THE SYNTHESIS OF SOME ORGANO-PHOSPHORUS ANHYDRIDES

A Thesis presented for the degree of
Doctor of Philosophy
of the University of London

by

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ABSTRACT

Mixed anhydrides of carboxylic acids and diesters of orthophosphoric acid are described in the literature as acylating agents. Theoretically these compounds could also be phosphorylating agents. The mechanisms of nucleophilic reactions of anhydrides of orthophosphoric acid - the pyrophosphates - and carboxylic-carboxylic anhydrides, differ considerably. In order to obtain a clearer understanding of the reactions of phosphoric-carboxylic anhydrides, relevant aspects of the reported chemistry of carboxylic-carboxylic anhydrides and pyrophosphates have been compared.

Nine phosphoric-carboxylic anhydrides have been prepared, namely those from diethyl phosphoric acid and acetic, trifluoracetic, trimethylacetic, triphenylacetic, benzoic, 2,3,6-trichlorobenzoic, 2,3,5,6-tetrachlorobenzoic, 2,3,4,5,6-pentachlorobenzoic acids, and the hypothetical ethylcarbonic acid. With the exception of the acetyl and benzoyl compounds these anhydrides have not been described before. They were prepared by interacting a salt and an acid chloride, and it has been shown that it is critical which moiety is present as the salt or acid chloride. In general the salt should be derived from the stronger acid. However when the carbonyl group is subject to considerable steric hindrance, e.g. triphenylacetic acid, the salt of the latter must be used.

It has been shown that acetyl and trimethylacetyl diethyl phosphates exclusively acylate aniline, but as the steric hindrance at the carbonyl group increases, phosphorylation becomes more important.
until it is the exclusive reaction with the tetra- and penta-chloro anhydrides above. Contrary to suggestions in the literature, trifluoracetyl diethyl phosphate was shown to acylate aniline.

A number of hitherto unreported compounds required as intermediates have been prepared, viz. 2,3,6-trichlorobenzyl acetate, 2,3,6-trichlorobenzanilide, 2,3,6-trichlorobenzoyl chloride, 2,3,5,6-tetrachlorobenzyl alcohol and the corresponding bromide and acetate, and 2,3,4,5,6-pentachlorobenzyl bromide. An improved method has been developed for the preparation of the polychlorobenzoic acids from the corresponding benzyl alcohols by potassium permanganate oxidation in pyridine.
ACKNOWLEDGEMENTS

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INTRODUCTION

In the last fifteen years a considerable effort has been devoted to the study of methods of phosphorylation, stimulated by the recognised importance of phosphorylation mechanisms in biological systems. Anhydrides, both symmetrical and unsymmetrical, of diesters of orthophosphoric acid feature predominantly in this work.

It is evident from an examination of the literature that a nucleophilic reaction involving an unsymmetrical phosphoric anhydride (e.g. a diester of orthophosphoric acid and a second acid) differs in some essential way from a similar reaction of an unsymmetrical carboxylic-carboxylic anhydride, but some of the reactions purporting to show this difference are inadequately authenticated.

Todd\(^1\) has commented briefly on this difference and given an explanation for it. The reaction between an unsymmetrical pyrophosphate and a nucleophile under basic conditions, (equation 1) and a similar reaction between a carboxylic anhydride and the same nucleophile (equation 2) demonstrate the difference.

\[
\begin{align*}
\text{RO} & \quad \text{O} \quad \text{O} \quad \text{OR'} \\
\text{RO} & \quad \text{P} - \text{O} - \text{P} \quad \text{OR'} + \text{H} - \text{Y} \quad \text{base} \quad \text{RO} & \quad \text{O} \\
\text{RO} & \quad \text{P} - \text{Y} + \text{R'O} & \quad \text{O} \\
\text{RO} & \quad \text{O} + \text{R'O} & \quad \text{P} - \text{O}^- \quad \text{......(1)}
\end{align*}
\]

ion of stronger acid.

\[
\begin{align*}
\text{R'} & \quad \text{O} \quad \text{O} \quad \text{R} \\
\text{R'} & \quad \text{C} - \text{O} - \text{C} \cdot \text{R} + \text{H} - \text{Y} \quad \text{base} \quad \text{R'} & \quad \text{C} - \text{Y} \\
\text{R'} & \quad \text{O} + \text{R'} & \quad \text{C} - \text{O} \quad \text{......(2)}
\end{align*}
\]

ion of weaker acid.
In the first case the ionic product is derived from the stronger of the two constituent acids, while in the second the ion of the weaker constituent acid of the carboxylic anhydride is formed. The difference in behaviour of the two classes of anhydride is attributed to the inability of the phosphoryl group to form an addition complex as an intermediate in the nucleophilic bimolecular reaction. By contrast, the additive properties of the carbonyl group are well known for this type of reaction. It follows from this that in the case of the pyrophosphates, the course of the reaction will be determined by the relative ease with which the P–O bonds break to form a stable ion. This mechanism favours fission occurring in such a manner that the ion of the stronger of the two possible acids is liberated.

The literature on the reactivity of carboxylic anhydrides contains data that shows the importance of steric effects. It has been established by Gold and co-workers\textsuperscript{2–4} that the normal course of a nucleophilic reaction with an unsymmetrical carboxylic anhydride may be changed in cases where the carbonyl group of the stronger of the two acids comprising the anhydride is sterically hindered. However, in the field of mixed phosphoric anhydrides steric effects have received little attention.

