydrolysis:

\[ \text{Phosphoryl group} \]

1.2 Nucleophilicity of Phosphorothiono and Thiolo Sulphur.

Sulphur in the phosphorothiono group has long been known to be strongly nucleophilic towards reagents such as alkyl and acyl halides. One of the earliest examples reported was the addition of methyl iodide to trimethyl-phosphine sulphide.\(^{12}\) The stable adduct was hydrolysed by boiling water to methanethiol:

\[
\text{Me}_3\text{PS} + \text{MeI} \rightarrow \text{Me}_3\overset{\delta^-}{\text{PSMe}} + \text{MeSH} + \text{HI}
\]

The analogous addition of an alkyl iodide to a phosphorothionate was reported by Pishohimuka.\(^{19}\) The adduct was unstable, however, and decomposed as follows to give a thiolate:

\[
(\text{MeO})_3\overset{\delta^-}{\text{SMe}} + \text{H}_2\text{O} \rightarrow (\text{MeO})_2\text{P(O)}\text{SMe} + \text{MeI}
\]
The attack of iodide ion on the methoxyl rather than the methylthio carbon reflects the higher nucleophilic character of sulphur compared with oxygen.

Burn and Cadogan\textsuperscript{20} have extended the Pishchimuka reaction to phosphoroamidothionates, the reaction proceeding as follows:

\[
(\text{RO})_2\text{P(S)}\text{NH}_2 + \text{RI} \rightarrow (\text{RO})_2\text{P(SR')}\text{NH}_2 \text{ I}^- \rightarrow \\
(\text{RO})\text{R'}\text{S}\text{P(O)}\text{NH}_2 + \text{RI}
\]

They then investigated the effect of varying the substituent \(X\), in \((\text{RO})_2\text{P(S)}X\), on the rate of reaction with propyl iodide and showed that the nucleophilicity of the phosphorothiono sulphur decreased in the following order for \(X = \text{NH}_2 > \text{NHR} > \text{NR}_2 > \text{NHRX} > \text{Me} > \text{p-tolyl} > \text{EtO} > \text{EtS} > \text{Cl}\). Kabachnik and co-workers\textsuperscript{21} reported that phosphonothionates reacted with alkyl bromides at a similar rate and in a manner analogous to that of phosphorothionates with alkyl iodides, showing that the sulphur of the phosphonothionates must be more nucleophilic since alkyl bromides are less electrophilic than the corresponding alkyl iodides. The enhanced reactivity of phosphonothionates compared with phosphorothionates was further demonstrated by Cadogan\textsuperscript{7} who found that diethyl methylphosphonothionate reacted readily with carbonyl...
chloride, whereas triethyl phosphorothionate was unreactive.

\[
\text{MeP}(S)(\text{OEt})_2 + \text{COCl}_2 \rightarrow \text{MeP}(\text{OEt})_2S\cdot\text{CO}_2\cdot\text{Cl} \cdot \text{Cl}^-
\]

\[
\rightarrow \text{MeP}(\text{O})(\text{OEt})\text{Cl} + \text{COS} + \text{EtCl}
\]

Trimethyl phosphorothionate and related compounds were found to isomerise to the thiolate even on heating in the absence of methyl iodide\(^\text{22,23}\) and it is thought that self-alkylation of the phosphorothiono- group occurred in the following way:

\[
2(\text{MeO})_3\text{PS} \rightarrow (\text{MeO})_3\overset{\text{.}}{P}\text{SMe} \quad [\overset{\text{.}}{\text{MeO}}_2\overset{\text{.}}{\text{PO}}\text{S}]^-\]

The \(\overset{\text{.}}{\text{PO}}\text{S}^-\) ion then reacted as the nucleophile in place of iodide ion towards the methoxyl carbon, giving the thiolate, \((\text{MeO})_2\overset{\text{.}}{P}(\text{O})\text{SMe}\). Interesting examples of this thermal isomerisation reaction are furnished where neighbouring group participation is possible. 2-Dialkylaminoethyl- and 2-ethylthioethyl phosphorothionates form the ethyleniminium\(^\text{24,25}\) and sulphonium\(^\text{26}\) cations respectively, which are then attacked by the \(\overset{\text{.}}{\text{PO}}\text{S}^-\) ion to give the thiolate:
Several examples of the nucleophilic character of sulphur in the phosphorothiolo group have recently been recorded. Hilgetag and co-workers\textsuperscript{23} showed that OS-dimethyl alkyl (or aryl) phosphorothiolate gave trimethylsulphonium iodide and a triphosphate derivative on heating.

\textsuperscript{E.g.} \[ 2(\text{PhO})(\text{MeO})\text{P(O)SMMe} \rightarrow (\text{PhO})(\text{MeO})\text{P}^+\text{SMe}_2 (\text{PhO})(\text{MeS})\text{PO}_2^- \]

\[ \rightarrow \text{Me}_2\text{S}^+ (\text{PhO})(\text{MeO})\text{PO}_2\text{OPo}(\text{SMe})(\text{OPh}) \]

This further self-alkylated to give \[ [(\text{PhO})(\text{MeO})\text{PO}_2\text{OPh})_2]\text{PO}_2\text{OPh}. Dimethyl sulphide then dealkylated the methoxyl groups giving the salt \[ 2\text{Me}_3\text{S}^+ [(\text{PhO})(\text{O}^-)\text{PO}_2\text{OPh})_2.\]

The reaction of thiolates with alkyl iodides first reported by Emmett and Jones\textsuperscript{22} has been extensively studied...
by Burn, Cadogan and Moulden who found that trimethylsulphonium iodide and inorganic phosphate were formed and proposed that alkylation of the sulphur was the first step:

\[(\text{EtO})_2\text{PO} \cdot \text{SR} + \text{MeI} \rightarrow (\text{EtO})_2\text{PO} \cdot \text{S}(\text{R})\text{Me} \cdot \text{I}^- \quad \ldots \quad (4)\]

\[(\text{R} = \text{PhCH}_2\text{Me})\]

\[\rightarrow \text{EtO} \cdot \text{PO} \cdot \text{I} + \text{EtI} + \text{RSMe}\]

\[\text{RSMe} + 2\text{MeI} \rightarrow \text{Me}_3\text{S}^+ \cdot \text{I}^- + \text{RI}\]

Reaction (4) was reversible with loss of RI as well as MeI leading to the formation of (EtO)_2PO•SMMe, which is an example of an alkyl exchange reaction occurring at sulphur.

Divinskii and co-workers have reported a reaction of triethyl phosphorotrithiolate with acetyl chloride involving nucleophilic attack by sulphur:

\[(\text{EtS})_3\text{PO} + \text{MeCOCl} \rightarrow \text{EtS} \cdot \text{CO} \cdot \text{Me} + (\text{EtS})_2\text{PO} \cdot \text{Cl}\]

In contrast to this, Cadogan found that when carbonyl chloride replaced acetyl chloride, the phosphonyl rather than the thiolo centre was the more nucleophilic site in phosphonothiolates. The relative nucleophilicities of thiono- and thiolo-sulphurs are calculated by Hudson, who shows that while the most stable form in phosphorothioclates is
1.3. Nucleophilicity of Nitrogen in Imides, Imidates and Amidates.

The nucleophilicity of nitrogen in phosphine imides has long been established. Staudinger and Hauser\textsuperscript{30} reported that \( \text{N-methyl-} \) and \( \text{N-ethyl-} \) phosphine imides reacted readily with a variety of compounds as follows:

\[
\begin{align*}
R_3\text{P}=\text{NR}^1 & \quad \rightarrow \quad R_3\text{P}=\text{NR}^1 + R_3\text{PO} \\
R_3\text{NO}^1 & \quad \rightarrow \quad R_3\text{PO} + R_3\text{PO} \\
R_2\text{C}=\text{C}=\text{O} & \quad \rightarrow \quad R_2\text{PO} + R_3\text{PO} \\
R_2\text{C}=\text{C}=\text{NR}^{1} & \quad \rightarrow \quad R_3\text{PO} + R_3\text{PO} \\
\text{RN=C}=\text{NR}^{1} & \quad \rightarrow \quad \text{mustard oils} \\
\text{RN=C}=\text{NR}^{1} & \quad \rightarrow \quad R_2\text{C}=\text{NR}^{1} \\
\text{RN=C}=\text{NR}^{1} & \quad \rightarrow \quad \text{mustard oils} \\
\end{align*}
\]

A novel reaction of triphenyl-\( \text{N-} \) alkylphosphine imides with nitrosyl chloride is reported by Zimmer and Singh\textsuperscript{31},

\[
\text{Ph}_3\text{P}=\text{NR} + \text{NOCl} \quad \rightarrow \quad \text{Ph}_3\text{P}=\text{NR}.\text{NO} \quad \rightarrow \quad \text{Ph}_3\text{PO} + \text{RN}_2^+ \text{Cl}^{-}
\]

Phosphorimidates are also appreciably nucleophilic, reactions with methyl iodide and acetyl chloride being reported by Kabachnik and Gilrayov\textsuperscript{32}.
This is a more facile reaction than that of thionates with methyl iodide. However, they found that the reactivity of the nitrogen was markedly affected by the nature of its substituent. For example, triethyl N-acetylphosphorimidate does not react with ethyl iodide at 160°, whereas the parent triethyl phosphorimidate is so reactive that it undergoes self-alkylation during its preparation to give the isomeric diethyl N-ethylphosphorimidate.

\[
\text{(EtO)}_3\text{P=NH} \rightarrow \text{(EtO)}_3\text{P.NH} \rightarrow \text{(EtO)}_2\text{PO.NH}^-
\]

Even in the phosphonitrilic series of compounds the ring nitrogen shows appreciable nucleophilic character, as in the rearrangement of alkoxyphosphazenes to oxophosphazanes reported by Shaw and his co-workers. 

\[
\text{O}
\]

---

\[
\text{O}
\]

---

\[
\text{O}
\]

---

\[
\text{O}
\]
The reaction is catalysed by alkyl halides.

The nucleophilic nature of nitrogen in amidates has not been so extensively investigated, thermal self-alkylation and reaction with carboxylic acids and anhydrides being the only examples of nucleophilicity towards carbon. Thus Cadogan found that diethyl phosphoramidates decomposed at high temperature to give amines as follows:

\[
2(\text{EtO})_2\text{PO.NHPh} \rightarrow (\text{EtO})_2\text{PO}^+\text{NEt.Ph} (\text{EtO})\text{PO.NHPh.O}^-
\]

\[
\rightarrow \text{PhNEt} + \text{EtO.PO} + (\text{EtO})_2\text{PO.NHPh}
\]

\[
\text{PhNEt} + (\text{EtO})_2\text{P(O)NHPh} \rightarrow \text{PhNEt}_2 + (\text{EtO})\text{P(O)NHPh.CH etc.}
\]

Pyrolysis of dimethyl \text{N-} alkylphosphoramidates, where the \text{N-} alkyl substituent is greater than ethyl, was shown by Baumgarten and Setterquest to give olefins, alkyl-dimethylamines and polymeric phosphorus residues. The formation of olefin does not require \text{N-} alkylation as shown by the pyrolysis of diphenyl \text{N-} alkylphosphoramidates to give olefins. The appearance of amine in the former case, however, suggests that a mechanism, similar to that proposed by Cadogan above, may apply:

\[
2(\text{MeO})_2\text{PO.NHR} \rightarrow (\text{MeO})_2\text{PO}^+\text{NHMe.R} (\text{MeO})\text{R(NH)PO}^-
\]

\[
\rightarrow (\text{MeO})_2\text{P(O).OP(C) (OMe)NHR} + \text{MeNHR}
\]
Then the amine could alkylate further by reaction with a methoxyl group:

$$\text{Me}_2\text{NHR} + (\text{MeO})_2\text{P}^- \rightarrow \text{Me}_2\text{NHR} + \text{HOP}^-$$

Acylation of the amidate nitrogen, using acrylic anhydride and catalytic amounts of acetyl chloride, occurs without subsequent breaking of the phosphorus-nitrogen bond.³⁶

Thus:

$$\text{(BuO)}_2\text{PO.NH}_2 + (\text{CH}_2=\text{CH.CO})_2\text{O} \rightarrow \text{(BuO)}_2\text{PO.NH.CO.CH=CH}_2$$

$$+ \text{CH}_2=\text{CH.CO}_2\text{H}$$

Skrowaczewska and Masterlars³⁷ have shown that a carboxylic acid will also react with a phosphoramidate, presumably via nucleophilic attack by nitrogen on the acyl carbon:

$$\text{(PhO)}_2\text{PO.NMe}_2 + \text{RCO}_2\text{H} \rightarrow \text{(PhO)}_2\text{PO.NMe}_2.\text{CO.R CH}^-$$

$$\rightarrow \text{(PhO)}_2\text{PO}_2\text{H} + \text{RCO.NMe}_2$$

Both chlorination and nitrosation of phosphoramidate nitrogen have been effected by Cadogan and his co-workers.³⁸,³⁹

_N-Arylphosphoramidates reacted with a hypochlorite/borax/methanol solution to give N-chloroamidates, (RO)_2PO.NAr.Cl, which undergo an intramolecular rearrangement to give a chlorinated aryl substituent on nitrogen, (RO)_2PO.NHArCl._
Reaction of amidates with nitrosyl chloride is thought to first produce the $N$-nitroso compound which immediately gives a diazonium salt:

$$(\text{RO})_2\text{PO}\cdot\text{N(NO)}\cdot\text{Ar} \rightarrow (\text{RO})_2\text{PO}\cdot\text{N}=\text{N}\cdot\text{Ar} \rightarrow (\text{RO})_2\text{PO}^-\text{ArN}^+$$

Hamer has reported a similar nitrosation of mono salts of $N$-alkyl-phosphoramidates giving a nitroso compound, 

$$(\text{PhO})(\text{NaO})\text{PO}\cdot\text{NR}\cdot\text{NO},$$

which is stable in cold solution but liberates a mixture of phenyl phosphate and diphenyl pyrophosphate on warming. Stock, Hopwood and Regan found that by changing the nitrosating agent from nitrous acid to acidic pentyl nitrite, quantitative yields of dialkyl and diaryl phosphates were obtained from the corresponding dialkyl and diaryl phosphoramidates. They favoured a mechanism of decomposition similar to that proposed by Cadogan.

1.4. Relative Nucleophilicities of Sulphur and Nitrogen in Amidothionates.

Stable addition products between tri-amino phosphorothionates and alkyl iodides were reported by both Burn and Cadogan and Tolkmit. The alkyl group is thought to be associated with the sulphur rather than the nitrogen since hydrolysis gives a thiol.
In support of this, H-ethyl-p-toluidine was not obtained when ethyl iodide was allowed to react with diethyl H-p-tolyl-phosphoramidothionate thus showing that attack on sulphur was very much more favoured than attack on nitrogen.

Thus, in the reactions of neutral organophosphorus compounds described above, sulphur is much more nucleophilic than either nitrogen or oxygen. It will be shown in the Discussion of this thesis that nitrogen and oxygen are of comparable nucleophilicity in reaction with alkyl halides, whereas reactions previously described have occurred exclusively at nitrogen.

2. NUCLEOPHILICITY OF PENTAVALENT ORGANOPHOSPHORUS COMPOUNDS
BEARING A FORMAL NEGATIVE CHARGE.

The anions to be discussed are:
The related anion, \( \text{P=O} \), whose reactions are described by Horner and his co-workers \(^{44}\) is outside the scope of this investigation and will not be further discussed. The last four examples are ambident ions i.e. an electrophile may attack at either X or Y (where X and Y are O,N or S), since the ambident ion may react in either of the two possible forms:

\[
\begin{align*}
\text{P=O} & \quad \text{e} \quad \text{P=O} \\
\text{X} & \quad \text{Y} & \quad \text{X}^- & \quad \text{Y}^- \\
\end{align*}
\]

The concept of ambident nucleophiles was first introduced by Kornblum and co-workers \(^{45}\) who proposed that, the greater the \( S_N^1 \) character of the transition state, the greater is the tendency for covalency formation with the atom (X or Y) of higher electronegativity. Gompper \(^{46}\) considers the situation in much greater detail and distinguishes between thermodynamically and kinetically controlled reactions. The temperature at which a thermodynamically controlled reaction can occur, is lowered when a stable cation is formed in the transition state or when the electrophilic reagent possesses multiple bonds. In such a reaction, attack occurs at the centre of highest basicity.
In kinetically controlled reactions, strongly polar reagents attack at the position of greater electron density, whereas weakly polar reagents attack at the most easily polarisable atom. However atoms of greater electron density are shielded by a solvent sheath in polar solvents, particularly where hydrogen bonding is possible, thus assisting attack at the less electronegative atom.

These principles may be applied in explaining the ambident reactions discussed in sections 2.3, 2.4, 2.5 and 2.6.

2.1 Nucleophilicity of the Phosphate and Phosphonate Anions.

The $\text{PO}_2^-$ ion is a very poor nucleophile and has not been reported to react with alkyl or acyl halides for instance. On the other hand, Cadogan and Thomas$^{47}$ have shown that the following alkylation reaction occurs at 180°:

\[
2\text{(EtO)}_2\text{PO}^-\text{Et}_2\text{N}^- + \text{NET}_2 \rightarrow 2\text{(EtO)}_3\text{PO} + \text{EtN}^-\text{NET}
\]

More reactive agents such as diazomethane$^{48}$ and carbodi-imides$^{49,50}$ are readily attacked giving methyl esters and pyrophosphates respectively.
One of the most extensively studied nucleophilic reactions of phosphates is that involving epoxides, the product being a 2-hydroxy-alkyl phosphate ester:

\[
(\text{RO})_2\text{PO}_2\text{H} + \text{CH}_2\text{CH}_2 \rightarrow (\text{RO})_2\text{PO}_\text{O}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OH}
\]

The interesting property of these 2-hydroxyalkyl esters is the ease with which the alkyl group (R) is hydrolysed in either acidic or basic solution. Detailed reviews of this hydrolysis have been provided by Brown\textsuperscript{52} and Westheimer.\textsuperscript{53} The reaction is thought to proceed via a cyclic five-membered intermediate, the formation of which is sterically favourable:

\[
\text{CH}_2\cdot\text{OH} \text{ OR} \text{ OR} \text{ OR} \rightarrow \text{CH}_2\cdot\text{OR} \text{ OR} \text{ OR} \rightarrow \text{CH}_2\cdot\text{OH} \text{ OR} \text{ OR} \text{ OR}
\]

Jensen and Clayton\textsuperscript{54} reported the analogous reaction of a phosphonate with ethylene oxide:

\[
\text{RP(C)(OH)}_2 + 2\text{CH}_2\text{CH}_2 \rightarrow \text{R.P(O)(CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OH})_2
\]

Further work on this reaction is reported in this thesis.

A somewhat similar addition reaction between phosphate or phosphonate salts and isocyanates has been reported by
A very useful reaction from the biosynthetic point of view, is that of phosphates with phosphoramic monoesters to give pyrophosphates as described by Clark, Kirby and Todd:

\[
e.g. \text{PhP(O)(CH)O}^- + \text{PhNCO} \rightarrow \text{PhP(O)(O^-)O.CO.NPh}
\]

Several other reagents for converting phosphate to pyrophosphate are known, but the field is far too extensive to be covered in the present report (see, however, the review by Clark and co-workers).