Mixed phosphoric-carboxylic anhydrides have been prepared and, in general, have been found to be acylating agents\textsuperscript{5}. However Todd has suggested that the mixed anhydride formed from a phosphodiester and trifluoracetic acid may be a phosphorylating agent\textsuperscript{1}. Literature evidence, which will be presented later, also suggests that some
degree of phosphorylation does take place when phosphoric-carboxylic anhydrides react with nucleophiles.

The main result of the work described in the practical section of this thesis is to show that extreme steric hindrance, at the carbonyl group of mixed anhydrides of carboxylic acids and diethyl phosphoric acid, causes the normal course of the reaction to be altered to such an extent that the compounds may be classified as phosphorylating agents rather than acylating agents.

The chemistry of phosphoric-carboxylic anhydrides will obviously be related to some aspects of the chemistry of pyrophosphates on the one hand and carboxylic anhydrides on the other. In order to compare the relevant data of these two classes of anhydride, the nucleophilic reactions of these compounds are reviewed. Of particular importance is the mechanism of reactions at carbonyl and phosphoryl groups. A detailed comparison of these is made.
THEORETICAL SECTION

NUCLEOPHILIC REACTIONS OF ANHYDRIDES

1) Symmetrical Carboxylic Anhydrides

The spontaneous hydrolysis of acetic anhydride, benzoic anhydride and a number of p-substituted benzoic anhydrides has been studied, and the data analysed in terms of the parameters of the Arrhenius equation. In the former case both A and E were markedly temperature dependent and the frequency factor A was low. Mechanically these anhydrides hydrolyse by a bimolecular nucleophilic reaction. Variations in activation energy with the structure of the benzoic anhydrides was greater than in the cases of the corresponding esters and amides. The effects of steric hindrance were far more pronounced in reactions between benzoic anhydrides and ortho substituted anilines, than in reactions between benzyl bromide and the same anilines.

These reactions with anhydrides take place via an intermediate complex, the formation of which is generally the rate limiting step. Using water labelled with $^{18}$O, Bunton and collaborators have shown that the life of the intermediate complex was sufficiently long for oxygen exchange to occur. This exchange took place between the solvent and the carbonyl group of the anhydride (equation 3) and

$$\begin{align*}
\text{PhC-0-OPh} + H_2^18O & \overset{k_1}{\rightleftharpoons} \left[ \begin{array}{c}
\text{Ph-C-OCOPh} \\
18O
\end{array} \right] + H^+ \overset{k_3}{\longrightarrow} 2\text{PhCO}_2H \quad \cdots \cdots (3)
\end{align*}$$
the rate of exchange was determined. The intermediate complex partitioned forward to the product (rate $k_3$) and back to the reactants (rate $k_2$), the velocity of the latter reaction being appreciable. In the generalised carbonyl compound, $R-\hat{C}-X$, the rate $k_2$ decreases relative to $k_3$ with the increase of electron attracting powers of $X$, i.e., with the ease with which the ion $X^-$ is formed.

Interchange of acetate ions in acetic anhydride has been shown to occur with great facility. The exchange reaction (equation 4)

$$\text{CH}_3\text{COO}^- + \text{CH}_2\text{COO.COCCH}_3 \rightleftharpoons \text{CH}_2\text{COO.COCCH}_3 + \text{CH}_3\text{COO}^- \quad \ldots (4)$$

was studied using C\text{\textsuperscript{14}} labelled sodium acetate. Although the latter had an extremely low solubility in acetic anhydride, a very rapid exchange took place at room temperature. Bunton and co-workers have shown that tertiary bases accelerate both this exchange reaction and the hydrolysis of acetic anhydride. The following sequence of reactions had been postulated (equation 5). The rate of step 2,

$$\text{CH}_3\text{COO.COCCH}_3 + \text{C}_5\text{H}_5\text{N} \xrightarrow{1} \text{CH}_3\text{COC}_6\text{H}_5 + \text{CH}_3\text{COO}^-$$

$$\xrightarrow{3} \text{H}_2\text{O} \quad \ldots (5)$$

the reversion of the acyppyridinium ion to the reactants, is about 25 times as fast as step 3.

Koskikallis\textsuperscript{12} has made an extensive study of the hydrolysis and alcoholysis of carboxylic anhydrides. He determined the rate
constant for the hydrolysis of acetic, succinic, glutaric, methyl succinic, β-<wbr/>dimethyl succinic and maleic anhydrides in a number of aqueous organic solvent systems. The alkaline hydrolysis rates were determined for the first three anhydrides listed. The rate constants were also determined for the ethanolysis of all the anhydrides listed above and, in addition, benzoic and phthalic anhydrides (Table I). Relevant data published by other workers were critically reviewed and analysed thus showing that the hydrolysis rates decrease in the order:— formic, acetic, propionic and butyric anhydrides. This order is as would be expected for a bimolecular nucleophilic mechanism.

Table I

<table>
<thead>
<tr>
<th>Anhydride</th>
<th>$k_2 \times 10^7$</th>
<th>$t^0$</th>
<th>log A</th>
<th>E kcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic</td>
<td>19.8</td>
<td>30</td>
<td>6.672</td>
<td>17.71</td>
</tr>
<tr>
<td>Benzoic</td>
<td>0.915</td>
<td>40</td>
<td>5.910</td>
<td>18.52</td>
</tr>
<tr>
<td>Succinic</td>
<td>12.03</td>
<td>30</td>
<td>4.207</td>
<td>14.55</td>
</tr>
<tr>
<td>Maleic</td>
<td>200.5</td>
<td>30</td>
<td>5.346</td>
<td>14.34</td>
</tr>
<tr>
<td>Phthalic</td>
<td>135.3</td>
<td>30</td>
<td>4.736</td>
<td>13.81</td>
</tr>
</tbody>
</table>

The effect of conjugation between the carbonyl group and aromatic ring is shown by the high activation energy for the ethanolysis of benzoic anhydride.