2.2 Nucleophilicity of the Dithiate Anion.

The reaction of dialkyl phosphorodithioates with ethylene oxide, which is analogous to that of dialkyl phosphates (section 2.1), has been reported by Kabachnik and co-workers:

\[
\text{(RO)}_2\text{PS}_2\text{H} + \text{CH}_2\text{-CH}_2 \rightarrow \text{(RO)}_2\text{P(S)S.CH}_2\text{-CH}_2\text{-CH}
\]

A somewhat similar addition reaction occurs between dialkyl phosphorodithioates and phenyl isocyanate:

\[
\text{(RO)}_2\text{PS}_2\text{H} + \text{PhNCO} \rightarrow \text{(RO)}_2\text{P(S)S.CO.NPh}
\]
Reactions of both carbonyl chloride and methyl chloroformate with potassium diethyl phosphorodithioate have been reported by Cadogan:

\[
\text{(EtO)}_2\text{PS}_2\text{K} + \text{COCl}_2 \rightarrow \text{(EtO)}_2\text{P(S)}_\text{S} \cdot \text{CO} \cdot \text{Cl} + \text{KCl}
\]

\[
\text{(EtO)}_2\text{PS}_2\text{K} + \text{Cl} \cdot \text{CO}_2\text{Me} \rightarrow \text{(EtO)}_2\text{P(S)}_\text{S} \cdot \text{CO}_2\text{Me} + \text{KCl}
\]

However, Fischer found that reaction at low temperature with carbonyl chloride yielded the product \([\text{(EtO)}_2\text{P(S)}_\text{S}]_2\text{CO}\).

Reaction with N-chloro-N-methylacetamide gave the following:

\[
\text{(EtO)}_2\text{PS}_2\text{K} + \text{Ac} \cdot \text{NCI} \cdot \text{Me} \rightarrow \text{(EtO)}_2\text{P(S)}_\text{S} \cdot \text{NMe} \cdot \text{Ac} + \text{KCl}
\]

2.3 Nucleophilicity of the Amidimide Anion.

In contrast with the anions discussed above, the anions of diethyl N,N'-diaryl phosphoramidimides are ambident nucleophiles. The anion may react in either of the two forms:

\[
\text{(EtO)}_2\text{P} \text{NR} \quad \text{and} \quad \text{(EtO)}_2\text{P} \text{NR}_1
\]

Kabachnik and co-workers have investigated the reaction of a series of such compounds with methyl iodide and have found that the nitrogen bearing the more powerful electron donating substituent (A or B) was the more nucleophilic centre. The
reaction may be expressed in a general way as:

\[
\text{(EtO)}_2\text{P} \quad \text{MeI} \quad \text{(EtO)}_2\text{P} + \text{(EtO)}_2\text{P}
\]

2.4 *Nucleophilicity of the Monothioate Anion.*

Both the possible forms \( \text{P} \quad \text{S} \quad \text{O} \) have been shown to react with electrophilic agents in varying proportions, depending on the type of reagent and the reaction conditions. For example, Kabachnik and co-workers\(^{63}\) carried out the reaction of \( \text{OCS-diethyl phosphorothioate with d} \)

\[
\text{EtO}:\text{PO} \quad . \text{SH} + \text{CH}_2\text{N}_2 \quad \rightarrow \quad \text{EtO} \quad \text{MeS} \quad \text{PO} + \text{EtO} \quad \text{MeO} \quad \text{PS}
\]

Methylation involving quaternary salts has been described by Hilgastag and co-workers\(^{64}\) as follows:

\[
\text{(MeO)}_2\text{PO}^- \quad \text{Me}_4\text{N}^+ \quad \Delta H \quad \rightarrow \quad \text{(MeO)}_2\text{PO} \quad \text{MeS} + \text{Me}_3\text{N}
\]

\[
\text{(or Me}_3\text{S}^+) \quad \text{(or Me}_2\text{S})
\]

\[
\rightarrow \quad \text{(MeS)}(\text{MeO})_2\text{PO}^- \quad \text{Me}_4\text{N}^+
\]

\[
\text{(or Me}_3\text{S}^+)
\]
The course of the reaction thus reflects the greater nucleophilicity of the $\text{\textsuperscript{31}PO\textsuperscript{2-}}$ anion compared with $\text{\textsuperscript{31}PO\textsuperscript{-}}$. Similar alkylation reactions have been observed by Cadogan.\textsuperscript{47,65} Thus, 1,1,4,4-tetraethylpiperazinium bis-(OO-diethyl phosphorothionate) rearranged at 60-100° to give the bis-(OS-diethyl phosphorothiolate) salt:

\[
\text{Et}_2\text{N}^+ + \text{NET}_2 \cdot 2(\text{EtO})_2\text{PO.S}^- \rightarrow \text{Et}_2\text{N}^+ \cdot \text{NET}_2 \cdot 2(\text{EtS})(\text{EtO})\text{PO}^-
\]

Heating of the former at 210° yielded both sulphur and oxygen alkylated products:

\[
\text{Et}_2\text{N}^+ + \text{NET}_2 \cdot 2(\text{EtO})_2\text{PO.S}^- \rightarrow (\text{EtO})_2(\text{EtS})\text{PO} + (\text{EtO})_3\text{PS} + \text{EtN NEO}\]

\[
(38\%) \quad (2\%) \quad (5\%)
\]

Several reactions of sodium, potassium, or silver salts of thioic acids with alkyl halides have been investigated and the conflicting results are difficult to explain without further evidence. For instance Kabachnik and co-workers\textsuperscript{66(a),(c)} report that the reaction between sodium OO-diethyl phosphorothionate and ethyl bromide or benzyl chloride in ethanol yielded only sulphur-alkylated product, whereas Arbuzov and Shapshinskaya\textsuperscript{67} reported that, in all reactions studied between sodium, potassium or silver salts of thioic acids
and alkyl halides in ethanol, only the oxygen alkylated product was obtained. Thus in the former case:

\[
\text{(EtO)}_2\text{PO.SNa} + \text{EtBr} \xrightarrow{4 \text{ hr} \cdot 100^\circ} \text{(EtO)}_2\text{P(O)SeEt} + \text{NaBr}
\]

Under these conditions it does not seem likely that the thionate would be formed and subsequently isomerised to the thiolate. The latter case is exemplified by:

\[
\text{(EtO)}_2\text{PO.SNa} + \text{EtI} \xrightarrow{30^\circ} \text{(EtO)}_3\text{PS} + \text{NaI}
\]

The reaction of potassium diphenylphosphinothionate with ethyl or benzyl iodide is reported by Mastryukova and co-workers\(^\text{68}\) to give only sulphur-alkylated product:

\[
\text{Ph}_2\text{PO.SK} + \text{EtI} \xrightarrow{} \text{Ph}_2\text{P(O)SeEt} + \text{KI}
\]

However when silver O\text{-diethyl phosphorothionate and N\text{-p-nitrophenyliodoacetamide are allowed to react together both sulphur- and oxygen-alkylated products are obtained:}\(^\text{69}\)

\[
\text{(EtO)}_2\text{PO.SAg} + \text{I.CH}_2\cdot\text{CO.NHC}_6\text{H}_4\cdot\text{p-NO}_2 \xrightarrow{} \text{(EtO)}_2\text{P(O).S.CH}_2\cdot\text{CO.NH.C}_6\text{H}_4\cdot\text{p-NO}_2
\]

\[
(86\%)
\]

\[
+ \text{(EtO)}_2\text{P(S).CH}_2\cdot\text{CO.NH.C}_6\text{H}_4\cdot\text{p-NO}_2
\]

\[
(10\%)
\]
No general trend can be distinguished in the above cases, nor in reactions with carbonyl-containing compounds such as acyl chlorides, carbonyl chloride and methyl chloroformate. For example acetyl chloride attacks at the oxygen site:

$$\text{Me(ETO)}_2 \text{PO.SNa} + \text{Me.CO.Cl} \rightarrow \text{Me(ETO)}_2 \text{P(S)O.CO.Me} + \text{NaCl}$$

while methyl chloroformate reacts at the sulphur site:

$$\text{(ETO)}_2 \text{PO.SK} + \text{ClCO}_2 \text{Me} \rightarrow \text{(ETO)}_2 \text{P(O).S.CO}_2 \text{Me} + \text{KCl}$$

For the reaction with carbonyl chloride, a similar attack at sulphur was postulated leading to the series of reactions:

$$\text{(ETO)}_2 \text{PO.SK} + \text{COCl}_2 \rightarrow \text{(ETO)}_2 \text{P(O).S.CO.Cl} + \text{KCl}$$

$$\text{(ETO)}_2 \text{PO.S.CO.Cl} \xrightarrow{\text{Cl}^-} \text{(ETO)}_2 \text{PO.Cl} + \text{CO.S}$$

$$\text{(ETO)}_2 \text{PO.Cl} + \text{(ETO)}_2 \text{PO.SK} \rightarrow \text{(ETO)}_2 \text{P(O)OP(S)(OEt)}_2$$

The addition of aryl isocyanates to dialkyl phosphate thioclates occurs exclusively at sulphur. Thus:

$$\text{(RO)}_2 \text{PO.SH} + \text{ArNCO} \rightarrow \text{(RO)}_2 \text{P(O).S.CO.NHAr}.$$  

The end-product is stable. However, when the two alkoxy groups are replaced by an alkyl and a dialkylamino group,
the addition product is not isolated but undergoes an intramolecular decomposition:

\[
\begin{align*}
R & \quad \text{R} \\
\text{P} & \quad \text{O} \\
\text{R}_{2}\text{N} & \quad \text{S} \\
\text{ArNHCO} & \quad \text{=O}
\end{align*}
\]

It is evident that before the ambident nature of the phosphorothiolate group can be fully described, a much more detailed study of its reactions is required.

2.5 **Nucleophilicity of the Amidate Anion.**

The amidate anion, which can react in the forms

\[
\begin{align*}
\text{P} & \quad \text{=O} \\
\text{NR} & \quad \text{P} \\
\text{N} & \quad \text{R}
\end{align*}
\]

has been found to do so only at the nitrogen atom, thus indicating that the nucleophilicity of oxygen is very much lower than that of nitrogen.

Thus Gutmann et al. found that reaction of both diphenylphosphiniminate and phenylphosphondiamidate with an alkyl iodide gave nitrogen alkylation:

\[
\begin{align*}
\text{Ph}_2\text{P(O).NPh} + \text{RI} & \quad \rightarrow \quad \text{Ph}_2\text{P(O).NPh.R} + \text{I}^- \\
\text{PhP(O)(NPh)}_2 + 2\text{RI} & \quad \rightarrow \quad \text{PhP(O)(NPh.R)}_2 + 2\text{I}^- 
\end{align*}
\]
Alimov and his co-workers\textsuperscript{72} allowed sodium diethyl N-methyl-phosphoramidate to react with a number of halogenated compounds to give $N$-substituted products as outlined in (5) and (6).

\[ (\text{EtO})_2P(O)\text{NMe} + RX \rightarrow (\text{EtO})_2P(O)\text{NMe}_2R + X^- \quad \ldots \quad (5) \]

(where $R = \text{alkyl}; \quad \text{CO}_2\text{Et}; \quad \text{CH}_2\cdot\text{CO}_2\text{Et}; \quad \text{CO} \cdot \text{NEt}_2$)

\[ 2(\text{EtO})_2P(O)\text{NMe} + R \cdot X_2 \rightarrow [(\text{EtO})_2P(O)\text{NMe}]_2R + 2X^- \quad \ldots \quad (6) \]

(where $R^1 = \gg \text{CO}; \gg \text{S}; \gg \text{CH}_2$)

A number of unsaturated compounds have been shown by Wadsworth and Emmons\textsuperscript{73} to react with the nitrogen of the diethyl phosphoramidate anion giving the diethyl phosphate (or phosphorothionate) anion and the following nitrogen-containing products:

\[
\begin{align*}
\text{RNCO} & \quad \text{R}^-\text{CHO} & \quad \text{CS}_2 & \quad \text{CO}_2 & \quad \text{RR}^-\text{C}^\equiv\text{C}=\text{O} \\
\text{RN=C=NR} & \quad \text{RR}^-\text{C}=\text{C}^\equiv\text{N} & \quad \text{RNCS} & \quad \text{RNCO} & \quad \text{RNCS} & \quad \text{RNCO} & \quad \text{RNCS} & \quad \text{RNCO}
\end{align*}
\]

However Stock, Hopwood and Regan\textsuperscript{41} were unable to extend this reaction to the synthesis of diphenyl phosphate.

2.6 **Nucleophilicity of the Amidothionate Ion.**

Again, although there are two possible classical forms
of the amidothionate ion, namely

\[
\begin{align*}
&P \square S \\
&\text{NR} \\
&\text{NR}
\end{align*}
\]

and

\[
\begin{align*}
&P \square S \\
&\text{NR} \\
&\text{NR}
\end{align*}
\]

it has been found that reaction occurs only at the nitrogen centre; this is in marked contrast to the neutral amidothionates discussed in section 1.2, where the sulphur was found to be the more nucleophilic atom.

Reactions of potassium \(\text{OO-diethyl N-phenylphosphor}
\) amidothionate with alkyl iodides, dialkyl sulphates and methyl chloroacetate have been reported by Miller and O'Leary,\(^{74}\) giving diethyl \(\text{N-alkyl-N-phenylphosphoramidothionate}\) in the first two cases and diethyl \(\text{N-methoxycarbonylmethyl-N'-phenylphosphoramidothionate}\) in the last case.

In general, in the reactions of ambident ions discussed above, nitrogen is more nucleophilic than either oxygen or sulphur, reaction occurring exclusively at nitrogen. Perhaps the reactions considered are of the thermodynamically controlled type (see introduction to section 2) in which case, since nitrogen is a much stronger base than oxygen or sulphur, one would expect reaction exclusively at nitrogen. Sulphur and oxygen are of similar reactivity, the site of reaction being influenced by the type of reagent and the conditions employed.
PROGRAMME OF RESEARCH

The inhibition of acetyl-cholinesterase and related esterases by organophosphorus compounds, reviewed by O'Brien and Heath, occurs by reaction of a phosphate or phosphonate derivative with the esteratic site of the enzyme as follows:

\[ R_2PO.X + EOH \rightarrow R_2PO.EH + XM \]

where EOH denotes the enzyme, R is an alkyl or alkoxyl group and X is an acidic residue such as F, \( P-NO\cdot C\cdot H_4 \) or \( (RO)_2PO \).

The inhibited cholinesterase is then unable to hydrolyse the acetylcholine generated by nerve impulses in both insects and mammals. The accumulation of acetylcholine results in muscular paralysis and death.

In some cases the phosphorylating group is spontaneously hydrolysed and the enzymatic activity renewed, but, in general, recovery is only effected by the addition of suitable nucleophiles such as the anions of certain oximes and hydroxamic acids. The overall reactivation reaction may be written:

\[ R_2PO.EH + H_2O \rightarrow R_2PO.OH + EOH \]

A plot of \( \log k_2 \) versus pH, where \( k_2 \) is the bimolecular rate constant for the reactivation of phosphorylated enzyme, shows a
maximum in the region of pH 7 to 8. The shape of the curve can be quantitatively accounted for by the assumptions that only the anion of the oxime is active and this can attack only a protonated form of the inhibited enzyme. The rate of reaction is therefore governed by the equilibrium constants $K_1$ and $K_2$.

\[
\text{NOH} \rightleftharpoons \text{NO}^- + \text{H}^+ \quad \cdots K_1 \\
\text{E-P} + \text{H}^+ \rightleftharpoons \text{EP}^+ \quad \cdots K_2 \\
\text{EP}^+ + \text{NO}^- \xrightarrow{k_2} \text{EH} + \text{P-ON}
\]

The extent to which reactivation can be achieved is dependent on the length of time the inhibitor has been in contact with the enzyme i.e., the inhibited enzyme slowly changes to a more stable form which cannot be decomposed by oxime. This process is known as "ageing" and the rate of ageing is dependent on the nature of the organophosphate substituent ($R$). It has been found\textsuperscript{77} that pseudocholinesterase, which had been inhibited with di-isopropylphosphorofluoridate, contained only the mono-isopropyl phosphate substituent, thus establishing that the ageing process corresponded to de-alkylation of the di-isopropyl phosphate:

\[
\text{EOP(O)(OPr}^\text{i})_2 \rightarrow \text{EOP(O)(OPr}^\text{i})(O^-) + \text{Pr}^\text{i}^+
\]
Recently, Coult, Marsh and Read\textsuperscript{78} have determined the rates of dealkylation of secondary-alkyl methylphosphonylated acetylcholinesterases and noted that the rates paralleled the ease of formation of the carbonium ion from the secondary-alkyl group. In support of this finding, Cadogan and his co-workers\textsuperscript{79} have shown that the rates of acid-catalysed hydrolysis of a series of dialkyl methylphosphonates also parallels the ease of formation of the carbonium ions:

\textit{i.e.} \((\text{RO})_2\text{P(O)Me} \xrightarrow{\text{H}^+} (\text{RO})_2\text{P}^+(\text{OH})\text{Me} \rightarrow \text{R}^+ + (\text{NO})(\text{Me})\text{PO}_2\text{H}\)

This evidence suggests that ageing of phosphorylated cholinesterase, which occurs more readily in phosphonates containing a secondary-alkyl group, is an acid-catalysed dealkylation leading to the phosphonate anion:

\[
\text{Me(EO)PO.OR} \xrightarrow{\text{Enzyme H}^+} \text{Me(EO)}\text{P}^+(\text{OH})(\text{OR}) \\
\xrightarrow{} \text{Me(EO)PO.CH} + \text{R}^+
\]

Thus, in the aged inhibited enzyme, the negative charge located on the phosphate or phosphonate moiety would prevent approach by the oximate anion. Ageing therefore leads to a breakdown of oxime therapy for organophosphorus-poisoned cholinesterase, and, to date, no solution of this problem has been found.
A possible mode of reversal of this ageing process could involve the realkylation of the phosphate or phosphonate anion. Unfortunately, this anion is a poor nucleophile (see Introduction, 2.1).

In view of this, research was directed towards reaction of phosphate and related ions with electrophilic reagents. The alkylation of phosphate by an epoxide (see Introduction 2.1) resulting in a 2-hydroxyalkyl ester seemed a useful starting point, since the presence of the 2-hydroxyalkyl group aided rapid hydrolysis of the phosphate ester by formation of a sterically favourable five-membered ring. Therefore the reaction of phosphonate ion with epoxides and with the related oxaziridines (I) and nitrile oxides (II) seemed worthy of investigation since those reagents would be expected to give rise to >N-O⁻ functions in sterically advantageous positions.

Thus these reagents could lead to alkylation of the phosphonate ion and then the hydroxyl function so obtained
might aid hydrolysis of the ester group.

\[
\text{Me} \quad \text{EtO} \quad \text{P} \quad \text{CH} \quad + \quad \text{R}^+\text{C}\equiv\text{N}\text{O}^- \quad \rightarrow \quad \text{Me} \quad \text{EtO} \quad \text{P} \quad \text{O} \quad \text{N} \quad \text{C} \quad \text{R} \quad \text{O}
\]

This ester hydrolysis corresponds to regeneration of the free enzyme from the inhibited enzyme, for which the oxime function is particularly effective.

In addition to the above investigation, a study of the effect of substituents on the nucleophilicity of the phosphoryl oxygen was to be carried out. Since replacement of an alkoxyl- by an amino- substituent has been shown to cause a large increase in the nucleophilicity of the phosphorothioio sulphur (Introduction, 1.2), it was decided to investigate the nucleophilicity of the phosphoryl oxygen in phosphoramidates, particularly towards alkyl halides as this had not previously been studied, and to compare this with other well-established reactivities of phosphoryl oxygen towards alkyl halides (Introduction 1.1).
All solvents were redistilled. Ether, benzene and light petroleum were dried over sodium. Dioxan was purified by the method of Vogel, and stored over sodium under nitrogen. Starting materials used were those commercially available and were not further purified unless stated otherwise. Ethyl phosphorodichloridate, methylphosphonic dichloride and potassium CO-diethyl phosphorodithioate were supplied by the Chemical Defence Experimental Establishment, Porton and dihexylphosphine oxide by British Petroleum Ltd. Molecular-sieve, Type 4A, 1/16" pellets (supplied by B.D.H.) was used as a drying agent where a very low water content was required. Neutral alumina was prepared from "Type H" alumina (Spence and Sons) by neutralisation to pH7 with hydrochloric acid (2N), followed by treatment with ammonium hydroxide (2%) at 75°. After washing free of chloride ion, the alumina was calcined at 600° for 3 hr.

**Instrumentation:**

Gas-liquid chromatographic analysis was carried out on a Griffin D6 Gas-Density-Balance Chromatograph using 2-metre columns and nitrogen carrier gas. Column packings used were 10% silicone oil on celite (100-120 mesh) (abbreviated to 10% SIL), 10% polyethylene glycol adipate on celite
(100-120 mesh) (10% PEGA) and 10% apiezon "L" grease on silocel (100-120 mesh) (10% APL). Injection of a mixture of authentic and unknown samples was used to confirm the identity of each eluted component.

The mole % of each component can be calculated directly from the area of the peak since the Griffin D6 chromatograph employs a gas density balance as detector. The area \( A \) of the peak is directly proportional to the molecular weight \( M \) of the eluted compound. The relation is as follows:

\[
n = \frac{kA}{M-m}
\]

where \( n \) = no of moles injected
\( m \) = molecular weight of the carrier gas
\( k \) = constant dependent on the characteristics of the chromatograph.

Therefore for a mixture of compounds:

\[
\frac{n_i}{n_s} = \frac{A_i}{A_s} \frac{(M_i-m)}{(M_s-m)}
\]

where \( s \) = internal standard
\( i \) = \( i \)th component

Areas were measured by the "half-width method". The area is equal to the product of the maximum height and the peak
width at half this height measured to the nearest 0.1 mm. from the outer edge of one side of the peak to the inner edge of the other.

Infrared spectra were recorded on Perkin-Elmer Spectrophotometers, either Model 137 (rocksalt prism) or Model 237 (grating). Solids were examined as Nujol mulls and liquids as thin films, except where otherwise stated.

Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer Nuclear Magnetic Resonance Spectrometer, Model R-10, operating at a frequency of 60 Mc./sec. for proton nuclei and 24.3 Mc./sec. for phosphorus (\(P^{31}\)) nuclei at a probe temperature of 33.5°C. The abbreviation p.m.r. refers to proton magnetic resonance measurements.

Equivalent weights were determined from pH titration curves obtained using a Radiometer TTT1, SBR2, TTA3 Titration Assembly with the normal settings. Kinetic measurements of the formation of an acid at constant pH were also carried out on this instrument, adjusted to give the fastest possible rate of titration by using both chart and pen drive motors of 30 r.p.m. and a pen gear setting of 4% per revolution.

Microanalyses were carried out by Bernhardt of Iulhein, Germany and Weiler and Strauss, Oxford.
1. MISCELLANEOUS PREPARATIONS

1.1 Tripropyl Phosphate

This was prepared according to the method of Noller and Dutton by reacting excess propanol with phosphorus oxychloride. The tripropyl phosphate so obtained had b.p. 100-103°/1 mm. Noller and Dutton reported b.p. 128-134°/15 mm.

1.2 Triethyl Phosphorothionate

Sulphur (16.0 g., 0.5 mole) was added over ½ hour to stirred, cooled triethyl phosphite (63 g., 0.5 mole) under nitrogen. Distillation of the filtered liquid under nitrogen gave triethyl phosphorothionate (89.4 g., 90%), b.p. 92-93°/12 mm., \( n_D^{17} 1.4488 \) (Strecker and Spitaler gave \( n_D^{25} 1.4464 \)).

1.3 Potassium O,O-Diethyl Phosphorothionate

A solution of triethyl phosphorothionate (62.3 g., 0.31 mole) and potassium hydroxide (18.0 g., 0.32 mole) in ethanol (300 ml.) was boiled under reflux for 5 hr. Ethanol was removed by evaporation and light petroleum (150 ml., b.p. 60-80°) was added, precipitating white needles of potassium O,O-diethyl phosphorothionate (31.1 g., 47%), m.p. 190-191°.

1.4 O,O-Diethyl Phosphorothionate

Potassium O,O-diethyl phosphorothionate (1.1 g.) was acidified
with hydrochloric acid (10 ml. of 2N) and the aqueous solution extracted with ether (4 x 20 ml.). Distillation gave Q Q-diethyl phosphorothionate (0.3 g., 67%) b.p. 66-68°/0.05 mm., nD16 1.4700, anilinium salt, m.p. 94-95°. P31 n.m.r. on a 20% solution of the acid in chloroform showed a chemical shift of -60.4 p.p.m. (relative to 85% phosphoric acid). The p.m.r. spectrum is recorded in the Appendix. Michalski and Pliszka63 reported b.p. 75°/0.05 mm., anilinium salt m.p. 97-98°.

1.5 Diethyl Phosphate.

The method of Cadogan and Moulden92 employing the reaction of diethyl hydrogen phosphonate with chloramine-T was used, giving diethyl phosphate, equivalent wt. 157 (calc. for C4H11O4P: 154).

1.6 Dihexylphosphinic Acid.

Bromine (3.20 g., 20 m.mole) in carbon tetrachloride (10 ml.) was added dropwise to a stirred solution of dihexylphosphine oxide (4.35 g., 20 m.mole) in carbon tetrachloride (50 ml.). The mixture was allowed to react overnight at room temperature. Shaking with a solution of sodium carbonate (6.45 g., 100 m.mole) in water (10 ml.), acidification with sulphuric acid (2N), washing with water (3 x 50 ml.) and drying (MgSO4) of the carbon tetrachloride
solution gave dihexylphosphinic acid on evaporation of solvent.
Recrystallisation from light petroleum (b.p. 60-80°C) containing ani
inal charcoal yielded pure product (2.7 g., 58%), m.p. 75.5 -
77.0°C, equivalent weight 240 (Calc. for C₁₂H₂₇O₂P: 234).
Williams and Hamilton gave m.p. 77.0 - 78.5°C.

1.7 p-Nitrobenzhydroxamic Acid.

This was prepared by the method of Jones and Hurd. To p-nitrobenzoyl chloride (1.3 g., 10 m.mole) in ether
(30 ml.) was added a finely ground mixture of sodium carbonate
(1.05 g., 10 m.mole) and hydroxylammonium chloride (0.7 g.,
10 m.mole). Water (1.75 ml.) was added to the suspension
and the mixture shaken for 30 mins. Sodium chloride was
removed by filtration and the solvent by evaporation. The
residual solid was washed with ether (2 x 10 ml.) leaving
p-nitrobenzhydroxamic acid, m.p. 171°C. Ref. 83 gives
m.p. 177°C (d).

1.8 p-Nitrobenzamide.

This was prepared by reacting p-nitrobenzoyl chloride
with aqueous ammonia (50%). The product on recrystallisation
from water, gave p-nitrobenzamide, m.p. 193-195°C. Ref. 83
gives m.p. 197-3°C.
2. ALKYLATION OF THE PHOSPHONATE, PHOSPHINATE, PHOSPHORODITHIOATE AND PHOSPHOROTHIOATE ANIONS.

2.1. Reaction of 2-Methyloxiran with Ethyl Methylphosphonate.

Ethyl methylphosphonate was prepared by hydrolysis of ethyl methyl-phosphonochloridate (27.5 g., 0.19 mole) in an ice/water mixture. Distillation gave the acid (12.2 g., 58%), b.p. 110°/0.05 mm., n\textsubscript{D}^25 1.4213. Hudson and Keay\textsuperscript{87} reported b.p. 120°/0.3 mm.

Ethyl methylphosphonate (35.0 g., 0.29 mole) and 2-methyloxiran (58.0 g., 1.00 mole) in ether (300 ml.) were boiled under reflux for 20 hr. Volatile components were removed under reduced pressure; the residue gave an acid reaction to litmus, presumably due to unreacted phosphonate. This was removed by passing an aqueous solution of the product through a column of Permutite "Deacidite E" (a weakly basic anion exchange resin) which had been washed with sodium hydroxide (200 ml. of 2N), then with water (500 ml.). Water was removed from the neutral eluate at 35°/0.05 mm. and the residual oil distilled giving ethyl 2-hydroxypropyl methylphosphonate (17 g., 77%), b.p. 56°/1 micron (Found: C, 39.6; H, 8.2. C\textsubscript{6}H\textsubscript{15}O\textsubscript{4}P requires C, 39.6; H, 8.3%). Infrared and p.m.r. analyses (see Appendix) supported this structure.
Attempted confirmation of the structure by examination of
the splitting of the hydroxyl proton signal failed,
possibly due to the traces of acid present in the product
(cf. Chapman and King 82).

The neutral ester became acidic when allowed to stand
for 2 months at room temperature or when heated at 110°C for
8 hr. (infrared analysis showed P-OH absorptions at 2300 and
1640 cm⁻¹). This impurity was presumably an alkyl methyl-
phosphonate (see Discussion) which was present in too small
a quantity to be isolated.

Attempted methylation of the hydroxyl group using
methyl iodide/silver oxide in acetone at the boiling point
for 4 hr. showed (infrared) that oxidation to a ketonic
function (1725 cm⁻¹) rather than methylation, had occurred.

Acetylation of the hydroxylic function was carried out
by reacting acetyl chloride (1.17 g., 15 m.mole) with the
phosphonate (1.18 g., 10 m.mole) in pyridine (10 ml.) at
room temperature for 17 hr. The reaction mixture was added
to cold nitric acid (2N) and the product extracted with
chloroform. Infrared analysis showed the disappearance of
the (C)-O-H(3400 cm⁻¹) and the appearance of the >C=O
absorption at 1750 cm⁻¹. The pure acetylated derivative
could not be isolated.
Hydrolysis of the ester was carried out as follows.

Ethyl 2-hydroxypropyl methylphosphonate (2.28 g., 12.5 m.mole) was treated with sodium hydroxide (20 ml. of 2N, 40 m.mole) whereupon a precipitate was formed immediately. This dissolved after 3 days at room temperature. Water was removed at 20°C/0.05 mm. and the residue extracted with chloroform. A neutral ester was not obtained. The residue was acidified with hydrochloric acid (2N) and extracted with chloroform (6 x 25 ml.) giving crude 2-hydroxypropyl methylphosphonate (1.05 g., 55%) the infrared spectrum showed (C)-OH at 3330 cm⁻¹ and (P)-OH at 2280 and 1670 cm⁻¹.

Infrared analysis showed loss of (C)-OH absorption on attempted purification by distillation at 80°C/0.1 mm., presumably due to decomposition in a manner similar to the thermal decomposition of the diester described above.

2.2. Preparation of Oxaziridines.

2.2.1. Preparation of anilines. - A mixture of benzaldehyde (31.8 g., 0.3 mole), t-butylamine (26.3 g., 0.36 mole) and benzene (160 ml.) was boiled under reflux and water (5 ml., 92%) was removed by means of a Dean-Stark apparatus.

Distillation of the reaction mixture yielded N-benzylidene-t-butylamine, b.p. 89-91°C/10 mm., \( n_{D}^{25} 1.5170 \). Emmons reported b.p. 90-92°C/11 mm., \( n_{D}^{25} 1.5211 \).
N-p-nitrobenzylidene-t-butylamine was similarly prepared from p-nitrobenzaldehyde (15.1 g., 0.1 mole) and t-butylamine (8.8 g., 0.12 mole) in benzene (350 ml.). The solid residue was chromatographed on alumina. Elution with light petroleum (b.p. 40-60°) gave the anil (7 g., 50%) m.p. 74-75°. Emmons gave m.p. 73-75°.

2.2.2. Oxidation of anilts.- Perbenzoic acid, prepared according to the method of Vogel was used to oxidize the anils to oxaziridines. (c.f. the use of peroxylic acid by Emmons and perbutyric acid by Krim as oxidizing agents). The "active" oxygen in both perbenzoic acid and the prepared oxaziridines was determined iodimetrically.

Thus, when perbenzoic acid (23 m.mole, 80 ml. of a 4.0% solution in chloroform) was allowed to react with N-benzylidene-t-butyamine (3.22 g., 20 m.mole) at room temperature for 2 hr., and unreacted perbenzoic acid together with benzoic acid was removed by washing the solution with sodium carbonate (4 x 25 ml. of 2N) followed by drying (Na₂SO₄), the residual 2-t-butyl-3-phenyl oxaziridine was present in at least 80% yield as shown by iodide/thiosulphate titration of the "active" oxygen.

2-t-Butyl-3-p-nitrophenyloxaziridine was similarly prepared from perbenzoic acid (16 m.mole, 42.5 ml. of a
5.2% solution in chloroform) and N-p-nitro-benzylidene-t-butylamine (3.15 g., 15 m.mole) in chloroform (5 ml.). The residual solid after removal of the solvent was recrystallised from light petroleum (b.p. 40-60°) giving the oxaziridine (2.2 g., 66%), m.p. 51.5 - 52.5°. P.m.r. analysis on a 5% solution in carbon tetrachloride using tetramethylsilane as an internal standard showed C-(CH₃)₃ as a singlet (τ, 8.85), →CH as a singlet (τ, 5.40), p-NO₂Ph-protons as a quartet (AB system, τ_A 2.43, τ_B 1.89, J_HH 8 cycles/sec.). The product had 99% active oxygen estimated by iodide/thiosulphate titration. Emmons reported m.p. 65-66°.

2.3 Attempted Reaction of Oxaziridines with Ethyl Methylphosphonate.

2.3.1. Reaction of 2-t-butyl-3-phenyloxaziridine with ethyl methylphosphonate. - To ethyl methylphosphonate (1.74 g., 14 m.mole) in chloroform (10 ml.) was added 2-t-butyl-3-phenyloxaziridine (2.8 g., 14 m.mole) in chloroform (50 ml.) and the mixture was boiled under reflux for 166 hr. The rate of reaction was followed by withdrawal of 2 ml. aliquots of solution and titration of the residual active oxygen with iodide/thiosulphate. The reaction mixture was washed with water (3 x 20 ml.) and chloroform
was distilled off. Treatment of the residue with light petroleum (b.p. 40-60°) gave N-t-butylbenzamide (0.66 g., 36%) m.p. 136-137°, mixed m.p. 135-136° with an authentic sample, m.p. 135.5 - 136.5°, prepared from benzoyl chloride and t-butylamine. Distillation of the petrol filtrate yielded benzaldehyde (0.38 g., 58%) b.p. 76-78°/20 mm. identified by its infrared spectrum. Wild² reported b.p. 179°. The nitrogen-containing fragment corresponding to benzaldehyde was not isolated. Evaporation of water at 60°/0.05 mm. from the aqueous extract gave, on treatment with chloroform, an unidentified product (0.1 g.) which sublimed at 295°. The mother liquors yielded starting phosphonate (1.3 g., 93%) identified by its infrared spectrum.

2.3.2. Reaction of 2-t-butyl-3-p-nitrophenyl oxaziridine with ethyl methylphosphonate. - Ethyl methylphosphonate (0.89 g., 7.2 m.mole) in chloroform (10 ml.) was mixed with 2-t-butyl-3-p-nitrophenyloxaziridine (1.6 g., 7.2 m.mole) in chloroform (15 ml.) and boiled under reflux for 150 hrs. The rate of loss of "active" oxygen was determined as before and compared with that of a control reaction containing no phosphonate. The presence of the phosphonate had no effect on the rate of reaction.
Removal of chloroform from the control reaction followed by treatment with cold light petroleum (b.p. 40-60°) gave unchanged oxaziridine (0.5 g., 30%), m.p. 56-58°, mixed m.p. 56-58° with authentic sample. Addition of ether to the filtrate, followed by recrystallisation of the precipitated solid from ether/light petroleum (b.p. 40-60°) gave N-t-butyl-p-nitrobenzamide (0.31 g., 19%), m.p. 161-162°, mixed m.p. 161-162° with an authentic sample prepared from p-nitrobenzoyl chloride and t-butylamine. Chromatography on alumina of the ether/petroleum filtrate using ether as elution solvent yielded an unidentified solid (0.16 g.) m.p. 112°.

2.4 Preparation of Nitrile Oxides.

2.4.1 Preparation of aldoximes. These were prepared by the general method cited in Wild, by allowing the aldehyde to react with hydroxylammonium chloride under alkaline conditions.

Thus, acetaldehyde yielded acetaldoxime, b.p. 114-115°, which on p.m.r. analysis on an 8% solution in carbon tetrachloride was shown to be a 40-60 mixture of syn- and anti-isomers. The MeCH proton appeared as two quartets (Ze 2.65, 3.25; JH-H: 6.0, 5.4) where tetramethylsilane was the internal standard. The oxime, on drying over molecular sieve and recrystallisation from cold light petroleum (b.p. 40-60°), was obtained as deliquescent crystals,
m.p. 33°. Field et al.\textsuperscript{93} reported m.p. 42-43°.

\(p\)-Nitrobenzaldehyde yielded \(p\)-nitrobenzaldoxime which had m.p. 123-124° on recrystallisation from aqueous ethanol. Wild\textsuperscript{92(a)} reports m.p. 184° (syn-isomer) and 133° (anti-isomer).

Mesitaldehyde yielded mesitaldoxime which had m.p. 118-120° on recrystallisation from chloroform/light petroleum (b.p. 40-60°). Grundmann and Dean\textsuperscript{94} reported m.p. 124-127°.

2.4.2 Chlorination of aldoximes. - Oximes were chlorinated by the method of Benn.\textsuperscript{95} Dry chlorine was passed into a solution of the oxime in chloroform (dried by passing through a column of alumina) at 0° for \(\frac{1}{2}\) - 1\(\frac{1}{2}\) hr. Volatile components were removed under reduced pressure leaving the crude hydroxamoyl chloride.

Acetohydroxamoyl chloride was obtained as a liquid which decomposed in 1-2 hr. at room temperature. Its chloroform solution was stable for several days. P.m.r. analysis of a 20% solution in carbon tetrachloride using tetramethyldisilane as internal standard showed absorption of \(\text{C-CH}_3\) proton as a singlet, \(\tau 7.73\), and the \(\text{NOH}\) proton as a singlet, \(\tau 0.63\).

\(p\)-Nitrobenzhydroxamoyl chloride had m.p. 122-123° on recrystallization from benzene. Bianchetti et al.\textsuperscript{96} gave m.p. 116°.
2.4.3. Preparation of nitrile oxides. - The unstable acetonitrile oxide was prepared by the method of Benn immediately before use by addition of triethylamine (1 mole) to acetyldroxamoyl chloride (1 mole) at 0° in ether solution. Triethylammonium chloride was removed by filtration leaving the nitrile oxide in solution. Grundmann reported that the oxide was stable at -15° but dimerised rapidly at room temperature.

p-Nitrobenzonitrile oxide was similarly prepared but it co-precipitated with the triethylammonium chloride. The mixed precipitate was washed with dioxan (4 x 25 ml.) and evaporation of solvent from the filtrate gave the nitrile oxide (2.44 g., 100%), m.p. 85-86° Grundmann reported m.p. 95°.

2,4,6-Trimethylbenzonitrile oxide was prepared directly from the oxime by reaction with sodium hypobromite according to the method of Grundmann and Dean and on recrystallisation from methanol had m.p. 107-108°. Grundmann and Dean reported m.p. 114°.