To summarise, the reactions of anhydrides closely follow the pattern of the reactions of other carboxylic acid derivatives.
However a corollary may be added. In comparison with other carboxylic acid derivatives the steric effects are probably enhanced in the reactions of anhydrides with nucleophilic reagents, possibly because of the rigid form of the molecule. Solvation and hydrogen bonding effects aggravate any steric effect, thus in the solvolytic reaction described above, this effect is of greater importance.

2) Unsymmetrical Carboxylic Anhydrides

Compared with the symmetrical anhydrides, the nucleophilic reactions of unsymmetrical anhydrides are complicated by three additional features. Firstly, they readily disproportionate into two symmetrical anhydrides (equation 6). Secondly, the products

$$2 \text{R.CO.O.CO.R'} \rightarrow \text{R.CO.O.CO.R} + \text{R'.CO.O.CO.R'} \quad \text{(6)}$$

will vary depending upon which of the two carbonyl carbon atoms is attacked by the nucleophile (equations 7 and 8). Thirdly, the anhydride may ionise (equation 9) and the nucleophile will then

$$\text{R.CO.O.CO.R'} + \text{Y-H} \rightarrow \text{R.COOH} + \text{R'.CO-Y} \quad \text{(7)}$$

$$\text{R.CO.O.CO.R} + \text{Y-H} \rightarrow \text{R'.COOH} + \text{R.CO-Y} \quad \text{(8)}$$

react with the cation. This last possibility exists in the case of the symmetrical anhydrides, but in contrast to the unsymmetrical
compounds, it makes no difference to the identity of the product.

As the following evidence will show, the principal acidic product of the reaction between a nucleophile and a neutral unsymmetrical anhydride molecule may stem from either acid residue. In the absence of steric hindrance the distinction rests upon the nature of the nucleophile: whether it is a neutral molecule, such as aniline, or an anion, for example, the butyrate ion.

The simplest member of the mixed carboxylic anhydride series is formic acetic anhydride first reported by Bekalx who showed that it formylates alcohols and amines. Under mild conditions it exclusively formylates aniline and nitro alcohols. However, at elevated temperatures, formic acetic anhydride disproportionate and, as formic anhydride does not exist, the products are acetic anhydride, carbon monoxide and water. Under conditions favouring disproportionation, acetylation occurs.

More recently Emery and Gold have conducted a systematic study of the reaction mechanisms of some unsymmetrical carboxylic anhydrides. These workers studied the reactions of anhydrides derived from acetic acid and mono-, di- and trichloroacetic acids, with aniline and 2,4-dichloroaniline. They showed that aniline could react at either carbonyl group of chloracetic acetic anhydride, both chloracetanilide and acetanilide being formed (equations 10 and 11).

\[
\begin{align*}
\text{CH}_2\text{ClCOO} \cdot \text{COCH}_3 + 2\text{NH}_2\text{Ph} & \rightarrow \text{CH}_2\text{ClCOO} \cdot \text{NHPH} + \text{PHNH}_2\text{CH}_2\text{CO}_2^- & \ldots \ldots \ldots (10) \\
\text{CH}_2\text{ClCOO} \cdot \text{CO} \cdot \text{CH}_3 + 2\text{NH}_2\text{Ph} & \rightarrow \text{CH}_3\text{CO} \cdot \text{NHPH} + \text{PHNH}_2\text{CH}_2\text{ClCO}_2^- & \ldots \ldots \ldots (11)
\end{align*}
\]
In non-polar solvents the acylated product was predominantly a derivative of the stronger constituent acid. The salt was derived from the weaker acid (equation 10). The ratio of the amount of chloracetanilide to the acotanilide formed in the reaction was termed by these authors the chloracetylation ratio and this was found to vary from $> 6$ in benzene to $\sim 0.4$ in 50% aqueous acetone. This could be construed to indicate at least some contribution by a unimolecular reaction mechanism. However more will be said of this later. In all other respects the reaction behaved as a second order reaction, the rate being proportional to amine and anhydride concentration. It was affected by acetate and chloracetate ions, but the results did not permit a simple interpretation$^3$. Although the rate was appreciably slower with 2,4-dichloraniline, the chloracetylation ratio was virtually the same under comparable conditions.

The alternative first order mechanism was considered$^3$. In this case, the anion would stem from the acid which was the stronger of the derived pair, namely chloracetic acid (equation 12). The aniline would then react with the acetylum cation by first order kinetics (equation 13). The reaction rate should be independent

$$\text{CH}_3\text{Cl.CO.O.CO.CH}_3 \rightleftharpoons \text{CH}_3\text{Cl.CO}^- + \text{CH}_3\text{CO}^+ \quad \text{.........(12)}$$

$$\text{CH}_3\text{CO}^+ + \text{PhNH}_2 \rightarrow \text{CH}_3\text{CONHPh} + \text{H}^+ \quad \text{.........(13)}$$

of amine concentration, and it should be increased by polar solvents and retarded by chloracetate ions. If there was some contribution from this mechanism, the amount of acotanilide formed would be increased by polar solvents, i.e., the chloracetylation ratio would
decrease. This indeed, as mentioned above, was the case. However the rate was not decreased by chloracetate ions. Hence the first order mechanism could be dismissed.

The fall in the chloracetylation ratio with increased polarity of the solvent was attributed to steric hindrance arising from the solvation of the aniline. As a consequence of this solvent attachment, the reaction between the aniline and the less heavily substituted half of the anhydride, namely the acetyl moiety, was favoured.

When more highly chlorinated acids replaced the chloracetyl residue in the mixed anhydrides with acetic acid, evidence of steric hindrance was clearly manifested. (Table II. Chloracetylation ratio represents polychloracetylation where applicable. The rate constant \( k \) = acetylation + chloracetylation rates.)

<table>
<thead>
<tr>
<th>R</th>
<th>Chloracetylation Ratio</th>
<th>Overall Rate Constant ( k ) 1.\text{mol.}^{-1}\text{sec.}^{-1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{CH}_2\text{Cl} )</td>
<td>6.1</td>
<td>( 7.4 \times 10^6 )</td>
</tr>
<tr>
<td>( \text{CHCl}_2 )</td>
<td>2.25</td>
<td>( 2.2 \times 10^3 )</td>
</tr>
<tr>
<td>( \text{CH}_3 )</td>
<td>1.0</td>
<td>( 3.3 \times 10^5 )</td>
</tr>
<tr>
<td>( \text{CCl}_3 )</td>
<td>0.08</td>
<td>Too rapid for measurement</td>
</tr>
</tbody>
</table>

The decrease in the chloracetylation ratio in the series \( \text{CH}_2\text{Cl}^- \), \( \text{CHCl}_2^- \), \( \text{CCl}_3^- \) is opposite to the expected trend if the only governing
factor was the reactivity of the carbonyl group of the stronger acid residue. The decrease in the ratio must be a consequence of the increased steric hindrance at the α-carbon atom with the consecutive introduction of chlorine atoms.

It may be seen that the overall reaction rate of these anhydrides increases in the order of the strengths of the chloro acids. As the chloracetylation ratio decreases in the same order, this must mean that the inductive effects operating at the carbonyl groups of the chloro acids is transmitted along the C—O—C anhydride linkage to the acetyl carbonyl group, thereby increasing the rate of reaction at this carbonyl group.

Examples of first order mechanisms with nucleophilic reactions of mixed anhydrides are known. The facility with which a mixed anhydride will ionize depends upon the relative strengths of the acids that have formed the anhydride. This point may be demonstrated by the trifluoracetic carboxylic anhydrides.

Trifluoracetic acid, being a very strong acid compared with other carboxylic acids, will form anhydrides with the latter, which ionize fairly readily (equation 14). Polar solvents assist the

$$CF_3COO\cdotCO\cdotR \rightarrow CF_3COO^- + R.CO^+$$

(14)

ionization and the use of such anhydrides to promote acylations, is well known. Very few mixed anhydrides of trifluoracetic acid and carboxylic acids have been isolated in the pure state. Bourne and collaborators have prepared the trifluoracetic anhydrides with
acetic, benzoic and phenylacetic acids, and investigated their nucleophilic reactions.

Trifluoracetic acetic anhydride and aniline react in ether to yield mainly trifluoracetanilide, only 10% acetanilide being formed. This proportion was increased to 25% when the more polar solvent, nitromethane, was used. Trifluoracetic benzoic anhydride has a greater tendency to effect trifluoracetylation than the corresponding acetic anhydride, while trifluoracetic phenylacetic anhydride occupies an intermediate position. Unlike the case of chloracetic acetic anhydride, it has been shown that there were competing first and second order reactions taking place. Under these circumstances the steric features and basicity of the nucleophile have considerable influence on the course of the reaction. The relatively small cation $\text{R.CO}^+$ will be less affected by steric hindrance occurring at the nucleophile than the larger neutral anhydride molecule. Further, small differences in basicity will have little influence on the rate of reaction with an ion bearing a formal positive charge, whereas a decrease in the basicity of the nucleophile may markedly retard the rate of reaction with the neutral molecule.

In conclusion it may be stated that, although ionization of trifluoracetic carboxylic anhydrides is of greater importance than with other carboxylic anhydrides, the second order reaction between the neutral molecule and a nucleophile falls into the same general pattern as with all other carboxylic anhydrides.

The hypothetical alkyl carbonic acids $\text{R}_2\text{CO.CO}_2\text{H}$ may be classified with the carboxylic acids. Mixed anhydrides of ethyl carbonic
acid and N-acylated amino acids have been used extensively in peptide synthesis. These compounds are acylating agents. For example, the anhydride derived from ethyl carbonic acid and N-carbobenzoxy glycine has been shown to react with aniline to yield carboxbenzoxycarbonyl glycine anilide, carbon dioxide and ethanol \(^{19}\) (equation 15).

\[
\text{EtO.CO.O.COCH}_2\text{NHX} + \text{PhNH}_2 \rightarrow \text{PhNH.CO.CH}_2\text{NHX} + \text{CO}_2 + \text{EtOH} \quad \ldots \ldots \ldots \ldots (15)
\]

\(\text{X} \rightarrow -\text{CO.OCH}_2\text{Ph}\)

No phenyl urethane was formed, indicating that the reaction took place exclusively at the carbonyl group of the amino acid. The strength of ethyl carbonic acid must be a matter for conjecture. However it would probably not be weaker than glycine although the assessment is further complicated by the fact that the ethoxy group may conjugate with the carbonyl group \(
\text{EtO} = \text{C} = \text{O}\)
thereby deactivating it \(^{20}\). In this respect it resembles benzoic acid where the carbonyl group is deactivated by conjugation with the aromatic ring.