2.5. Reaction of Nitrile Oxides with Ethyl Methylphosphonate

2.5.1. Reaction of acetonitrile oxide with ethyl methylphosphonate. - A solution of acetonitrile oxide in carbon tetrachloride was prepared as in 2.4.3 and used in
the following mixtures each made up to a volume of 1 ml.
A. Acetonitrile oxide (0.5 m.mole).
B. Acetonitrile oxide (0.5 m.mole), ethyl methylphosphonate (0.5 m.mole).
C. Acetonitrile oxide (0.5 m.mole) triethylammonium ethyl methylphosphonate (0.5 m.mole).

The infrared spectra of these solutions were recorded in solution cells (thickness 0.1 mm.) at times of 0.1 and 12 hr. Solution B showed disappearance of the strong \(-\text{C}=-\text{(O)}^\text{=}\) band at 2300 cm\(^{-1}\) within 1 hr. whereas solutions A and C showed this only after 12 hr.

Reaction B was carried out on a larger scale. Ethyl methylphosphonate (3.38 g., 27.3 m.mole) in ether (25 ml.) was added to a solution of acetonitrile oxide (27.3 m.mole) in ether (100 ml.) and allowed to react at room temperature for 2 hr. Evaporation of solvent under reduced pressure yielded an oil (5.85 g.) which was strongly acidic and could not be eluted from an alumina column. Chromatography on silica gel using chloroform as elution solvent yielded dimethyl-furoxan (0.26 g., 7\%) identified by comparison of its infrared spectrum with that of authentic product prepared by dimerisation of the nitrile oxide, and an oil (3.15 g., which was 78\% of the weight of the starting materials).
Infrared analysis showed the presence of (N)OH at 3100, 2800; (P)OH at 2250; P=O at 1220; (P)OC at 1040, 820 cm\(^{-1}\). This product was regenerated from its triethylammonium salt (also an oil) by ion exchange chromatography using Amberlite IR120 resin. Further purification could not be achieved.

2.5.2. Reaction of 2,4,6-trimethylbenzonitrile oxide with ethyl methylphosphonate. - Ethyl methylphosphonate (1.24 g., 10 m.mole) in ether (30 ml.) was added to a stirred solution of 2,4,6-trimethylbenzonitrile oxide (1.98 g., 12.3 m.mole) in ether (30 ml.) and allowed to react for 76 hr. at room temperature. The white solid formed (0.03 g., m.p. 814\(^{0}\)), was removed by filtration. Infrared analysis showed that it was a trisubstituted aryl compound containing no POH, P=O or POC groups; it was not further characterised (Found: C, 72.8; H, 7.7\%). On evaporation of the filtrate to a small volume, 2,4,6-trimethylbenzonitrile oxide (1.10 g., 55\%) (correct infrared spectrum) was recovered.

2.5.3. Reaction of p-nitrobenzonitrile oxide with ethyl methylphosphonate. - Ethyl methylphosphonate (1.24 g., 10 m.mole) in dry dioxan (20 ml.) was added to p-nitrobenzonitrile oxide (2.44 g., 15 m.mole) in dry dioxan (100 ml.) and allowed to react for 24 hr. at room
temperature with exclusion of moisture (CaCl$_2$ tube).

Dioxan (90 ml.) was removed under reduced pressure at 20° C.
The precipitated product was washed with ethanol giving
α-hydroxyimino-4-nitrobenzyl methylphosphonate (1.12 g., 30%),
m.p. 145-146° (Found: C, 36.3; H, 3.7; N, 10.6. C$_8$H$_9$N$_2$O$_3$P
requires C, 36.9; H, 3.5; N, 10.8%). Infrared analysis
(hexachlorobutadiene melt) showed (P)-O-H at 2950 cm$^{-1}$ and
(N)OH at 2650 cm$^{-1}$. The p.m.r. spectrum (see Appendix)
was consistent with the structure. Titration of the phosphonate
with 0.2 N sodium hydroxide showed an end-point at pH 3.3
corresponding to titration of the -OH proton (equiv. wt,
260, theoretical 260), and a further end-point at pH 2.7
corresponding to titration of the NH proton (equiv. wt.
126, theoretical 130).

Addition of ether to the filtrate gave a solid (0.35 g.)
which, on recrystallisation from methanol, yielded di-β-
-nitrophenylfuroxan (13.4%), m.p. 201-202°, mixed m.p.
201-202° with authentic material, m.p. 201-202°, prepared
by the dimerisation of β-nitrobenzonitrile oxide in dioxan
at room temperature. The infrared spectra of both furoxans
were identical. Kornblum and Weaver$^{28}$ reported m.p. 163-201°.

Further addition of ether yielded β-nitrobenzhydroxamic
acid (0.45 g., 12%) m.p. 162°, mixed m.p. 171° with authentic
product, m.p. 171°. Attempted purification by chromatographing on silica gel and neutral alumina columns yielded no identifiable products and much of the product adhered strongly to the columns.

In a separate experiment ethyl methylphosphonate (1.24 g., 10 m.mole) was allowed to react with p-nitrobenzonitrile oxide (2.44 g., 15 m.mole) in dioxan (120 ml.) in the presence of water (1.2 ml.) for 24 hr. at room temperature. No solid was precipitated. From the reaction mixture, in a manner similar to that described above, was isolated di-p-nitrophényl-furoxan (0.21 g., 9% calculated on the nitrile oxide) m.p. 200-201°, mixed m.p. 200-201°, and p-nitrobenzhydroxamic acid (1.38 g., 36%) m.p. 170-171°, mixed m.p. 171-172° with an authentic sample m.p. 172-173° (correct infrared spectrum). The residue, on trituration with ether, precipitated α-hydroxyimino-4-nitrobenzyl methylphosphonate (0.11 g., 4%) identified by its infrared spectrum. The ether-soluble residue contained ethyl methylphosphonate (0.75 g., 60%) which was identified by its infrared spectrum.

The above reaction was then carried out with rigid exclusion of moisture by performing all operations in a dry box.

Ethyl methylphosphonate (1.24 g., 10 m.mole, dried
over phosphorus pentoxide at 0.05 mm. for 2 hrs.) in dry dioxan (50 ml.) was mixed with \( p \)-nitrobenzonitrile oxide (3.23g., 20 m.mole) in dry dioxan (50 ml.) and allowed to react at room temperature for 24 hr. The dioxan was removed at room temperature and 0.05 mm. pressure leaving a solid residue, which was shaken three times with 25 ml. portions of ethanol (dried by the \( \text{Mg} / \text{I}_2 \) method.) leaving di-\( p \)-nitrophenylfurozan (1.34 g., 41% calculated on the nitrile oxide), m.p. 192-198°, mixed m.p. 196-7° with an authentic sample m.p. 200-201°, correct infrared spectrum. The solvent was removed at 20°/0.05 mm. pressure from each separate ethanol extract, the first extract yielding a gum, from which, after addition of ether (25 ml.) was slowly precipitated \( \alpha \)-hydroxyimino-4-nitrobenzyl methylphosphonate (0.69 g., 77%), m.p. 130°, correct infrared spectrum. The two remaining extracts yielded identical solids which on being washed with ether had m.p. 110° (d). The infrared spectrum showed an absorption peak at 2290 cm\(^{-1}\) (hexachlorobutadiene mull) attributed to \( \text{NOH} \), but no \( \text{P} = \text{O} \) peak was evident. The fingerprint region showed a peak at 1220 cm\(^{-1}\) assigned to \( \text{P} = \text{O} \) and was markedly different from that of the phosphonate obtained in the above experiments. P.m.r. investigations on a 5% solution
in dry CDCl$_3$ confirmed that the product was ethyl $\alpha$-hydroxy-
imino-4-nitrobenzyl methylphosphonate (1.06 g., 37%),
showing the expected POCH$_2$ multiplet at 7 5.75 in the correct
proportion to the $\mu$-NO$_2$-phenyl protons (see Appendix for a
full analysis). (Found: C, 39.0 ; H, 4.3 ; N, 10.2
C$_{10}$H$_{13}$N$_2$O$_6$P requires C,41.7; H,4.5; N,9.7%). This product
was slowly decomposed by light and instantaneously
decomposed in wet solutions (see section 2.11.1).

2.6. Reaction of $p$-Nitrobenzhydroxamoyl Chloride with
Sodium Ethyl Methylphosphonate.

Sodium ethyl methylphosphonate was prepared by
neutralisation of ethyl methylphosphonate with sodium
bicarbonate (1N) followed by removal of water under
reduced pressure and extraction of the residue with dry
ethanol.

Sodium ethyl methylphosphonate (0.95 g., 6.5 m.mole)
and $p$-nitrobenzhydroxamoyl chloride (1.3 g., 6.5 m.mole)
were allowed to react in dry ethanol (20 ml.)$^{20a}$ in a dry
bom for 3 hr. The precipitated solid (0.44 g.) was removed
by filtration and washed with water to remove sodium chloride
leaving $p$-nitrobenzonitrile oxide (0.25 g., 23%) (correct
infrared spectrum). The loss of weight on washing was
0.19 g., indicating that sodium chloride had been formed in only
50% yield.
2.7. Reaction of \( p \)-Nitrobenzonitrile Oxide with Diethyl Phosphate.

A solution of diethyl phosphate (1.54 g., 10 m.mole) and \( p \)-nitrobenzonitrile oxide (1.54 g., 10 m.mole) in dry dioxan (100 ml.) was allowed to react at room temperature for 41 hr. Dioxan was removed at 20\(^\circ\)/0.05 mm. and dry ether added to the residue. Filtration gave di-\( p \)-nitrophenylfuroxan (0.70 g., 43%), m.p. 107\(^\circ\), m.m.p. 190\(^\circ\) with authentic sample m.p. 192\(^\circ\). Addition of light petroleum (b.p. 40-60\(^\circ\)) to the filtrate yielded an oil, which on titration with sodium hydroxide gave a pH curve with three indistinct points of inflexion indicating that the oil was a mixture of phosphoric acids. Further purification could not be achieved.

2.8. Reaction of Dihexylphosphinic Acid with \( p \)-Nitrobenzonitrile Oxide.

Dihexylphosphinic acid (2.34 g., 10 m.mole) and \( p \)-nitrobenzonitrile oxide (2.46 g., 15 m.mole) were allowed to react in dry dioxan (100 ml.) in a closed vessel at room temperature for 18 hr. Dioxan was removed at 20\(^\circ\)/0.05 mm. and the residue extracted with dry ethanol (2 x 30 ml.) removing di-\( p \)-nitrophenylfuroxan (0.32 g., 13% calculated on the nitrile oxide)(correct infrared
spectrum). Ethanol was removed from the solution at 20°/0.05 mm., the residue dissolved in ether (25 ml.) and light petroleum (b.p. 60-80°) added giving α-hydroxyimino-4-nitrobenzyl dihexylphosphinate (2.92 g., 73%) as colourless crystals which had m.p. 97-99° on recrystallisation from ether/light petroleum (b.p. 60-80°) (Found: C, 57.2; H, 7.3; N, 7.3; equivalent wt. 404. \(\text{C}_{19}\text{H}_{31}\text{N}_{2}\text{O}_{5}\text{P}\) requires C, 57.3; N, 7.9; N, 7.0%; equivalent wt. 398). Its infrared spectrum obtained on a hexachlorobutadiene mull showed absorptions at 3030 and 2790 cm\(^{-1}\) attributed to (N)OH. The p.m.r. spectrum was consistent with the above structure (see Appendix). The apparent \(pK_a\) at 20° determined by titration of a solution of the acid in 50% aqueous ethanol with sodium hydroxide was 5.6.

2.9. Reaction of p-Nitrobenzhydroxamoyl Chloride with Salts of OO-Diethyl Phosphorodithioate.

2.9.1. Reaction of p-nitrobenzhydroxamoyl chloride with potassium OO-diethyl phosphorodithioate. - A solution of p-nitrobenzhydroxamoyl chloride (2.00 g., 10 m.mole) in dioxan (50 ml.) was added to a suspension of potassium OO-diethyl phosphorodithioate (2.24 g., 10 m.mole) in dioxan (80 ml.) and the mixture boiled under reflux for 13 hr. Potassium chloride (0.74 g., 100%) was removed by filtration.
Dioxan (40 ml.) was removed under reduced pressure and sulphur (0.14 g., 44% of one sulphur atom) removed by filtration and washed with ether. Dry ether (100 ml.) was added to the filtrate to precipitate p-nitrobenzonitrile (0.34 g.), m.p. 138°, mixed m.p. 142° with an authentic sample, m.p. 142°, correct infrared spectrum.

The filtrate was evaporated to dryness and light petroleum (100 ml., b.p. 40-60°) added. The precipitated p-nitrobenzonitrile was purified by sublimation at 80°/0.05 mm. and had m.p. 136°, thus giving a total yield of 1.03 g., (7%). Distillation of the liquid residue gave CO-diethyl phosphorothioate (1.1 g., 65%), b.p. 75°/0.05 mm. The infrared and p.m.r. spectra were identical with those of an authentic sample. 31P n.m.r. analysis on a 20% solution in chloroform gave a chemical shift of -62.3 p.p.m. (relative to 85% aqueous phosphoric acid). Authentic CO-diethyl phosphorothioate had a shift of -60.4 p.p.m. The anilinium salt, recrystallised from ether/light petroleum (b.p. 40-60°) had m.p. 91-93°, mixed 90-91° with authentic anilinium CO-diethyl phosphorothioate, m.p. 94-95°. The infrared spectra of these salts were identical.

In a separate experiment a solution of p-nitrobenzhydrazonium chloride (2.00 g., 10 m.mole) in ether (125 ml.)
was allowed to react with a solution of potassium \(\text{CO}_2\text{-diethyl phosphorodithioate}\) (2.24 g., 10 m.mole) in dry methanol (20 ml.) at room temperature for 30 hr. The reaction mixture was worked up as described above and the products isolated were potassium chloride (0.35 g., 47%), sulphur (0.08 g., 19% of one sulphur atom), \(\text{p-nitrobenzonitrile}\) (0.62 g., 46%) and \(\text{CO}_2\text{-diethyl phosphorothioate}\) (0.31 g., 18%). Other solids precipitated by ether and light petroleum (b.p. 40-60°) were shown by infrared analysis to be unreacted phosphorodithioate (0.43 g., 22%) and hydrozamoyl chloride (0.4 g., 23%) respectively.

2.9.2. Reaction of \(\text{p-nitrobenzhydroxamoyl chloride}\) with nickel \(\text{bis-(CO-diethyl phosphorodithioate)}\). — Nickel \(\text{bis-(CO-diethyl phosphorodithioate)}\), precipitated as purple crystals from the mixed aqueous solutions of nickel sulphate and potassium \(\text{CO}_2\text{-diethyl phosphorodithioate}\), had m.p. 87-88° on recrystallisation from light petroleum (b.p. 40-60°) (Found: C,22.6; H,4.4. \(\text{C}_6\text{H}_2\text{O}_2\text{NiPS}_4\) requires C,22.4; H,4.7%).

Nickel \(\text{bis-(CO-diethyl phosphorodithioate)}\)(1.3 g., 6 m.mole) and \(\text{p-nitrobenzhydroxamoyl chloride}\) (1.2 g., 6 m.mole) in dry dioxan (100 ml.) was boiled under reflux for 5 hr. The precipitated nickel chloride (0.29 g., 76%)
was removed by filtration. Dioxan was removed at 20°/0.05 mm. and light petroleum (b.p. 40-60°) added (A). The residual solid was dissolved in benzene, and on addition of light petroleum (b.p. 40-60°) (B), p-nitrobenzonitrile (0.5 g., 56%) (correct infrared spectrum) was obtained. On recrystallisation from benzene/light petroleum (b.p. 40-60°), the nitrile had m.p. 138°, mixed m.p. 142° with an authentic sample, m.p. 140°.

Evaporation of solvent from petroleum filtrate (B) left crude starting hydroxamoyl chloride (0.4 g., 33%) m.p. 77-80° (correct infrared spectrum). On recrystallisation from benzene, the chloride had m.p. 115°, mixed m.p. 120° with an authentic sample, m.p. 122°.

Partial evaporation of solvent from petroleum extract (A) yielded purple crystals, m.p. 75° shown by infrared analysis to be the starting nickel salt (0.4 g., 33%). The residual petroleum solution gave a black gum on evaporation of solvent and addition of aniline failed to precipitate any phosphorus-containing product.

In a separate experiment a solution of p-nitrobenzohydroxamoyl chloride (1.4 g., 7 m.mole) in dry ether (30 ml.) was allowed to react with nickel bis-(CO-diethyl phosphorodithioate) (1.5 g., 7 m.mole) in light petroleum (b.p. 60-80°, 150 ml.) at the boiling point for 27 hr. Solvent
was removed by evaporation and the residue washed with hot light petroleum (b.p. 40-60°) leaving unchanged

\( p \)-nitrobenzhydroxamoyl chloride (1.2 g., 83%), m.p. 120°,
mixed m.p. 120° with authentic sample, m.p. 121°. Evaporation of
of the petroleum filtrate left the starting nickel salt
(1.3 g., 67%) m.p. 97°, mixed m.p. 97° with authentic sample
m.p. 101°.

2.10. Reaction of \( p \)-Nitrobenzhydroxamoyl Chloride with
Potassium CO-Diethyl Phosphorothioate.

A solution of potassium CO-diethyl phosphorothioate
(5.20 g., 25 m.mole) and \( p \)-nitrobenzhydroxamoyl chloride
(5.00 g., 25 m.mole) in dry dioxan (200 ml.) was allowed to
react at room temperature for 70 hr. Precipitated potassium
chloride (1.3 g., 97%) was removed by filtration and the
dioxan removed by evaporation. Addition of ether gave a
solid (0.73 g.) which on repeated recrystallisation from
water yielded \( p \)-nitrobenzamide (0.18 g., 8%) m.p. 190-191°,
mixed m.p. 190-191° with an authentic sample, m.p. 193-195°,
correct infrared spectrum. The ethereal filtrate was
evaporated to dryness and the residue treated with carbon
tetrachloride to give a solid. Sublimation of this solid at
80°/0.05 mm. gave a sublimate (0.87 g.), m.p. 110°, and
a hygroscopic residue (0.27 g.). Chromatography of the
The carbon tetrachloride filtrate was evaporated to dryness and treated with methanol giving an insoluble solid. Washing of the solid with chloroform left sulphur (0.05 g., 13%). The chloroform filtrate was chromatographed on alumina using chloroform as elution solvent giving crude \( p \)-nitrophenylisothiocyanate (0.67 g., 17%); m.p. 100°, identified by the very strong peak at 2035 cm\(^{-1}\) attributed to \(-\text{N}=\text{C}=\text{S},\) in the infrared spectrum obtained on a 4% solution in chloroform.

Caldow and Thomson\(^9\) reported a strong absorption peak at 2045 cm\(^{-1}\) obtained on a chloroform solution of \( p \)-nitrophenylisothiocyanate. The isothiocyanate was further characterised by its reaction in cold ethanolic solution with aniline.

Addition of water precipitated the adduct, \( \text{N-}p\text{-nitrophenyl-N-phenylthiourea} \) which on recrystallisation from benzene/light petroleum (b.p. 60-80°) had m.p. 161-163° (Found: C, 57.5; H, 4.1; N, 15.7. \( \text{C}_{13}\text{H}_{11}\text{N}_{3}\text{O}_2\text{S} \) requires C, 57.2; H, 4.1; N, 15.4%).

When \( p \)-nitrophenylisothiocyanate was boiled under reflux in ethanol for \( \frac{1}{2} \) hr., ethyl \( \text{N-}p\text{-nitrophenyl thiocarbamate} \) was obtained, which, on recrystallisation from benzene had m.p. 175.5 - 176.5°. Browne and Dyson\(^{100} \) reported m.p. 175°.
The methanolic filtrate was distilled to give diethyl phosphate (0.2 g., 5%), b.p. 105°/0.05 mm., \( {\text{P}}^{31} \) n.m.r. analysis on a 20% solution in chloroform showed a chemical shift of +0.1 p.p.m. (relative to 85% phosphoric acid). Jones and Katritzky\(^{101} \) reported +0.5 p.p.m. The p.m.r. spectrum consistent with the above structure is reported in the Appendix.