The mixed anhydride of benzoic acid and ethyl carbonic acid has been shown to yield predominantly the carbamate when it reacts with amines \(^{21}\) (equation 16). This reaction reveals another factor

\[
\text{PhCO.O.COEt} + 2\text{NH}_2\text{R} \rightarrow \text{RNHCOOEt} + \text{RNH}_2^+\text{PhCO}_2^- \quad \ldots \ldots \ldots (16)
\]

that may govern these reactions. Benzoic acid is a far stronger acid than glycine, and as reported above, glycine ethyl carbonic anhydride acylates. Therefore one might expect benzoic ethyl carbonic anhydride to benzylate. The failure of this to occur must be attributed to the deactivation of the benzoic carbonyl group by
conjugation with the aromatic ring.

The same argument must apply to the reaction of benzoic acetic anhydride. Benzoic acid is a stronger acid than acetic acid (pKa 4.2 and 4.76), yet benzoic acetic acid reacts with aniline to yield acetanilide, no benzanilide being detected22.

Finally, charged nucleophiles can be considered. The interchange of acetate ions in acetic acid has already been noted (page 9). This exchange reaction is effected by carboxylate ions and carboxylic anhydrides in general. Sodium butyrate behaves similarly to sodium acetate in acetic anhydride, and it was found that after removing the excess of the latter, a high boiling residue remained. When this residue was hydrolysed it was found to comprise 72% butyric acid and 28% acetic acid by weight. (Butyric acetic anhydride would yield 60% butyric acid and 40% acetic acid.) The product must have contained appreciable amounts of butyric anhydride10.

The hydrolysis of acetic anhydride is catalysed by formate ions23. Both acetate and formate ions catalyse the hydrolysis of propionic anhydride24, formate ions being the more effective. These accelerations of hydrolysis rate can best be explained on the basis of a nucleophilic exchange reaction which is shown here for the reaction with acetic anhydride and formate ions (equation 17).

\[
\text{CH}_3\text{CO.COOCH}_3 + \text{HCOO}^- \rightleftharpoons \text{CH}_3\text{CO.O.COH} + \text{CH}_3\text{CO}^- \quad \text{......(17)}
\]

Since acetic formic anhydride is hydrolysed 100 times as fast as acetic anhydride15, the formation of formic acetic anhydride by an exchange reaction would increase the hydrolysis rate. A catalytic
effect is only to be expected if the intermediate anhydride formed is more susceptible to hydrolysis than the original\textsuperscript{3}. This hypothesis is verified experimentally since the order of reactivity is formic $>$ acetic $>$ propionic for anhydrides. (page 10).

The literature contains no data on equilibrium constants for these reactions, but in the generalised exchange reaction (equation 18), it seems probable that the equilibrium lies well to the side

$$R\text{CO}_2\text{COR} + R'\text{CO}_2^- \rightleftharpoons R\text{CO}_2\text{COR}' + R'\text{CO}_2^- \quad \text{(18)}$$

where the anion is derived from the stronger acid.

Comparing the two extreme forms of reactions between nucleophiles and carboxylic-carboxylic anhydrides, we find that in the irreversible bimolecular reactions, the acylated product stems from the stronger acid moiety of the anhydride (steric factors and conjugation with the carbonyl group permitting), e.g., reactions with amines, the weaker acid moiety appearing as an anion or free acid. With reversible reactions between carboxylate ions and anhydrides there is a tendency for the opposite to apply. The carboxylate ion is acylated by the weaker of the constituent acid moieties of the anhydrides and the ion of the stronger acid appears as the other product in solution.

This difference in behaviour distinguishes kinetic and thermodynamic controlled reactions. The reactions between carboxylic anhydrides and carboxylate ions are reversible and therefore subject to thermodynamic control. The stronger constituent acid of an anhydride will have a greater heat of ionization. Consequently,
the system will have a lower energy when the ion of the stronger acid is in solution (equation 18).

By contrast, the reactions between basic amines and anhydrides are irreversible. Competition for the amine exists between the two carbonyl groups of the anhydride. As these dual reactions are not reversible and the products of each are not interconvertible, the relative amounts of products formed cannot be thermodynamically controlled but rather must be kinetically controlled. The ratio of the products represents the ratio of the reaction rates at the two centres.

From the foregoing facts, the following conclusions are drawn.

(1) A nucleophilic reagent may react with a mixed anhydride in two ways, depending upon conditions of the reaction
   a) by a first order reaction with the cation of the ion pair from the anhydride,
   b) by a second order reaction with the neutral molecule.

(2) Ionization of mixed anhydrides will be favoured by polar solvents.

(3) The tendency for a mixed anhydride to ionize will be directly related to the relative strengths of the constituent acids.

(4) The reaction between acid anhydrides and acid anions will be reversible and therefore able to reach equilibrium.

(5) With irreversible reactions in the absence of steric effects and deactivation of the carbonyl group by conjugation, nucleophilic attack on the neutral anhydride molecule will occur at the most positive carbonyl group.
(i.e., that associated with the strongest acid).