2.11. **Aqueous Decomposition of \( \alpha \)-Hydroxyimino-4-nitrobenzyl-Phosphonate and Phosphinate Esters.**

2.11.1 **Acidic decomposition of ethyl \( \alpha \)-hydroxyimino-4-nitrobenzyl methylphosphonate.** - An ethanolic solution of ethyl \( \alpha \)-hydroxyimino-4-nitrobenzyl methylphosphonate (10 mg., in 0.5 ml.) was added to water (25 ml.) and kept at a constant pH of 3.6 by addition of sodium hydroxide (0.1N) by means of the automatic titration assembly. The reaction was complete in 15 mins. Titration of the resultant solution with sodium hydroxide (0.1N) showed that two equivalents of acid had been produced, one having an end-point at pH 4.9 and the second at pH 9.5. The equivalent weights calculated from these end-points were 299 and 147.5 respectively. Ethyl \( \alpha \)-hydroxyimino-4-nitrobenzyl methylphosphonate requires equivalent weights 288 and 144. The titration curve was similar to that of \( \alpha \)-hydroxyimino-4-nitrobenzyl methylphosphonate
which shows no detectable decomposition between pH 2 and 3.

In addition, the p.m.r. spectra in dry deuterochloroform and hexadeuterodimethyl sulfoxide were recorded (see Appendix). Addition of a trace of water to the deuterochloroform solution containing 5% of the phosphonate caused, within 15 mins., disappearance of the multiplet due to POCH$_2$ protons ($\tau$, 5.75) and the POCH$_2$CH$_3$ protons ($\tau$, 3.65) and the appearance of a quartet ($\tau$, 6.25) and a triplet ($\tau$, 8.75) attributed to the methylene and methyl protons of ethanol. Absorptions attributed to the $\text{p-NO}_2\cdot\text{C}_6\text{H}_4$ ($\tau$, 1.75) and the PCH$_3$ protons ($\tau$, 8.23) disappeared and a white solid was precipitated. This was shown to be $\alpha$-hydroxyimino-4-nitrobenzyl methyl-phosphonate by infrared analysis.

Addition of a small amount of deuterium oxide to a 20% solution of the phosphonate in hexadeuterodimethyl sulfoxide caused a similar change in spectrum, the multiplets at $\tau$, 5.65 and 8.65 disappearing and a quartet ($\tau$, 6.45) and triplet ($\tau$, 8.20) appearing. The phosphorus-containing product remained in solution and had a spectrum identical with that of authentic $\alpha$-hydroxyimino-4-nitrobenzyl methyl-phosphonate.

2.11.2. Decomposition of ethyl $\alpha$-hydroxyimino-4-nitrobenzyl methylphosphonate at pH5. - Ethyl $\alpha$-hydroxy-
imino-4-nitrobenzyl methylphosphonate (60 mg., 0.2 m.mole) was allowed to stand for 3 hr. in a buffer solution, pH5, consisting of potassium hydrogen phthalate (50 ml. of 0.1M) and sodium hydroxide (25 ml. of 0.1N). The yellow solution was extracted with ether (3 x 30 ml.), which was washed with water (2 x 10 ml.), dried (MgSO₄) and the solvent was removed by evaporation to leave a yellow solid. This formed a diazonium salt which gave a red precipitate with β-naphthol. Recrystallisation of the yellow solid from water gave a small yield of p-nitroaniline, m.p. and mixed m.p. 143-144°.

2.11.3. Decomposition of α-hydroxyimino-4-nitrobenzyl dihexylphosphinate at pH5. — α-Hydroxyimino-4-nitrobenzyl dihexylphosphinate (0.1 g., 0.25 m.mole) in ethanol (150 ml.) was mixed with a pH5 buffer consisting of potassium hydrogen phthalate (250 ml. of 0.1 M) and sodium hydroxide (125 ml. of 0.1N) and allowed to react for 10 hr. Acidification with hydrochloric acid (1N), extraction with ether (3 x 100 ml.) to remove any unreacted material, basification of the aqueous solution with sodium carbonate (1N) and extraction with ether, followed by drying (MgSO₄) and evaporation of the ethereal extract gave p-nitroaniline (10 mg., 33%), m.p. and mixed m.p. 143-144°, correct infrared spectrum.
2.12. Kinetic Measurements on the Aqueous Decomposition of
Ethyl α-Hydroxyimino-4-nitrobenzyl Methylphosphonate.

The rate of hydrolysis of ethyl α-hydroxyimino-4-
nitrobenzyl methylphosphonate was measured in
the pH range 2 to 5 by titration of the acid formed, with
sodium hydroxide (0.1 N) using the automatic titration
assembly described in the Instrumentation section. The
instrument was adjusted for maximum rate of addition of
sodium hydroxide. Below pH 2 the instrument was not
sufficiently sensitive to record the small change in pH
caused by the hydrolysis. Above pH 5 a competing reaction
occurred (see section 2.11.2) and the kinetics were not
further investigated.

The method used was to add 0.5 ml. aliquots of an
ethanolic solution containing ethyl α-hydroxyimino-4-
nitrobenzyl methylphosphonate (0.04 m.mole) by means of a
hypodermic syringe to a titration vessel containing 25 ml.
of an aqueous solution of the required pH and ionic
strength. The vessel was thermostatted to ± 0.05° and
nitrogen, free from carbon dioxide, was continuously
bubbled through the solution. The stock solution was
prepared from distilled water, freshly boiled to remove
carbon dioxide and was 0.01 N in hydrochloric acid and
0.09 M in sodium chloride. The pH of 25 ml. aliquots of this solution was approximately adjusted by the dropwise addition of sodium hydroxide (0.5 N), final adjustment being made by automatic titration with sodium hydroxide (0.1 N). During the titration, not more than 0.5 ml. of sodium hydroxide (0.1 N) was added. Thus the ionic strength of the solution was 0.1M ±0.002M.

Duplicate measurements were made in the pH range 2.0 to 4.5 in intervals of 0.5 pH unit at a temperature of 24.99°C and also at a constant pH of 3.0 with temperatures ranging from 0° to 25° in 5° intervals.

From the rate of formation of acid, the unimolecular rate constant was obtained and its dependence on pH determined. These results together with the calculation of the energy and entropy of activation for the reaction are recorded in the Discussion, 1.3.3.
3. REACTIONS OF PHOSPHORAMIDATES.

3.1 Preparation of Phosphono- and Phosphorochloridates.

3.1.1 Diethyl phosphorochloridate. - This was prepared by the method of Kenner, Todd and Weymouth. \(^{2}\)

N-Chlorosuccinimide (26.6 g., 0.2 mole) was added in one lot to a solution of diethyl hydrogen phosphite (27.6 g., 0.2 mole) in carbon tetrachloride (250 ml.) and the reaction mixture was stirred for 6 hr. at room temperature. Succinimide (19.9 g., 100%) was removed by filtration and the residual solution of diethyl phosphorochloridate used as such in the preparation of diethyl phosphoramidates described below.

3.1.2 Ethyl propyl phosphorochloridate. - Ethyl phosphorodichloridate (8.1 g., 50 m.mole) in dry benzene (25 ml.) was added dropwise with stirring to a solution of triethylamine (5.05 g., 50 m.mole) and propanol (3.0 g., 50 m.mole; dried by distillation from calcium hydride) in dry benzene (100 ml.). The solution was heated under reflux for 3 hr., cooled and dry ether (100 ml.) added. The precipitated triethylammonium chloride (6.6 g., 96%) was removed by filtration. Distillation of the filtrate yielded ethyl propyl phosphorochloridate (5.5 g., 59%), b.p. 89°/3 mm., \(\text{n}^\circ_D 1.5640\) (Found: C,32.1; H,6.5. \(\text{C}_5\text{H}_12\text{ClO}_3\text{P}\) requires C,32.2; H,6.5%). Further confirmation of the structure
was obtained by hydrolysis as follows. Ethyl propyl phosphoro-
chloridate (5.0 g., 27 m.mole) was added dropwise with ice-
cooling to water (25 ml.). Distillation gave ethyl propyl
phosphate (3.0 g., 73%), b.p. 123°/0.2 mm., \( n_D^{14} 1.4210 \). (Found:
C, 36.3; H, 8.1. \( C_5H_{13}O_4P \) requires C, 35.8; H, 7.8%).

3.1.3 Dipropyl phosphorochloridate. — This was prepared
by the method of Fiszer and Michalski.\(^{103}\) Phosphorus trichloride
(13.7 g., 0.1 mole) in dry benzene (25 ml.) was added dropwise
to a stirred solution of propanol (18 g., 0.3 mole); dried by
distillation from calcium hydride) in dry benzene (75 ml.)
at 10°. Sulphuryl chloride (8.1 g., 0.1 mole) was slowly
added to the reaction mixture and a stream of dry nitrogen
was passed through the solution to remove the evolved sulphur
dioxide and hydrogen chloride. Distillation yielded dipropyl
phosphorochloridate (16.1 g., 81%), b.p. 51°/0.05 mm.,
\( n_D^{21} 1.4240 \). Fiszer and Michalski\(^ {103}\) reported b.p. 76°/1.5 mm.,
\( n_D^{25} 1.4236 \).

3.1.4 1-Methyl-2,2-dimethylpropyl methylphosphonochloridate. —
This was prepared by the method of Bunyan and Cadogan.\(^{104}\) Methyl-
phosphonic dichloride (13.2 g., 0.1 mole) in dry benzene
(25 ml.) was added to triethylamine (15.0 g., 0.15 mole)
and 1-methyl-2,2-dimethylpropanol (15.0 g., 0.15 mole) in
dry benzene (100 ml.), and the mixture was boiled under
reflux for 4 hr. Dry ether (100 ml.) was added and triethylammonium chloride (13.7 g., 100%) removed by filtration. Distillation yielded the chloridate (9.7 g., 49%), b.p. 52-54°/0.02 mm., \( n_D^{13} \) 1.4430. Bunyan and Cadogan\(^ {104} \) reported b.p. 42-43°/0.01 mm., \( n_D^{25} \) 1.4380.

3.1.5 Ethyl methylphosphonochloridate. - A solution of dry ethanol (13.8 g., 0.3 mole) and triethylamine (30.4 g., 0.3 mole) in dry ether (50 ml.) was added dropwise to methylphosphonic dichloride (39.6 g., 0.3 mole) in dry ether (300 ml.) at a rate such that the ether boiled gently. Triethylammonium chloride was removed by filtration and the filtrate distilled giving ethyl methylphosphonochloridate (33.5 g., 80%) b.p. 32°/1 mm. Hudson and Key\(^ {105} \) reported 40-41°/1 mm.

3.2 Preparation of Phosphoramidates.

The method of Atherton, Openshaw and Todd\(^ {106} \) was used in the preparation of diethyl phosphoramidate and diethyl \( N \)-phenylphosphoramidate. This involved the reaction of excess ammonia, or aniline (1 mole) in the presence of \( NN \)-dimethyl-aniline (1 mole) with diethyl hydrogen phosphonate (1 mole) and carbon tetrachloride (1 mole) in an inert solvent.

The remainder of the phosphon- and phosphoramidates
were prepared by reaction of the phosphono- or phosphoro-
chloridate (1 mole) with excess ammonia or the appropriate
amine (2 mole) in an inert solvent at room temperature unless
otherwise stated. Ammonium or alkylammonium chloride was
removed by either filtration or washing with water. The
resultant amidate was distilled or recrystallised.

The reaction conditions and yields are recorded in
Table 1, whilst Table 2 records the physical constants, and
literature values and Table 3 gives the analytical figures
where appropriate. The p.m.r. spectra are tabulated in the
Appendix.
### TABLE 1. PREPARATION OF PHOSPHON- AND PHOSPHORAMIDATES.

<table>
<thead>
<tr>
<th>Phosphoramidate</th>
<th>Solvent</th>
<th>Time (hr.)</th>
<th>Yield (%)</th>
</tr>
</thead>
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<tr>
<td>((\text{EtO})_2\text{P(O)NH}_2)</td>
<td>Xylene</td>
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<tr>
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<td>60</td>
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<td>54</td>
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<tr>
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<td>CCl₄</td>
<td>24</td>
<td>50</td>
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<tr>
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<td>33</td>
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<tr>
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<td>54</td>
</tr>
<tr>
<td>((\text{EtO})(\text{Pr}^{n}\text{O})\text{P(O)NP}^{n})</td>
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<td>64</td>
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<tr>
<td>((\text{Pr}^{n}\text{O})_2\text{P(O)NH}_2)</td>
<td>Light Petroleum (b.p. 40-80°)</td>
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<td>30</td>
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<td>33</td>
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<tr>
<td>((\text{Pr}^{n}\text{O})_2\text{P(O)NP}^{n})</td>
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<td>61</td>
</tr>
<tr>
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<td>68</td>
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<tr>
<td>Me(\text{Me}_3\text{C.CHMe.O})\text{P(O)NHC}<em>6\text{H}</em>{11})</td>
<td>Ether</td>
<td>17</td>
<td>98</td>
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* At 80°
<table>
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<th>Phosphoramidates</th>
<th>b.p.(^{\circ}\mathrm{C}/\text{mm} )</th>
<th>n(_D)(^{\circ}\mathrm{C} )</th>
<th>m.p.(^{\circ}\mathrm{C} )</th>
<th>Literature Constant</th>
<th>Ref.</th>
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<tr>
<td>(EtO)(_2)P(O)NH(_2)</td>
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<td>-</td>
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<td>103</td>
</tr>
<tr>
<td>(EtO)(_2)P(O)NHPh</td>
<td>-</td>
<td>-</td>
<td>62-64</td>
<td>m.96.5</td>
<td>107</td>
</tr>
<tr>
<td>(EtO)(_2)P(O)NPr(_n)</td>
<td>94-95/0.5</td>
<td>1.4266(21)</td>
<td>-</td>
<td>b.112/3</td>
<td>108</td>
</tr>
<tr>
<td>(EtO)(_2)P(O)NPz(_2)</td>
<td>73-75/0.5</td>
<td>1.4290(22)</td>
<td>-</td>
<td>b.105-110/12</td>
<td>109</td>
</tr>
<tr>
<td>(EtO)(Pr(_n))P(O)NH(_2)</td>
<td>119/1</td>
<td>-</td>
<td>30-32</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(EtO)(Pr(_n))P(O)NPr(_n)</td>
<td>85-86/0.2</td>
<td>1.4270(21)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(EtO)(Pr(_n))P(O)NPz(_2)</td>
<td>76-78/0.5</td>
<td>1.4290(20)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(Pr(_n))(_2)P(O)NH(_2)</td>
<td>115-116/0.6</td>
<td>-</td>
<td>39-42</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(Pr(_n))(_2)P(O)NPr(_n)</td>
<td>82/0.1</td>
<td>1.4310(19)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(Pr(_n))(_2)P(O)NPz(_2)</td>
<td>78-79/0.07</td>
<td>1.4314(20)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(PhO)(_2)P(O)NHPz(_n)</td>
<td>-</td>
<td>-</td>
<td>52-54</td>
<td>b.208/8</td>
<td>108</td>
</tr>
<tr>
<td>Me(Me_3C.CHMe.O)PO.NHC_8-H(_n)</td>
<td>-</td>
<td>-</td>
<td>95-96</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Note:** All m.p. values are in \(^{\circ}\mathrm{C}\).
# TABLE 3. ANALYSES OF PREPARED PHOSPHON- AND PHOSPHORAMIDATES.

<table>
<thead>
<tr>
<th>Phosphoramidate</th>
<th>Formula</th>
<th>Calc. for</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C(%)</td>
<td>H(%)</td>
</tr>
<tr>
<td>(EtO)₂P(O)NHPr₉</td>
<td>C₇H₁₅NO₃P</td>
<td>43.1</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>43.1</td>
<td>9.2</td>
</tr>
<tr>
<td>(EtO)₂P(O)NPr₂</td>
<td>C₁₀H₂₄NO₃P</td>
<td>50.6</td>
<td>10.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50.95</td>
<td>10.3</td>
</tr>
<tr>
<td>(EtO)(Pr₉O)P(O)NH₂</td>
<td>C₅H₁₄NO₃P</td>
<td>35.9</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35.6</td>
<td>8.2</td>
</tr>
<tr>
<td>(EtO)(Pr₉P(O)NPr₉</td>
<td>C₆H₂₀NO₃P</td>
<td>45.9</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46.2</td>
<td>10.1</td>
</tr>
<tr>
<td>(EtO)(Pr₉O)P(O)NPr₂</td>
<td>C₁₁H₂₆NO₃P</td>
<td>52.0</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>52.6</td>
<td>10.3</td>
</tr>
<tr>
<td>(Pr₉O)₂P(O)NH₂</td>
<td>C₆H₁₆NO₃P</td>
<td>39.3</td>
<td>8.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>39.6</td>
<td>9.3</td>
</tr>
<tr>
<td>(Pr₉O)₂P(O)NHPr₉</td>
<td>C₉H₂₂NO₃P</td>
<td>48.5</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48.4</td>
<td>9.9</td>
</tr>
<tr>
<td>(Pr₉O)₂P(O)NPr₂</td>
<td>C₁₂H₂₈NO₃P</td>
<td>54.3</td>
<td>10.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>53.7</td>
<td>10.5</td>
</tr>
<tr>
<td>(PhO)₂P(O)NHPr₉</td>
<td>C₁₅H₁₆NO₃P</td>
<td>81.9</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>62.1</td>
<td>6.1</td>
</tr>
<tr>
<td>Me(Me₃C.CHMe.O)P(O)NHCH₂₆</td>
<td>C₁₃H₂₈NO₂P</td>
<td>59.8</td>
<td>10.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>59.6</td>
<td>10.4</td>
</tr>
</tbody>
</table>
3.3 Reaction of Propyl Iodide with Phosphon- and Phosphoramidates

3.3.1 Reaction of propyl iodide with diethyl phosphoramidate.

Diethyl phosphoramidate (16.4 g., 0.11 mole) in propyl iodide (85.0 g., 0.5 mole) was boiled under reflux for 6 days. No volatile products were trapped in a solid carbon dioxide-ethanol bath. The precipitated solid was removed by filtration, washed with ether and shown to be a mixture of alkylammonium alkyl phosphates (infrared absorptions for -NH₃⁺ at 3100 cm⁻¹, P=O at 1240 cm⁻¹ and P-O-(C) at 1000 and 875 cm⁻¹) and alkylammonium iodides (acidic silver nitrate) (7.42 g., 30% calculated on an average molecular weight). After removal of propyl iodide by distillation (20 mm.), extraction with cyclohexane (3 x 50 ml.) left a gum formulated as a mixture of ethyl and propyl polymetaphosphates (4.9 g., 40% calculated on the average molecular weight) since it contained no nitrogen (Na fusion) and the p.m.r. spectrum of a 20% deuterium oxide solution showed shifts relative to dioxan (τ 6.30) of τ 6.0, 8.3, 8.8 and 9.1 attributed to the POEt and POPr moieties.

The cyclohexane extract gave a mixture of dialkyl phosphoramidates (7.8 g., 35%) b.p. 80-125⁰/0.5 mm., which was analysed by gas-liquid chromatography using a 10% SIEL column at 125⁰ with a nitrogen flow rate of 60 ml./min.
2 μl samples of a 20% solution of the phosphoramidates in ether were injected. Larger quantities caused overloading of the column. Retention times of the components of the mixture were compared with those of the nine possible authentic phosphoramidates synthesised independently (see section 3.2). The identity of each component was then confirmed by injection of a mixture of the authentic and the unknown in ether. The results are recorded in Table 4.

Confirmation of the composition of the mixture on a separate column was attempted but the only two columns from which the phosphoramidates could be eluted were 10% PEGA at 148° and 10% APL at 175-200°; these gave unsatisfactory separations of the components.

3.3.2 Reaction of propyl iodide with ethyl propyl NN-dipropyl-phosphoramidate. Ethyl propyl NN-dipropyl-phosphoramidate (5.0 g., 20 m.mole) in propyl iodide (17.0 g., 100 m.mole) was boiled under reflux for 4 days. After removal by filtration and recrystallization from ethanol/ether, tetrapropyl-ammonium iodide (1.0 g., 16%) had m.p. 278°, mixed m.p. 261° and the correct infrared spectrum. Distillation of the filtrate under reduced pressure gave volatile products (8.49 g.) which were trapped in liquid air. These were shown to be ethyl iodide (11% by
### TABLE 4, COMPOSITION OF THE PHOSPHORAMIDATE MIXTURE.

<table>
<thead>
<tr>
<th>Phosphoramide</th>
<th>( \frac{A_i}{A_s} )</th>
<th>( M_s )</th>
<th>( M_{s-m} )</th>
<th>( M_{m-m} )</th>
<th>( n_i )</th>
<th>( % )</th>
</tr>
</thead>
<tbody>
<tr>
<td>(EtO)\textsubscript{2}PONH\textsubscript{2}</td>
<td>1.00</td>
<td>153</td>
<td>125</td>
<td>1.00</td>
<td>1.00</td>
<td>12.2</td>
</tr>
<tr>
<td>(EtO)(Pr\textsuperscript{n}O)PONH\textsubscript{2}</td>
<td>1.02</td>
<td>167</td>
<td>139</td>
<td>1.11</td>
<td>2.02</td>
<td>25.0</td>
</tr>
<tr>
<td>(EtO)\textsubscript{2}PONHPr\textsuperscript{n}</td>
<td>1.02</td>
<td>195</td>
<td>167</td>
<td>1.34</td>
<td>1.37</td>
<td>16.8</td>
</tr>
<tr>
<td>(Pr\textsuperscript{n}O)\textsubscript{2}PONH\textsubscript{2}</td>
<td>1.18</td>
<td>191</td>
<td>153</td>
<td>1.22</td>
<td>1.44</td>
<td>17.7</td>
</tr>
<tr>
<td>(EtO)(Pr\textsuperscript{n}O)POHPr\textsuperscript{n}</td>
<td>1.36</td>
<td>209</td>
<td>181</td>
<td>1.45</td>
<td>1.97</td>
<td>24.2</td>
</tr>
<tr>
<td>(Pr\textsuperscript{n}O)\textsubscript{2}POHPr\textsuperscript{n}</td>
<td>0.22</td>
<td>223</td>
<td>195</td>
<td>1.56</td>
<td>0.34</td>
<td>44.2</td>
</tr>
</tbody>
</table>

* See page 38
weight giving a yield of 30% based on the starting amidate) and propyl iodide (38% by weight) by gas-liquid chromatographic analysis on a 10% SIL column at 75° with a nitrogen flow rate of 60 ml./min.

Extraction of the distillation residue with light petroleum (b.p. 40-60°; 3 x 25 ml.) left a gum which was presumably a mixture of ethyl and propyl polymetaphosphates (0.24 g., 10%). Distillation of the petroleum extract yielded a mixture of alkyl phosphoramidates (1.3 g., 40%), b.p. 72-90°/0.5 mm. Analysis by gas-liquid chromatography on a 10% SIL column at 175° with a nitrogen flow rate of 60 ml./min. using 4 µl injections of a 20% solution in ether showed this to be a mixture of the unchanged amidate (73%) and dipropyl NN-dipropylphosphoramidate (27%).

Authentic tetrpropylammonium iodide was prepared by heating tripropylamine (1.43 g., 10 m.mole) and propyl iodide (1.70 g., 10 m.mole) in ethanol (20 ml.) under reflux for 18 hr. Addition of ether yielded the iodide (0.7 g., 23%), m.p. 286°.

3.3.3 Reaction of propyl iodide with 1-methyl-2,2-dimethylpropyl N-cyclohexyl-P-methyl-phosphonamidate. - A mixture of 1-methyl-2,2-dimethylpropyl N-cyclohexyl-P-methylphosphonamidate (6.0 g., 23 m.mole), propyl iodide
(35.2 g., 50 m. mole) and nitromethane (80 ml.) was boiled under reflux for 33 hr. Volatile materials were removed under reduced pressure. Treatment of the residue with light petroleum (b.p. 60-80°) gave a gum, presumably a polymetaphosphonate. Addition of ether to the petrol solution precipitated cyclohexylpropylammonium iodide (0.16 g., 3%) which after recrystallisation from ethanol/ether in the dark and drying over P₂O₅ at 80°/10 mm. had m.p. 255°. (Found: C, 39.3; H, 7.6. Calc. for C₉H₂₀NI: C, 40.2; H, 7.5%).

Chromatography of the petroleum/ether filtrate on alumina yielded the unchanged phosphonamidate (3.2 g., 53%) confirmed by m.p. and mixed m.p. 66-67° and infrared and proton magnetic resonance spectra.

In a separate experiment the reaction mixture was boiled under reflux for 4 days. Thin layer chromatography showed that there was no starting phosphonamidate. Crude cyclohexylammonium iodide (46%) was isolated and identified by its infrared spectrum.

When propyl iodide replaced nitromethane as solvent, the unchanged phosphonamidate (1.1 g., 73%) was recovered by recrystallisation from light petroleum (b.p. 60-80°)/ether after reaction for 24 hr. at the boiling point.
3.3.4 Equilibration of propylamine with propyl iodide. - Propylamine (0.59 g., 10 m.mole) in propyl iodide (17.0 g., 100 m.mole) was heated under reflux with exclusion of moisture for 6 days. Addition of ether gave a solid which, when recrystallised from ethanol/ether, yielded dipropylammonium iodide (1.23 g., 54%), m.p. 250-252°, (Found: C, 31.9; H, 7.1. Calc. for C<sub>6</sub>H<sub>22</sub>NI: C, 31.5; H, 7.0%). The residue was chromatographed on alumina. Elution with ethanol gave a further product which on recrystallisation from ethanol/ether yielded propylammonium iodide (0.56 g., 30%), (Found: C, 19.8; H, 5.3. Calc. for C<sub>3</sub>H<sub>16</sub>NI: C, 19.3; H, 5.4%).

3.4 Reaction of propyl iodide with phosphoramidates in the presence of hydroxyllic compounds.

3.4.1 Reaction of propyl iodide with diphenyl N-propylphosphoramidate in the presence of phenol. - A mixture of diphenyl N-propylphosphoramidate (2.9 g., 10 m.mole), phenol (0.94 g., 10 m.mole) and propyl iodide (17.0 g., 100 m.mole) was introduced into a tube through a capillary neck by means of a hypodermic syringe. The tube was sealed and heated at 125° for 4½ days. Addition of ether to the mixture precipitated a black oil. Repeated extraction of this oil with ether left dipropylammonium iodide (0.12 g., 5%)
which had the correct infrared spectrum. Chromatography of the ethereal solution on alumina using ethanol as elution solvent gave an oil which on treatment with light petroleum (b.p. 40-60°C) precipitated triphenyl phosphate (0.78 g., 24%), m.p. 47°C, mixed m.p. 45°C with an authentic sample, m.p. 45°C (correct infrared spectrum). Thin layer chromatography indicated the presence in the filtrate of triphenyl phosphate and the starting amide. No further separation of these components was achieved by further chromatography on alumina.

A control reaction, omitting propyl iodide, was performed. Diphenyl N-propyl-phosphoramidate (2.9 g., 10 m.mole) and phenol (0.94 g., 10 m.mole) in dry ether were introduced into a reaction tube as above. Ether was evaporated off, the tube was sealed and heated at 125°C for 4½ days. Thin layer chromatography showed that no triphenyl phosphate had been formed. Chromatography on alumina using ethanol as elution solvent yielded unchanged amide (1.2 g., 41%). The residue consisted of uncharacterised oils.

3.4.2 Reaction of propyl iodide with dipropyl N-
propylphosphoramidate in the presence of propanol. - A mixture of dipropyl N-propylphosphoramidate (2.23 g., 10 m.mole), propanol (3.0 g., 50 m.mole) and propyl iodide (17.0 g., 100 m.mole) was boiled under reflux with exclusion of
moisture for 6 days. Propylammonium iodide (0.33 g., 18%), correct infrared spectrum, was removed by filtration and washed with ether.

Propyl iodide was removed by distillation leaving an oil, and was analysed by gas-liquid chromatography on a 10% SIL column at 178° with a nitrogen flow rate of 60 ml./min. showed no starting material or dipropyl NN-dipropylphosphoramidate. Investigation at a column temperature of 150° and nitrogen flow rate of 60 ml./min. showed the absence of tripropyl phosphate. Paper chromatography using a basic developing solvent\(^{110}\) [isopropanol (40 ml.), isobutanol (20 ml.), ammonia (10 ml.) of s.g. 0.83] followed by spraying with a molybdate reagent\(^{110}\) [perchloric acid (5 ml. of 60%), hydrochloric acid (1 ml. of 12N), ammonium molybdate tetrahydrate (1 g.), water (95 ml.)], then treatment with hydrogen sulphide showed two phosphorus-containing compounds (\(R_F^1\)'s 0.42, 0.82) in this residual oil.
DISCUSSION

1. FORMATION AND DECOMPOSITION OF ALKYL ESTERS OF THE PHOSPHONATE, PHOSPHINATE, PHOSPHORODITHIOATE AND PHOSPHOROTHIOATE ANIONS.

1.1 Reaction of 2-Methyloxiran with Ethyl Methylphosphonate.

The reaction of epoxides with dialkyl phosphates has been extensively studied, the reaction of ethylene oxide with a phosphonic acid also being reported (Introduction, 2.1).

When ethyl methylphosphonate was allowed to react with 2-methyloxiran, the expected addition product was isolated. The isomer which was obtained was shown by p.m.r. analysis to be the one predictable for the acid-catalysed ring opening of an epoxide (Parker and Isaacs):\textsuperscript{111}

\[
\text{MeP(O)(OEt)O} \xrightarrow{\text{+}} \text{CH}_2\text{CH.CH.Me} \rightarrow \text{MeP(O)(OEt)OCH}_2\text{CH(OH)Me}
\]

The ester became acidic after a prolonged period at room temperature. Thermal decomposition at 110° caused the appearance of a (P)OH absorption in the infrared spectrum. Formation of the readily hydrolysed five-membered cyclic phosphonate (III) could lead to the observed phosphonic acid moiety:
Attempted methylation and acetylation of the hydroxylic function failed to give pure products probably because of the labile nature of the ester. Hydrolysis of the ester in sodium hydroxide (2N) for 3 days at 20° gave crude 2-hydroxypropyl methylphosphonate but attempted purification by distillation failed perhaps due to a thermal decomposition in a manner similar to the above. No further study of the hydrolysis reaction was made.

1.2. Attempted Reaction of Oxaziridines with Ethyl Methylphosphonate.

A phosphorus-containing product was not obtained when 2-t-butyl-3-phenyloxaziridine was heated at 80° for 166 hr. in the presence of ethyl methylphosphonate. Instead, the oxaziridine underwent thermal isomerisation to give \( N\)-t-butylbenzamide (35%), suggesting that the rearrangement was acid-catalysed, since a nitrone (IV) is obtained when
2-t-butyl-3-phenyloxaziridine is heated alone in diethylene-glycol dimethyl ether.\(^{112}\)

\[
\begin{align*}
\text{Ph.CH}=\text{N}^+\text{CMe}_3 \\
\end{align*}
\]

The acid-catalysed rearrangement may be formulated as follows:

\[
\begin{align*}
\text{Ph.CH} - \text{N.CMe}_3 & \xrightarrow{H^+} \text{Ph.CH} - \text{N.CMe}_3 \\
& \xrightarrow{H^+} \text{Ph.CO.NH.CMe}_3
\end{align*}
\]

(V)

Benzaldehyde (50%) was also obtained and this could arise from hydrolysis of either (IV) or (V). Ethyl methylphosphonate was recovered unchanged.

In the attempted reaction of 2-t-butyl-3-\(\underline{\text{p}}\)-nitrophenyl-oxaziridine with ethyl methylphosphonate at 30\(^\circ\) in chloroform the rate of loss of active oxygen was essentially the same as in the isomerisation of the oxaziridine itself in chloroform. Therefore it was concluded that the phosphonate took no part in the reaction. The corresponding benzamide was again obtained even in the absence of phosphonate. Perhaps this rearrangement is favoured in preference to nitrone formation by the presence of the electron-withdrawing \(\underline{\text{p}}\)-\(\text{NO}_2\) group.
Thus, oxaziridines do not appear to be promising alkylating agents for the $\text{PO}_2^-$ ion.

1.3. Reaction of Nitrile Oxides with Phosphonate, Phosphinate, Phosphorodithioate and Phosphorothioate Anions.

1.3.1 Preparation and reactivity of nitrile oxides. - The most common method of preparing nitrile oxides (VI) is by treatment of hydroxamoyl chlorides (VII) with a strong base, such as triethylamine:

\[
\text{RC(Cl)=NOH} + \text{Et}_3\text{N} \rightarrow \text{RC=NO}^- + \text{Et}_3\text{NH}^+ \\
\text{(VII)}
\]

Most nitrile oxides are very reactive compounds and in solution or the liquid state, dimerise rapidly to give furoxans:

\[
2 \text{RC=NO}^- \rightarrow \text{R} \cdot \text{C}=\text{N} \cdot \text{O} \\
\text{(VI)}
\]
The stability of nitrile oxides varies from a few minutes at 0° (R = Me) to > 30 days for the solid (R = p-NO₂·C₆H₄). Grundmann and Dean have reported that a series of o,o'-disubstituted aryl nitrile oxides are stable since dimerisation is sterically prevented. The three nitrile oxides (R = Me, p-NO₂·C₆H₄, 2,4,6-Me₃C₆H₂) used in the present investigation encompassed this large range of reactivity, p-nitrobenzonitrile oxide being particularly suitable because of its stability and of the tendency of p-nitrophenyl substituents to give solid products. Nitrile oxides undergo a variety of addition reactions which are summarised by Grundmann, reaction with compounds bearing a labile proton being of particular interest in the present investigation. For example reaction with thiols, amines and phenols occurs as follows:

\[ \text{HX} + \text{RC}-\text{NO}^- \rightarrow \text{RC(X)}=\text{NOH} \]

\[ (X = \text{RS}, \text{RNH}, \text{RO}) \]  

(VIII)

Of even greater bearing on the work described herein is the recently reported reaction of nitrile oxides with carboxylic acids and their sodium salts. Thus Grundmann and Frommeld have reported the following:
The same type of product had been made many years previously and was shown to readily rearrange:

\[
\text{PhC(Cl)=NOH} + \text{PhCO}_2\text{Ag} \quad \rightarrow \quad \text{PhC(OCOPh)=NOH} + \text{AgCl}
\]

When Alexandrou and Nicolaides attempted the reaction of benzonitrile oxide with salts of carboxylic acids, the initial addition product was not isolated but the rearranged product (IX) (an aryl benzamido) was obtained as above and they suggested an intramolecular acyl migration:

\[
\text{PhC=N} \quad \rightarrow \quad \text{Ph.CO.NH.O.CO.R} \quad \ldots \quad (7)
\]

(IX)

In the present work it has been shown that products of type \((\text{VIII})(\text{RC}(X)=\text{NOH}; \ X = \text{R}_2\text{PO}_2)\) are formed when a phosphonic or phosphinic acid is allowed to react with \(p\)-nitrobenzonitrile oxide. No evidence of phosphoryl migration analogous to (7) was found in the neutral products.
However when they were treated with base or when X was R₂PS₂ or R₂PO₄, compounds of typo (VIII) [RC(X) = NOH] were not isolated, but probably decomposed by a route similar to (7).

1.3.2 Reaction of ethyl methylphosphonate and dihexylphosphinic acid with nitrile oxides. - Reaction of ethyl methylphosphonate with acetonitrile oxide, 2,4,6-trimethylbenzonitrile oxide and p-nitrobenzonitrile oxide were attempted. An infra-red study showed that reaction between ethyl methylphosphonate and acetonitrile oxide was complete in 1 hr, whereas dimerisation of the nitrile oxide and also reaction of it with triethylammonium ethyl methylphosphonate occurred much more slowly. The product obtained from ethyl methylphosphonate and acetonitrile oxide was a labile oil which could not be purified. In the light of later work this product was probably MeP(O)(OH)OC(Me)=NOH.

2,4,6-Trimethylbenzonitrile oxide, in which steric hindrance prevents dimerisation, formed no phosphorus-containing product when allowed to react with ethyl methylphosphonate possibly because approach of the bulky phosphoryl group was also hindered.

Reaction between ethyl methylphosphonate and p-nitrobenzonitrile oxide with rigid exclusion of moisture afforded the required adduct, ethyl α-hydroxyimino-4-nitrobenzyl
methylphosphonate, (X) (where Ar = \( p\)-NO\(_2\)C\(_6\)H\(_4\) in this and all subsequent formulae):

\[
\text{Ar}^+ = \text{NO}^- + \text{MeP(O)(OEt)CH} \rightarrow \text{MeP(O)(OEt)CC(Ar)=N=O} \quad \ldots (8)
\]

which was stable in the solid state in the absence of light but was immediately decomposed in solutions containing a trace of water. For this reason it was difficult to obtain good analytical figures, different professional analysts reporting quite different percentages of carbon, hydrogen and nitrogen. However, the identity of the product was established beyond all reasonable doubt by infra-red and p.m.r. analyses and equivalent weight measurements (see below).

When this reaction was repeated in the presence of traces of water, the stable \( \alpha \)-hydroxyimino-4-nitrobenzyl methylphosphonate (XI) was obtained, and this was shown to arise by hydrolysis of the ethyl phosphonate:

\[
\text{MeP(O)(OEt)C(Ar)=NO} + \text{H}_2\text{O} \rightarrow \text{MeP(O)(OH)OC(Ar)=NO} + \text{EtOH}
\]

(XI) 

The infra-red spectra of (X) and (XI) were quite different (see Figs. 1 and 2). P.m.r. studies showed the disappearance of the \( \text{PO}_2^\text{=} \) protons and appearance of the ethanolic protons on
Fig. 1. Infrared spectrum of ethyl 4-hydroxyimino-4-nitrobenzyl methylphosphonate (Nujol mull). It is of interest to note that the P=O band at 1030 cm⁻¹ has shifted to 1000 cm⁻¹ in the spectrum of a 4% solution of the ester in dioxane, indicating a considerable weakening of the P=O bond, perhaps due to hydrogen bonding with the oximo-group.
Fig. 2  Infrared spectrum of α-hydroxyimino-4-nitrobenzyl methylphosphonate (Nujol mull)
addition of a trace of water to a solution of (X). Titration of the decomposition product from (X) with sodium hydroxide showed that two equivalents of acid had been formed, the titration curve being similar to that obtained for the α-ethylated product (XI), and the equivalent weights so obtained confirmed that (X) contained very little impurity. By-products isolated from the reaction of the phosphonate with the nitrile oxide in the presence of a small amount of water were di-p-nitrophenylfuroxan and p-nitrobenzhydroxamic acid, arising from dimerisation and hydrolysis of the p-nitrobenzonitrile respectively; the amount of hydroxamic acid was increased at the expense of (XI) when the proportion of water in the reaction mixture was increased. Grundmann and Frommeld have reported that the reaction of water with a nitrile oxide to give a hydroxamic acid is acid-catalysed, thus explaining the formation of hydroxamic acid in our case. Kinetic studies of reaction (9) are reported in section 1.3.3 and possible mechanisms for the reaction are deduced.