(6) In the neutral molecule, the electronic effects operating at one carbonyl group will be transmitted through the oxygen bridge to the other carbonyl group. The effects will be attenuated, but the electron densities at each carbonyl group would not be expected to differ very much.

(7) If the more positive carbonyl group is sterically hindered, then the nucleophilic attack will occur at the alternative positive seat, i.e., the second carbonyl group. In this way the steric factors may dominate the course of the reaction and dictate the site of attack.

3) Tetraesters of Pyrophosphoric Acid

The completely esterified phosphoric-phosphoric anhydrides (I),

\[ \begin{array}{c}
RO - O - P - OR^1 \\
\text{RO} \\
\text{RO}
\end{array} \]

(I)

the pyrophosphates, are compared here with carboxylic-carboxylic anhydrides. Although these compounds have been known for a long time, they constitute a class of organo-phosphorus compound that is burdened by much confusing and contradictory information in the earlier literature. However, in the last fifteen years much has been done to clarify the chemistry of these compounds. This has been brought about by their practical utility as insecticides and also their academic use as phosphorylating agents in the field of
nucleotide research. The simplest member of the series, tetramethyl pyrophosphate (I, R = R' = Me), was first prepared in 1908\textsuperscript{26} by the classical method of alkylating tetrasilver pyrophosphate, but it was not characterised adequately. Apart from the preparation of tetra-benzyl pyrophosphate in 1945\textsuperscript{27}, the first reliable work on this class of compounds was not published until 1945\textsuperscript{28}.

Toy\textsuperscript{28} prepared five symmetrical pyrophosphates and later\textsuperscript{29} a series of eleven unsymmetrical pyrophosphates (I, R and R' different) and studied their hydrolysis. The alkaline and neutral hydrolysis of pyrophosphates was discussed by Heath\textsuperscript{30} who tabulated the first order rate constants of a number of them (Table III).

$$\text{Table III}$$

**Hydrolysis Rates for Some Pyrophosphates (RO)\textsubscript{2}PO\cdotO\cdotPO(OR')\textsubscript{2} in Neutral Solution at 25°C.**

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>$k \times 10^3$ min\textsuperscript{-1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Me</td>
<td>2.50</td>
</tr>
<tr>
<td>Me</td>
<td>Et</td>
<td>7.0</td>
</tr>
<tr>
<td>Me</td>
<td>Pr\textsubscript{n}</td>
<td>5.6</td>
</tr>
<tr>
<td>Et</td>
<td>Et</td>
<td>1.6</td>
</tr>
<tr>
<td>Me</td>
<td>Pr\textsubscript{i}</td>
<td>1.1</td>
</tr>
<tr>
<td>Et</td>
<td>Pr\textsubscript{n}</td>
<td>1.0</td>
</tr>
<tr>
<td>Et</td>
<td>Bu\textsubscript{n}</td>
<td>0.95</td>
</tr>
<tr>
<td>Pr\textsubscript{n}</td>
<td>Pr\textsubscript{n}</td>
<td>0.65</td>
</tr>
<tr>
<td>Et</td>
<td>Pr\textsubscript{i}</td>
<td>0.28</td>
</tr>
<tr>
<td>Pr</td>
<td>Pr\textsubscript{i}</td>
<td>0.20</td>
</tr>
<tr>
<td>Bu\textsubscript{n}</td>
<td>Pr\textsubscript{i}</td>
<td>0.20</td>
</tr>
<tr>
<td>Pr\textsubscript{i}</td>
<td>Pr\textsubscript{i}</td>
<td>0.09</td>
</tr>
</tbody>
</table>
The hydrolysis of pyrophosphates in alkaline and neutral solution proceeds according to an $S_{2}$ mechanism. The inductive effects of substituents are similar to those found in carbon chemistry for reactions of this type. The phosphorus atom of the phosphoryl group will carry some measure of positive charge and will be the site at which a nucleophile will attack. It follows that as the electron donating ability of the alkyl substituents increases in the recognised order $\text{Me} < \text{Et} < \text{Pr}^n < \text{Pr}^i$, the positive charge on the phosphorus atom will decrease. Therefore the hydrolysis rates of the pyrophosphates should decrease in this order. Inspection of the table confirms that this is the case. One point of particular note is the exceptional stability conferred by the isopropyl group. This stability is greater than would be expected from the inductive effect alone. Both Toy$^{28,29}$ and Heath$^{30}$ considered that the isopropyl group caused steric hindrance at the phosphoryl group.

Heath$^{30}$ endeavoured to correlate existing data in order to predict hydrolysis rates. He argued that the overall rate of reaction at $P^1$ and $P^2$ of the pyrophosphate molecule was the summation of independent $S_{N}^{2}$ reactions. These separate reaction rates decreased as the electron releasing effects of the substituents attached to the phosphorus atom increased. A further contention was that the inductive effects of substituents on $P^1$ were not conducted to any significant extent through the linkage $P^1 - O - P^2$ to $P^2$. Using rate constants derived from symmetrical pyrophosphates, Heath calculated the rate constants for some selected unsymmetrical pyrophosphates. In general, the agreement between
calculated and observed rates was poor and he attributed this to steric effects which he concluded were more important than the electronic effects.

Heath's conclusions were challenged by Brock. The latter showed that there was a linear correlation between the sum of Taft's free-energy/polar-energy coefficients and the groups attached to the two phosphorus atoms, and a function of the hydrolysis rates. Thus Taft's free-energy/polar-energy equation is obeyed, from which it follows that steric effects are negligible. However Brock accepted Heath's statement that electronic effects were not transmitted along the P-O-P linkage.