When the reaction between dihexylphosphinic acid and p-nitrobenzonitrile oxide was carried out, α-hydroxyimino-4-nitrobenzyl dihexylphosphinate (XII) was obtained:

\[
\left(\text{C}_6\text{H}_{13}\right)_2\text{PO}_2\text{H} + \text{Ar}^\dagger\text{C}=\text{NO}^- \rightarrow \left(\text{C}_6\text{H}_{13}\right)_2\text{PO}.\text{OC}^\text{Ar}^\dagger=\text{NCH}
\]

(XII)
This product was stable in both acidic and basic solution for at least \( \frac{1}{2} \) hr. in contrast to the ethyl phosphonate (X) above.

In the attempted reaction of diethyl phosphate with p-nitrobenzonitrile oxide a complex mixture of oils was obtained, which could not be separated. The titration curve suggested a mixture of phosphoric acids was present.

When the sodium salt of ethyl methylphosphonate was allowed to react with p-nitrobenzhydroxamoyl chloride in ethanolic solution, p-nitrobenzonitrile oxide was precipitated suggesting that the phosphonate anion acts as a base to remove the proton from the hydroxamoyl chloride, which then decomposes in the usual fashion to give nitrile oxide.

Since the salts of phosphorothioic and-dithioic acids are more stable than the acids themselves, they were employed in reaction with p-nitrobenzhydroxamoyl chloride (sections 1.3.4, 1.3.5), which would presumably first form the nitrile oxide in a manner similar to the above; this would then react with the phosphorothioic and-dithioic anions in a manner analogous to that of the phosphonate and phosphinato anions described above.

1.3.3 Kinetic results and mechanism of hydrolysis of ethyl O-hydroxyimino-\( \alpha \)-nitrobenzyl methylphosphonate. - The
kinetics of hydrolysis of ethyl O-hydroxyimino-4-nitrobenzyl methylphosphonate were investigated in the pH range 2 to 5:

\[
\text{MePO(OEt)}(\text{CC})\text{(Ar)}=\text{NOH} + \text{H}_2\text{O} \rightarrow \text{MePO(OH)(CC)(Ar)}=\text{NOH} + \text{EtOH}
\]

For a first order reaction:

\[
t = \frac{2.303}{k_1} \log \frac{n}{a-x} \quad \ldots (i)
\]

where \( k_1 \) = unimolecular rate constant

\( a \) = initial number of moles of ester

\( x \) = number of moles of ester decomposed after

\( \) time \( (t) \).

The reaction was followed by titration of the acid formed \((\text{POH})\) with sodium hydroxide. Since the extent of ionisation of \(\text{POH}\) is dependent on the \(\text{pH}\) of the reaction mixture, the number of moles \((n)\) of sodium hydroxide added at a given \(\text{pH}\) at time \((t)\) will be proportional to, but not equal to, the number of moles \((x)\) of ester hydrolysed.

\[i.e. \quad n = Kx\]

and therefore

\[V = K'x \quad \ldots (ii)\]

where \( V \) is the volume of sodium hydroxide added at time \((t)\)
and \( K, K^1 \) are constants. At \( t_\infty \), \( V \) becomes \( V_\infty \) and \( x \) becomes a giving

\[
V_\infty = K^1 a \quad \ldots \ (iii)
\]

Substitution of \( x \) and \( a \) from (ii) and (iii) in equation (i) gives

\[
t = \frac{2.303}{k_1} \left[ \log V_\infty - \log (V_\infty - V) - \log K^1 \right]
\]

and since \( V_\infty \) and \( K^1 \) are constant for a given run a plot of \( t \) versus \( \log (V_\infty - V) \) should give a straight line of slope 

\[-2.303/k_1\]

provided that hydrolysis reaction is first order with respect to the ester.

Straight line plots were indeed obtained in the pH range 2.0 to 4.5, typical plots at 25.0 and 0.4°C being shown in Fig. 3. The rate coefficients obtained are given in Table 6 and were reproducible to \( \pm \) 5%.

Reactions were carried out in 2% aqueous ethanol of ionic strength, 0.1M (see experimental). When the reaction medium was changed to 4% aqueous ethanol or 2% aqueous dioxan, no change in rate coefficient occurred.
Fig. 3. Typical first order plots obtained at pH 3.0; Θ 25.0°C; Δ 0.4°C
Table 5. Dependence of Rate Coefficient on pH

<table>
<thead>
<tr>
<th>pH</th>
<th>$k_1^{25}$</th>
<th>$2 + \log k_1^{25}$</th>
<th>$k_1^0$</th>
<th>$2 + \log k_1^0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>0.69</td>
<td>1.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>0.70</td>
<td>1.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.0</td>
<td>0.71</td>
<td>1.85</td>
<td>0.078</td>
<td>0.29</td>
</tr>
<tr>
<td>3.5</td>
<td>0.65</td>
<td>1.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.0</td>
<td>0.53</td>
<td>1.72</td>
<td>0.061</td>
<td>0.78</td>
</tr>
<tr>
<td>4.5</td>
<td>0.42</td>
<td>1.62</td>
<td>0.040</td>
<td>0.61</td>
</tr>
</tbody>
</table>

* $k_1^{25}$ is the unimolecular rate coefficient at 25.0°C

† $k_1^0$ is the unimolecular rate coefficient at 0.4°C.

A plot of pH versus $2 + \log k_1$ is given in Fig. 4. The temperature dependence of the rate coefficient was determined between 0°C and 25°C at a pH of 3.0. This was in the pH independent region and so slight inaccuracies in determining the pH of the solutions at lower temperatures would cause little change in the rate coefficient. The results are recorded in Table 6.
Fig. 4 Dependence of rate coefficient on pH: ○ 25.0°C; △ 0.4°C.
Table 3. Dependence of Rate Constant on Temperature at pH 3.0

<table>
<thead>
<tr>
<th>Temp. (°C)</th>
<th>Temp. (°K)</th>
<th>10^3/Tempr. (°K^-1)</th>
<th>k_1 (min^-1)</th>
<th>2 + log k_1</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.0</td>
<td>298.0</td>
<td>3.356</td>
<td>0.81</td>
<td>1.85</td>
</tr>
<tr>
<td>19.8</td>
<td>292.8</td>
<td>3.416</td>
<td>0.43</td>
<td>1.64</td>
</tr>
<tr>
<td>14.7</td>
<td>287.7</td>
<td>3.475</td>
<td>0.28</td>
<td>1.45</td>
</tr>
<tr>
<td>10.3</td>
<td>283.3</td>
<td>3.530</td>
<td>0.19</td>
<td>1.25</td>
</tr>
<tr>
<td>5.0</td>
<td>278.0</td>
<td>3.597</td>
<td>0.11</td>
<td>1.03</td>
</tr>
<tr>
<td>0.4</td>
<td>273.4</td>
<td>3.658</td>
<td>0.078</td>
<td>0.83</td>
</tr>
</tbody>
</table>

The straight line of best fit for the plot of log k_1 versus 1/T^°, where T^° is the absolute temperature, was determined by the method of least squares to be:

\[ \log k_1 = -3.247 \times 10^3 \left( \frac{1}{T} \right) + 10.738 \quad \ldots \quad (iv) \]

The energy of activation (E_A) for the reaction is related to the slope of this line by the equation:

\[ \text{slope} = -\frac{E_A}{2.303 R} \]

where R is the gas constant. E_A was hence found to have a value of 14.9 kcal.mole^-1.

The relation between rate constant, temperature,
energy of activation and entropy of activation ($\Delta S^\ddagger$) is given by Schaleger and Long:

$$k_1 = \frac{e^k}{h} T \exp(\Delta S^\ddagger / R) \exp(-E_A / RT) \quad \cdots (v)$$

where the composite constant ($\frac{e^k}{h}$) has the value $5.635 \times 10^{10}$ deg.$^{-1}$ sec.$^{-1}$ for reactions in solution. A value of $k_1$ equal to $0.070$ min.$^{-1}$ was obtained for a temperature of $273^\circ$K from equation (iv) and substitution of these values in (v) yielded an entropy of activation of $-19$ e.u.

Over the pH region 3.0 to 4.5 a steady fall in observed rate coefficient was obtained (Fig. 4.). The rate curve showed a very rapid initial uptake of alkali followed by the usual first-order decomposition. At pH 5.0, however, first order plots were no longer obtained, and decomposition was very slow (the nature of this decomposition was later investigated, see p. 107). When the solution was readjusted to pH 3.5 after 1 or 5 mins., the usual first-order plot was obtained and a rate-constant of $0.55$ min.$^{-1}$ calculated. After 5 min., the amount of the ethyl phosphonate regenerated was much less than that after 1 min., showing that the oximate anion was slowly decomposing. It was concluded
that the initial rapid uptake of alkali together with the steady fall-off in observed rate constant was due to the reversible ionisation of the NOH moiety, thus reducing the concentration of the protonated species. This occurred at a much lower pH than would be expected for the related p-nitrobenzaldoxime which has a $pK_a$ of 10. Thus the phosphoryl substituent must have a large perturbing effect on the acidity of the oxime. In support of this, the related $\alpha$-hydroxyimino-4-nitrobenzyl dihexylphosphinate had a $pK_a$ of 5.6 in 50% aqueous ethanol as measured by titration. The $pK_a$ in water would not be expected to differ by more than 0.4 units from this value, since Bell has shown that the change in $pK_a$ in going from water to ethanol for a series of carboxylic acids does not change by more than 0.7 units.

The $pK_a$ of the oxime group in $\alpha$-hydroxyimino-4-nitrobenzyl ethyl methylphosphonate can be calculated from the data in Table 5 over the pH region 3.0 to 4.5 by use of the relation:

$$K_a = [H^+] (k_1/k_1^1 - 1)$$

where

$K_a$ is the equilibrium constant for the ionisation of -NOH,

$k_1$ is the rate constant for decomposition of fully protonated oxime and $k_1^1$ is the observed rate constant for the decomposition
of the partially ionised species at the given \([H^+]\). This relation holds provided the rate of decomposition of the protonated oxime is very much faster than decomposition of the oximate anion. Since virtually constant values for \(K_a\) were obtained at both \(0^\circ\) and \(25^\circ\), this assumption is justified. The average calculated value of the \(pK_a\) was 4.6 at \(25^\circ\) and 4.5 at \(0^\circ\).

The most remarkable feature of this hydrolysis reaction is the large enhancement in rate compared with a simple phosphonate such as ethyl \(p\)-nitrophenyl methylphosphonate for which Hudson and Keay \(^{121}\) report a bimolecular rate constant of 0.055 l. mole\(^{-1}\) hr\(^{-1}\) at \(110^\circ\) for the acid-catalysed hydrolysis reaction to give ethanol plus \(p\)-nitrophenyl methylphosphonate. At pH 2 this would have a value of 0.91 \(\times\) 10\(^{-5}\) min\(^{-1}\) at \(110^\circ\). Calculation of \(k_1\) for ethyl \(\alpha\)-hydroxy-imino-4-nitrobenzyl methylphosphonate at a temperature of \(110^\circ\), from (iv) gives a value of 1.9 \(\times\) 10\(^2\) min\(^{-1}\) i.e. an enhancement in rate of 2 \(\times\) 10\(^7\). This strongly suggests an intramolecular acceleration involving neighbouring group participation by the fully protonated oxime. The possible transition states which can be envisaged are
The zwitterion (XV) can be excluded since the estor was insoluble in water and the related α-hydroxyimino-4-nitrobenzyl dihexylphosphinate titrated as a strong acid. The large negative entropy is consistent with a rigid transition state such as (XIII) or (XIV). Protonation on the phosphoryl oxygen (XIV) also seems unlikely as one would expect to find that the better leaving group would be eliminated to give a hydroxamic acid (c.f. p107 where the oximate anion is thought to cause elimination of hydroxamic acid rather than ethanol).
It should be noted that for formation of a transition state such as (XIII) or (XIV) the hydroxylic group must be anti to the aryl substituent. This form is probably stabilised in the ground state compared with the syn-form by hydrogen bonding to the phosphoryl or alkoxyl oxygen.

Decomposition of (XIII) could proceed by an $A_1$ mechanism, by attack by water in an $A_2$ mechanism, or by formation of the cyclic intermediate, which would be expected to be readily hydrolysed:

\[ \text{MeP(O)} \quad \text{O} \quad \text{O} \quad \text{Ar} \]

\[ (\Lambda_1) \]

\[ \text{Et} \quad \text{H} \quad \text{MeP} \quad \text{O} \quad \text{C=NN} \quad \text{O} \quad \text{Ar} \]

\[ (\Lambda_2) \]

\[ (\text{cyclic}) \]
However, it is not possible to establish which of these occurs and whether the decomposition is synchronous with the proton transfer without further investigation.

Similar neighbouring group participation by carboxylic, carbonyl and phenolic functions in phosphate and phosphonate ester hydrolyses have been reported, all showing an enhancement in rate of about $10^7$ compared with simple phosphonates. Thus, Gordon, Notaro and Griffin$^{122}$ showed that (XVI) had a half-life of 15 mins. at 36° in neutral solution and they favour a mechanism involving proton transfer:

$$\text{Et}$$
$$\text{O}$$
$$\text{P}$$
$$\text{O}$$
$$\text{H}$$
$$\rightarrow$$
$$\text{HO}_2\text{C.C}_6\text{H}_4\text{P(O)(OEt)}\text{(OH)} + \text{EtOH}$$

(XVI)

The $p$-carboxyl isomer of (XVI) and the $\sigma$-carboxylato anion of (XVI) hydrolysed at a much slower rate. The analogous phosphate below hydrolysed in 72 hr. at room temperature:$^{123}$

$$\text{Mo}$$
$$\text{O}$$
$$\text{P}$$
$$\text{O}$$
$$\text{H}$$
$$\rightarrow$$
$$\text{HO}_2\text{C}(=\text{CH}_2)\text{OP(O)(OH)}_2 + 2\text{MoOH}$$
Surprisingly, at pH 8 hydrolysis of the labile onolate ester linkage did not occur, the monomethyl ester, \(-O_2C.C(=CH_2)OP(0)-(OH)(OMe)\), being obtained instead and this is difficult to explain by the anionic decomposition schemes outlined on pp. 107, 108.

Stoinberg and co-workers\(^{124}\) have postulated that the acceleration of a phosphonate ester hydrolysis by a neighbouring carbonyl group involves the initial hydration of the carbonyl function:

![Chemical structure](image)

The observation that the reaction is general-base catalysed indicates that hydration of the carbonyl group is the slow step and thus the rate constant obtained will not be comparable to the value obtained in this work.

The work by Higuchi\(^{125}\) on the neighbouring group participation of a phenolic proton in the hydrolysis of the phosphonate (XVII) is analogous to the present investigation:

![Chemical structure](image)
He obtained a similar pH profile in the range pH 2 to 7 but the fall-off in rate constant began at pH 4.5, showing that the phenol is a slightly weaker acid than the oximo and, in accord with this, he found that the unimolecular rate constant was $2.3 \times 10^{-2} \text{ min}^{-1}$ at $30^\circ C$. This reaction is thus at least 30 times slower than the oximo-assisted reaction. The energy and entropy activation of 13.9 kcal and -30 e.u., respectively, correspond very well with the values obtained for the oxime assisted hydrolysis.

It is of interest to note that the related 2-hydroxyalkyl phosphate diesters$^{51,52}$ are more stable than the foregoing esters, uridine-3' dibenzyl phosphate decomposing at pH 2 in about 16 hr., the isolation of both the uridine-2' and -3' monobenzyl phosphates suggesting formation of a five-membered cyclic intermediate during the hydrolysis.$^{52}$

The foregoing systems, where a proton is readily transferable to an alkoxyl group, provide excellent models for the ageing of an inhibited cholinesterase (i.e. dealkylation of the phosphonyl moiety assisted by a proton from the enzyme). In addition, the realkylation of the $>\text{PO}_2^-$ ion by means of a nitrile oxide giving an oxime function in a position favourable to assist dealkylation, now provides the first viable model for the reactivation of aged phosphorylated
cholinesterase.

The nature of the decomposition of the oximate anion, \( \text{MeP(O)(OEt)CC(Ar)\text{=NO}^-} \), was investigated by allowing ethyl-\( \alpha \)-hydroxyimino-4-nitrobenzyl methylphosphonate to decompose in buffer solution, pH 5, at 20° for 2 hr. \( \mu \)-Nitroaniline was obtained from the above and from the decomposition of \( \alpha \)-hydroxyimino-4-nitrobenzyl dihexylphosphorinate in pH 5 buffer at 20° for 24 hr. This is thought to have arisen by a rearrangement analogous to (7) (p. 90) to give the intermediate (XVIII) which then decomposes via a L"ossen rearrangement:

\[
\begin{align*}
\text{R} & \quad \text{O} \quad \text{R}^1 \quad \text{O-C\text{--Ar}} \\
\text{R}^1 & \quad \text{O} \quad \text{R}^1 \quad \text{O-C\text{--Ar}} \\
\text{R} = \text{Me; } R^1 = \text{EtO} & \quad (\text{XVIII}) \\
R = R^1 = C_6H_{13} & \\
\end{align*}
\]

In support of this type of reaction, Samuel and Silver\textsuperscript{126} have shown that intermediates such as (XVIII) which contain an N-phosphonyl or N-sulphonyl substituent are so labile that they cannot be isolated in their attempted preparation from e.g. di-isopropyl phosphorofluoridate and benzhydroxamic acid. They confirmed by \( ^{18} \)O studies that the decomposition
products had arisen from a Lössen rearrangement of the desired hydroxamic acid:

\[ \text{e.g. } [(\text{Pr}^4\text{O})_2\text{PO.O.NH.COPh}] \rightarrow \text{PhNCO} + (\text{Pr}^4\text{O})_2\text{PO}_2\text{H} \]

\[ \text{PhCO.NHOH} \]

\[ \text{Ph.CO.NH.O.CO.NHPh.} \]

A somewhat comparable decomposition is reported by Ramirez et al.\textsuperscript{127} who found that the following phosphate ester rapidly hydrolysed at pH 8:

\[ (\text{MeO})_2\text{PO.O.CHMe.CO.Me} \xrightarrow{\text{H}_2\text{O}} (\text{MeO})_2\text{PO}_2\text{H} + \text{MeCO.CH(Me)OH} \]

They favour a base-catalysed hydration of the carbonyl group followed by formation of a five-membered intermediate by intramolecular attack. However the closely similar ester described by Steinberg and co-workers (p.105) decomposes in a different manner indicating that the factors affecting the route of decomposition must be very finely balanced.

Both the acidic and anionic intramolecular mechanisms for the hydrolysis of phosphate and phosphonate esters recorded above are in accord with the findings of Thanassi and Bruce\textsuperscript{128} on carboxylic acid and carboxylate ion neighbouring group participations in carboxylic ester hydrolysis. They report that in COOH participation the poorer leaving group is hydrolysed, while in COO\(^{-}\) participation the better leaving group is hydrolysed.
1.3.4 Reaction of p-nitrobenzhydroxamoyl chloride with the potassium and nickel salts of CO-diethyl phosphorodithioate.