These conflicting conclusions could be resolved if the inductive effects operating at each phosphoryl group were transmitted along the P-O-P linkage. Support for this idea is given in the experimental section of this thesis. A parallel may be drawn between the pyrophosphates and the carboxylic anhydrides. The hydrolysis rates of the acetic chloroacetic anhydrides were discussed earlier (p. 15). Clearly the inductive effects operating at each carbonyl group are transmitted along the C-O-C linkage. There seems no reason why the P-O-P linkage should be any more effective as an electronic insulator than the C-O-C linkage. If this assumption is justified, the hydrolysis rates will be related to the summation of the inductive effects of all the substituents of the pyrophosphate ester. Therefore they will obey Taft's free-energy/polar-energy equation, provided one of the phosphoryl groups is free from steric hindrance. Then, as with the carboxylic anhydrides, if the preferred
site of the reaction is sterically hindered and, provided that the
inductive effects operating at that site are transmitted to the
alternative centre of reaction, the effect of steric hindrance at
one group will be mitigated.

Tetraethyl pyrophosphate (I; \( R = R' = Et \)) has been widely used
as an insecticide. Like all phosphorus insecticides its toxicity
stems from its ability to phosphorylate an essential enzyme in
animals\(^{32}\). In studies on this topic it has been shown that tetra­
ethyl pyrophosphate reacts with amino acids yielding an N-diethyl­
phosphoryl product\(^{33,34}\).

From the foregoing discussion the parallel between the reac­
tions of symmetrical pyrophosphates and symmetrical carboxylic
anhydrides will be apparent. Without the use of isotopic tracers,
the hydrolysis reactions of unsymmetrical anhydrides afford no
information on the relative reactivities of the two reaction centres.
Data on this are most readily obtained by studying the reaction
between the anhydride and amines. When these reactions with the
unsymmetrical pyrophosphates are examined, a difference between
the latter and the unsymmetrical carboxylic-carboxylic anhydrides
is revealed.

The unsymmetrical pyrophosphate derived from diphenyl phos­
phoric acid and dibenzyl phosphoric acid, namely \( P^1_P^1 \) diphenyl
\( P^2_P^2 \) dibenzyl pyrophosphate, reacts with cyclohexylamine in benzene
to yield N-cyclohexyl 0,0-dibenzyl phosphoramidate (equation 19).
Similarly $\text{P}_1\text{P}_2$ di(p-methoxyphenyl) $\text{P}_2\text{P}_2^2$ diphenyl pyrophosphate reacts with anhydrous ammonia to yield di(p-methoxyphenyl) phosphoramidate. It has been demonstrated that diphenyl phosphoric acid is a stronger acid than either dibenzyl- or di(p-methoxyphenyl) phosphoric acid$^{35}$ Thus, in both examples, the nucleophilic attack by the amine has occurred at the phosphoryl group of the weaker constituent acid of the anhydride: a result that contrasts with the behaviour of carboxylic-carboxylic anhydrides in the absence of steric hindrance or conjugation.

Tetraphenyl pyrophosphate reacts with ions of dibenzyl phosphoric acid in polar solvents first to form $\text{P}_1\text{P}_2^2$ diphenyl $\text{P}_2\text{P}_2^2$ dibenzyl pyrophosphate (equation 20) which subsequently reacts further to form tetrabenzyl pyrophosphate (equation 21).

\[
\text{(Ph}_\text{O})_2\text{P} - \text{O} - \text{P(Ph)}_2 + \text{(Ph}_\text{CH}_2\text{O})_2\text{P} - \text{O}^- \quad \rightarrow \quad \text{(Ph}_\text{O})_2\text{P} - \text{O} - \text{P(Ph}_\text{CH}_2\text{Ph})_2 + \text{(Ph}_\text{O})_2\text{P} - \text{O}^- \quad \ldots \ldots \ldots \ldots (20)
\]

\[
\text{(Ph}_\text{O})_2\text{P} - \text{O} - \text{P(Ph}_\text{CH}_2\text{Ph})_2 + \text{(Ph}_\text{CH}_2\text{O})_2\text{P} - \text{O}^- \quad \rightarrow \quad \text{(Ph}_\text{CH}_2\text{O})_2\text{P} - \text{O} - \text{P(Ph}_\text{CH}_2\text{Ph})_2 + \text{(Ph}_\text{O})_2\text{P} - \text{O}^- \quad \ldots \ldots \ldots \ldots (21)
\]
It has been established that two moles of tertiary base are required to ionize the phosphoric acid (dibenzyl phosphoric acid) completely. The reaction will not proceed if only catalytic quantities of base are used, and may be stopped at the half way stage (equation 20) if only one mole is used. By this exchange reaction a pyrophosphate is converted into another less reactive pyrophosphate and a more stable ion, i.e., (PhO)$_2$POO$^-$ is more stable than (PhCH$_2$O)$_2$POO$^-$. 

In the light of the evidence recorded above for unsymmetrical pyrophosphates, the following generalisations have been made for these compounds by Todd.$^{1,35}$ If an anhydride is represented by A-B and the derived acids by A' and B', where A' is stronger than B', then, in the presence of a third acid C' which is intermediate in strength between A' and B', disproportionation will occur (equation 22). When A-B is involved in a phosphorylation reaction

\[ A - B + C' \rightarrow A' + B - C \]  \hspace{1cm} (22) 

it will yield a phosphorylated product derived from the weakest acid B' (equation 23).

\[ A - B + XH \rightarrow XB + AH \]  \hspace{1cm} (23) 

The nucleophilic reactions of tetraesters of pyrophosphates may be summarised as follows:

(1) The reactions take place by an $S_{N2}$ mechanism.
(2) The exchange reaction (equation 22) is reversible and thermodynamically controlled, the major ionic product being the ion of the strongest acid. (This is common to carboxylic anhydrides.)