The products obtained from the reaction at either 20° or 100° of potassium CO-diethyl phosphorodithioate with p-nitrobenzhydroxamoyl chloride were CO-diethyl phosphorothioate, p-nitrobenzonitrile, sulphur, and potassium chloride:

\[(\text{EtO})_2\text{PS} \cdot \text{SK} + \text{ArC(Cl)=NOH} \rightarrow (\text{EtO})_2\text{PSOH} + \text{ArCN} + S + \text{KCl} \ldots (10)\]

Sulphur and benzonitrile have been shown to arise from the thermal decomposition of benzthiohydroxamic acid: \(129(a)\)

\[
\text{PhC(SH)=NOH} \xrightarrow{\text{thermal}} \text{PhC(S)NH} \xrightarrow{\text{thermal}} \text{PhCN} + S + \text{H}_2\text{O}
\]

whereas the 5-benzyl ester gave equimolar amounts of dibenzyl disulphide, benzonitrile and benzoic acid. \(129(b)\)

The first step in reaction (10) is presumably the formation of the addition product, \((\text{EtO})_2\text{PS} \cdot \text{SC(Ar)=NOH}\), which may rearrange via a five-membered transition state as follows:

\[
(\text{EtO})_2\text{PS} + \text{Ar} \rightarrow (\text{EtO})_2\text{PSOH} + S + \text{ArCN} \ldots (11)
\]

The displacement of sulphur by oxygen attack at phosphorus
is a further indication of the greater nucleophilicity of oxygen compared with sulphur towards phosphorus.

Reaction of the more soluble nickel salt in place of the potassium salt of the dithioate with p-nitrobenzhydroxamoyl chloride yielded the same products after heating for 5½ hr. at 100°C in dioxan. However no reaction in light petroleum (b.p. 60-80°C) had occurred after 27 hr. at 70°C probably because the initial partial ionisation of the nickel salt, necessary to initiate the formation of nitrile oxide (see p. 94) did not occur in a solvent of such a low dielectric constant.

1.3.5. Reaction of p-nitrobenzhydroxamoyl chloride with potassium CO-diethyl phosphorothioate. - In the reaction of potassium CO-diethyl phosphorothioate with p-nitrobenzhydroxamoyl chloride, p-nitrobenzonitrile and sulphur together with some diethyl phosphato were again obtained probably by a concerted displacement similar to reaction (11) (p. 109). In addition, some p-nitrophenyl-isothiocyanate was isolated perhaps arising in a manner similar to a Lössen rearrangement.
Thus, two competitive pathways of decomposition of the initial adduct, \((\text{EtO})_2\text{PO}.\text{SC(Ar)}=\text{NOH}\), have been shown to exist. No evidence of formation of isothiocyanate in the decomposition of \((\text{EtO})_2\text{PS}.\text{SC(Ar)}=\text{NOH}\) was found and this may be because \(\text{>PO}^-\) is a poorer leaving group than \(\text{>PO}_2^-\) and requires the additional movement of electrons from the sulphur to assist O-N bond breaking [equation (11), p. 109].

The only reported Lössen rearrangement of a thiohydroxamic acid appears to be the enzyme catalysed rearrangement:

\[
\text{glucoside - S - C(CH}_2\text{Ph)} = \text{NOSO}_3^- \longrightarrow \text{PhCH}_2\text{NOCS}
\]

The formation of a small amount of \(p\)-nitrobenzamide in the reaction of the hydroxamoyl chloride with the phosphorothionate may indicate that the ambident \(\text{>PO}^-\) ion (see Introduction, 2-4) may react to a small extent in the form \(\text{>P}^-\) leading to \((\text{EtO})_2\text{P(S)CC(Ar)}=\text{NOH}\). However it is difficult to explain how \(p\)-nitrobenzamide would be formed from this on the basis of the above schemes.
2. REACTIONS OF PHOSPHON- AND PHOSPHORAMIDATES.

2.1 Reaction of Phosphon- and Phosphoramidates with Propyl Iodide.

Until now, the study of alkylation reactions of phosphoramidates has been restricted to thermal self-alkylations (see Introduction 1.3). Investigations reported in this thesis on the reaction of diethyl phosphoramidate with propyl iodide show that there are two sites of alkylation in the amide, leading to three types of reaction. Both oxygen and nitrogen are nucleophilic towards propyl iodide; the nucleophilicity of phosphoryl oxygen in related compounds has been well established (Introduction 1.1).

In the reaction of diethyl phosphoramidate with propyl iodide, attack by phosphoryl oxygen followed by dealkylation by iodide ion led to alkyl exchange reactions, giving ethyl propyl- and dipropyl- phosphoramidates:

\[(\text{EtO})_2\text{PO} \cdot \text{NH}_2 + \text{Pr}^n \text{I} \rightarrow (\text{EtO})_2\text{P(Pr}^n\text{O})\text{NH}_2 \text{I}^{-} \rightarrow (\text{EtO})(\text{Pr}^n\text{O})\text{PO} \cdot \text{NH}_2 + \text{EtI} \quad \ldots \quad (12)\]

\[(\text{EtO})(\text{Pr}^n\text{O})\text{PO} \cdot \text{NH}_2 + \text{PrI} \rightarrow (\text{EtO})_2\text{P(Pr}^n\text{O})\text{NH}_2 \text{I}^{-} \rightarrow (\text{Pr}^n\text{O})_2\text{PO} \cdot \text{NH}_2 + \text{EtI} \quad \ldots \quad (13)\]

The reaction conditions of 6 days at 100° suggest that the
phosphoryl oxygen in diethyl phosphoramidate, perhaps assisted by $p\pi - d\pi$ donation from the nitrogen lone pair, may be more nucleophilic than, for example, that of diethyl ethylphosphonate which undergoes alkyl exchange with butyl iodide at $160^\circ$ in 25 hr. 3

The nucleophilic reactions of the nitrogen in diethyl phosphoramidate with propyl iodide are comparable to those of sulphur in phosphorothiolates (see Introduction, 1.2), where alkyl exchange on the sulphur and also fragmentation of the P-S bond occurred on reaction with alkyl iodides. Thus diethyl-, ethyl propyl- and dipropyl-N-proplyphosphoramidates were obtained by (14), while fragmentation led to the formation of polymetaphosphate (15).

\[
(RO)_2PO.NH_2 + Pr^I \rightarrow (RO)_2PO.NH_2Pr^+ I^-
\]

\[
(RO)_2PO.NHPr^+ + HI \quad Pr^+NH_2 + RO.PO_2 + RI
\]

A complex mixture of alkylammonium iodides was also obtained. The elimination of hydrogen iodide by (14) would probably be aided by reaction with the propylamine produced in (15) leading to propylammonium iodide. Alternatively,
Propylamine could react with propyl iodide in a series of equilibria:

\[
\begin{align*}
Pr^+_2NH_2 + PrI^{-} & \rightleftharpoons Pr^+_2NH_2 + I^{-} \rightleftharpoons Pr^+_2\text{NH} + HI \\
Pr^+_2\text{NH} + I^{-} & \rightleftharpoons Pr^+_3\text{NH} + HI \\
Pr^+_3\text{NH} + I^{-} & \rightleftharpoons Pr^+_4\text{N} + HI
\end{align*}
\]

Further complexities in the iodide mixture would be provided by the presence of ethyl iodide arising from (12), (13) and (15). Thus, further characterisation of the iodide mixture was not attempted.

Some phosphate ion impurity was found in the iodide mixture which could arise as follows from traces of moisture present in the reaction mixture:

\[
(\text{RO})_2\text{PO}_n\text{NH}_2Pr^n I^- + H_2O \rightarrow (\text{RO})_2\text{PO} \cdot \text{OH} \rightarrow Pr^+_n\text{NH}_3 + I^-
\]

and further support for this type of reaction is provided by the reaction of propanol or phenol with a similar complex (see section 2.2).

As a result of the complexity of the reactions
occurring when diethyl phosphoramidate was allowed to react with propyl iodide, it was difficult to estimate the extent of each reaction. Approximately 40% of the mixed phosphoramidates underwent fragmentation as shown by the amount of polymeta-
phosphate obtained. Analysis of the phosphoramidate mixture showed that the amounts of nitrogen- and oxygen- propylation by (14) and (12), (13) respectively were roughly the same. The absence of NN-dipropylated phosphoramidates in the reaction mixture is unexpected since one would predict PrNH- to be more nucleophilic than NH2-. However, the approach of a second alkyl group may be sterically hindered.

The reaction of ethyl propyl NN-dipropyl-phosphoramidate with propyl iodide was also carried out, giving dipropyl NN-dipropylphosphoramidate and ethyl iodide by a route similar to (13). Fragmentation according to scheme (15) would lead to the observed products tetrapropylammonium iodide, ethyl iodide and polymetaphosphate. The use of the NN-dipropyl-amidate precluded the occurrence of an exchange reaction similar to (14), thus eliminating the formation of hydrogen iodide and also the alkylammonium exchange reactions possible in the previous scheme.

Due to the competition of the fragmentation reaction with the phosphoryl oxygen exchange reaction it was not
possible to determine, by simple product analysis, the effect of the amino-substituent on the nucleophilicity of the phosphoryl oxygen.

The fragmentation of 1-methyl-2,2-dimethylpropyl N-cyclohexyl-P-methylphosphonamidate in propyl iodide was found to give both cyclohexylpropyl- and cyclohexylammonium iodides. The mode of fragmentation is probably different from (15) since the 1-methyl-2,2-dimethylpropyl group could form a carbonium ion in a manner analogous to that reported by Cadogan and Mackie (see p.7):

$$\text{Me(Me}^\text{CHMe.O})\text{PO.NHC}_\text{CH}_\text{H}_\text{I}_\text{I} + \text{Pr}^\text{n} \text{I} \rightarrow \text{Me(Me}^\text{CHMe.O})\text{PO.NH(Pr}^\text{n})\text{C}_\text{H}_\text{I}_\text{I} \text{I}^-$$

$$\rightarrow \text{Me}^\text{CHMe} \text{I}^- + \text{MePO}_2 + \text{C}_\text{H}_\text{I}_\text{I} \cdot \text{NHPr}^\text{n}$$

Decomposition of the secondary carbonium ion would give hydrogen iodide and a mixture of hexenes. Reaction of the cyclohexylpropylamine with hydrogen iodide would then give the observed cyclohexylpropylammonium iodide. Additional hydrogen iodide could also arise from an alkyl exchange reaction analogous to (14). This could then protonate the amidate in place of the propylation reaction and fragmentation would give cyclohexylamine and hence cyclohexylammonium iodide.
2.2 Reaction of Phosphoramidates with Propyl Iodide in the Presence of Hydroxylic Compounds.

Further evidence for an N-propylated intermediate in the reaction of phosphoramidates with propyl iodide was obtained when diphenyl N-propylphosphoramidate was allowed to react in the presence of phenol. Since iodide ion is not nucleophilic towards the phenyl group, no possibility of fragmentation by dealkylation [route (15) p. 113] exists. Instead, phenol may now act as a nucleophile towards phosphorus leading to the formation of triphenyl phosphate as follows:

\[
(\text{PhO})_2\text{PO} \cdot \text{NHPr}^n + \text{Pr}^n\text{I} \rightarrow (\text{PhO})_2\text{PO} \cdot \text{NHPr}_2^n \text{I}^-
\]

That the triphenyl phosphate which was isolated did not arise by a reaction similar to the following (reported by Petrov et al.) was determined by a control experiment performed in the absence of propyl iodide, when no reaction occurred:

\[
\text{PhOH} + \text{MePO} \cdot (\text{NET}_2)_2 \rightarrow \text{MeP(O)(OPh)}_2
\]

The nature of the amidate derivative determines its reactivity towards phenol, since ethyl phenyl N-methyl-phosphoramidate was unreactive.
When dipropyl N-propylphosphoramidate was allowed to react with propyl iodide in the presence of propanol, tripropyl phosphate was not obtained. It seems likely that iodide ion could dealkylate the phosphate under the conditions of the reaction (cf. Serras and Pilaris):\(^\text{132}\)

\[
(\text{Pr}^n\text{O})_3\text{PO} + \text{I}^- \rightarrow (\text{Pr}^n\text{O})_2\text{PO.O}^- + \text{Pr}^n\text{I}
\]

The phosphate ion might conceivably act as a nucleophile towards phosphorus in the N-propylated intermediate resulting in the formation of a pyrophosphate in much the same way as in the reaction of phosphate with a phosphoramidate monoester (Introduction 2.1):

\[
(\text{Pr}^n\text{O})_2\text{PO} + \text{NHPr}_2^n \text{I}^- \rightarrow (\text{Pr}^n\text{O})_2\text{P(O)OP(O)(OPr}^n)\text{2} \quad + \text{Pr}_2^n\text{NH} + \text{I}^-
\]

Dealkylation of tetraalkylpyrophosphates by iodide ion under similar conditions is also known, and this would lead to [(Pr\(^n\)O)(O\(^-\)P(O)]\(_2\)O. The presence of two phosphorus-containing products in the residue was demonstrated by paper chromatography, but they were not further characterised.

The rates of reaction of the amidates with propyl iodide in the presence of hydroxyllic solvents can be
semi-quantitatively compared, assuming that the propylation and not the alcoholysis is the slow step. The reaction of the dipropyl amidate went to completion in 6 days at $100^\circ$ whereas the diphenyl amidate required $4^{1/2}$ days at $125^\circ$, thus indicating that the release of electrons to the nitrogen by the propoxy- was greater by the phenoxy- group.
APPENDIX. PROTON MAGNETIC RESONANCE DATA FOR ORGANOPHOSPHORUS DERIVATIVES.

Chemical shifts are recorded as $\tau$ values (p.p.m.) using tetramethylsilane ($\tau$ 0.0) as internal standard. The multiplicity of each peak is recorded in brackets after the chemical shift, a complex multiplet being signified by "m". Coupling constants (J) are given in cycles/sec. where possible.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Conc. (%)</th>
<th>POH</th>
<th>POCH</th>
<th>CCH2C</th>
<th>PCH</th>
<th>CH3CH2O</th>
<th>CH3CH2C</th>
<th>JPOCH</th>
<th>JPOCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>(EtO)(PrO)PO2H</td>
<td>20</td>
<td>-2.62</td>
<td>6.0(m)</td>
<td>3.25(m)</td>
<td>8.58(2)</td>
<td>8.65(3)</td>
<td>9.00(3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Me(EtO)PO2H</td>
<td>5</td>
<td>-2.55</td>
<td>5.95(5)</td>
<td>-</td>
<td>-</td>
<td>8.38(3)</td>
<td>8.98(3)</td>
<td>8.0</td>
<td>18</td>
</tr>
<tr>
<td>(EtO)2PO2H</td>
<td>20</td>
<td>-0.50</td>
<td>5.26(5)</td>
<td>-</td>
<td>-</td>
<td>8.31(3)</td>
<td>-</td>
<td>6.5</td>
<td>-</td>
</tr>
<tr>
<td>(EtO)2POSH</td>
<td>10</td>
<td>2.25</td>
<td>5.85(m)</td>
<td>-</td>
<td>-</td>
<td>8.82(3)</td>
<td>-</td>
<td>9.5</td>
<td>-</td>
</tr>
<tr>
<td>(C6H13)2PO2H</td>
<td>5</td>
<td>-2.1</td>
<td>-</td>
<td>9.5</td>
<td>2.5(2)</td>
<td>-</td>
<td>9.07(3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(EtO)(PrO)PO.C1</td>
<td>10</td>
<td>-</td>
<td>5.3(m)</td>
<td>8.2(m)</td>
<td>-</td>
<td>8.58(3)</td>
<td>8.98(3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(PrO)2PO.C1</td>
<td>20</td>
<td>-</td>
<td>5.36(m)</td>
<td>8.2(m)</td>
<td>-</td>
<td>-</td>
<td>8.98(3)</td>
<td>3.4</td>
<td>-</td>
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TABLE 3. Phosphoramidates
(20% solutions in carbon tetrachloride)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NH</td>
</tr>
<tr>
<td>((\text{EtO})_2\text{PO·NH}_2)</td>
<td>5.9</td>
</tr>
<tr>
<td>((\text{EtO})(\text{Pr}^n\text{O})\text{PO·NH}_2)</td>
<td>5.8</td>
</tr>
<tr>
<td>((\text{Pr}^n\text{O})_2\text{PO·NH}_2)</td>
<td>5.9</td>
</tr>
<tr>
<td>((\text{EtO})_2\text{PO·NHPr}^n)</td>
<td>5.2(m)</td>
</tr>
<tr>
<td>((\text{EtO})(\text{Pr}^n\text{O})\text{PO·NHPr}^n)</td>
<td>5.2(m)</td>
</tr>
<tr>
<td>((\text{Pr}^n\text{O})_2\text{PO·NHPr}^n)</td>
<td>5.2(m)</td>
</tr>
<tr>
<td>((\text{EtO})_2\text{PO·NPr}^n)</td>
<td>-</td>
</tr>
<tr>
<td>((\text{EtO})(\text{Pr}^n\text{O})\text{PO·NPr}^n)</td>
<td>-</td>
</tr>
<tr>
<td>((\text{Pr}^n\text{O})_2\text{PO·NPr}^n)</td>
<td>-</td>
</tr>
<tr>
<td>((\text{PhO})_2\text{PO·NHPr}^n*)</td>
<td>4.6(m)</td>
</tr>
</tbody>
</table>

* \(\text{C}_6\text{H}_5\), 2.8
<table>
<thead>
<tr>
<th>Ester</th>
<th>Solvent</th>
<th>Conc. (%)</th>
<th>$\text{P-NO}_2\cdot\text{C}_6\text{H}_4$</th>
<th>$\text{POCH}_2$</th>
<th>$\text{PCH}_2$</th>
<th>$\text{C-CH}_2\cdot\text{C}$</th>
<th>$\text{CH}_3\text{CH}_2\text{O}$</th>
<th>$\text{CH}_3\cdot\text{C-C}$</th>
<th>NOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me(EtO)PO. OR</td>
<td>CDCl$_3$</td>
<td>2.5</td>
<td>1.73(4)</td>
<td>5.77(5)</td>
<td>8.21(2)</td>
<td>-</td>
<td>8.64(3)</td>
<td>-</td>
<td>-0.92</td>
</tr>
<tr>
<td></td>
<td>DDMSO</td>
<td>20</td>
<td>1.67(4)</td>
<td>5.72(5)</td>
<td>8.25(2)</td>
<td>-</td>
<td>8.49(3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Me(HO)PO. OR</td>
<td>DDMSO</td>
<td>20</td>
<td>1.74(4)</td>
<td>-</td>
<td>8.39(2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.22</td>
</tr>
<tr>
<td>($\text{C}<em>6\text{H}</em>{13}$)$_2$PO. OR</td>
<td>CCl$_4$</td>
<td>10</td>
<td>1.75</td>
<td>-</td>
<td>8.35(2)</td>
<td>8.61</td>
<td>-</td>
<td>9.1(3)</td>
<td>-</td>
</tr>
</tbody>
</table>

* Coincides with PCH

DDMSO is hexadeuterodimethyl sulfoxide
### TABLE 1C. Miscellaneous
(solution in carbon tetrachloride)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Conc. (%</th>
<th>a</th>
<th>b</th>
<th>Assignment</th>
<th>c</th>
<th>d</th>
<th>e</th>
<th>f</th>
<th>g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me(Me₃C₂H₂Me₅O)PO₂NH₂</td>
<td>8.70(2)</td>
<td>8.12</td>
<td></td>
<td>5.9(m)</td>
<td>0.75</td>
<td></td>
<td>7.2</td>
<td></td>
<td>2.3</td>
</tr>
<tr>
<td>Me(CH₂·Me)PO₂C₂H₂·CH(OH)Me</td>
<td>8.56(2)</td>
<td>8.8(2)</td>
<td></td>
<td>8.05(m)</td>
<td>8.55(2)</td>
<td>5.45</td>
<td>8.75(2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[Diagram of molecules]
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