(3) Phosphorylation reactions (equation 23) yield the phosphorylated product derived from the weaker of the two constituent phosphoric acids, the stronger acid arising in the products as the ion. (This is in contrast to carboxylic anhydrides.)

(4) There is some evidence that nucleophilic reactions at the phosphoryl groups may be subject to steric hindrance when the phosphoryl group carries a bulky substituent such as the isoproxy group.
PHOSPHORIC-CARBOXYLIC ANHYDRIDES

The phosphoric carboxylic anhydrides discussed here are anhydrides of phosphodiesters and carboxylic acids (II). They differ

\[ \text{RO} - \begin{array}{c} P - O - C - R' \\ \text{RO} \end{array} \]

(II)

from the anhydrides considered earlier in that the two reactive centres are chemically different. The reactive centres of the carboxylic-carboxylic anhydrides are the carbonyl groups. While the reactivity of these will differ in unsymmetrical anhydrides, depending upon the inductive and electromeric effects operating at each group, the mechanism of the dual reactions will be identical. The same may be said for the two phosphoryl groups in the pyrophosphates. However the two reactive centres of the phosphoric carboxylic anhydrides are the carbonyl and phosphoryl groups. As will be shown later (p. 43) the mechanism of nucleophilic reactions at these groups are fundamentally different. Insufficient is known about this type of compound to predict with certainty the products of a reaction of a given phosphoric carboxylic anhydride and a nucleophile such as an amine. It is one of the aims of the work described in the experimental section of this thesis to shed more light on this subject.

Interest in phosphoric carboxylic anhydrides stems from suggestions that they are involved in biological acylation reactions.
Lynen first reported the preparation of an anhydride of a phosphodiester and acetic acid in 1940. He allowed acetyl chloride and silver dibenzyl phosphate to react together in ether at 0° (equation 24). After the removal of the solvent below 35°, he obtained a syrup which was not further purified. The product was authenticated by debenzylation to acetyl phosphate which was then characterised as the disilver salt.

Ten years later Sheehan and Frank were probing the possibility that phosphoric carboxylic anhydrides were involved in protein synthesis. They prepared as model compounds phthalylglycyl dibenzyl phosphate (III) and carbobenzyoxyglycyl dibenzyl phosphate (IV).

Silver dibenzyl phosphate and phthalylglycyl chloride or carbobenzyoxyglycyl chloride were interacted in benzene at room temperature. The products were low melting crystalline solids that readily disproportionated on recrystallisation from boiling benzene. Disproportionation to the symmetrical anhydrides also took place slowly on standing at room temperature or very rapidly in the presence of catalytic quantities of triethylamine (equation 25).
The glycyl phosphates (III and IV) were readily hydrolysed to their constituent acids. Phthalylglycyl dibenzyl phosphate (III) and aniline reacted rapidly and exothermically in dioxane affording a 91% yield of phthalylglycyl anilide (equation 26). Similarly

\[
(\text{PhCH}_2\text{O})_2\text{P} - \text{O} - \text{CCH}_2\text{N} \quad + \quad 2\text{PhNH}_2 \quad \rightarrow \\
\text{PhNHCOCH}_2\text{N} + (\text{PhCH}_2\text{O})_2\text{P} - \text{O}^- \cdot \text{NH}_3\text{Ph} \quad \cdots \cdots \text{(26)}
\]

benzylamine gave a 92% yield of the corresponding phthalylglycyl benzylamide. Glycine and phenylglycine were acylated efficiently under mild conditions by this anhydride (III) to yield dipeptides. These workers also showed that carbobenzoxyglycyl dibenzyl phosphate (IV) similarly acylated amines.

The high yield of the anilide and benzylamide obtained in the above reactions proved that substantially pure mixed anhydride had been formed and isolated. The other possibility, that the products
of the anhydride formation from the acid chloride and silver salt was an equimolar mixture of two symmetrical anhydrides, would have had half the acylating potential of the pure mixed anhydride.

Alternative methods of preparing phthalylglycyl dibenzyl phosphate were examined by Sheehan and Frank. Dibenzylphosphoro-chloridate and silver phthalylglycinate reacted together with the formation of tarry products from which the desired compound could not be isolated. Replacement of silver dibenzyl phosphate by the triethylammonium salt was also unsuccessful. Phthalylglycyl chloride and triethylammonium dibenzyl phosphate in benzene, interacted to yield phthalylglycyl anhydride (58%) and tetrabenzyl pyrophosphate (71%).

In contrast to these results of Sheehan and Frank, Cosmatos and collaborators obtained anhydrides of N-protected amino acids and diphenylphosphoric acid (V) from the reaction of the amino acid derivative and diphenylphosphorochloridate in the presence of pyridine in tetrahydrofuran. The reaction was applied successfully to N-derivatives of glycine, phenylalanine and leucine. The mixed anhydrides were not isolated. The crude reaction mixture was treated with aniline when the amino acid anilide was obtained, or allowed to react with another amino acid, when dipeptides were produced. The overall yields from these reactions ranged from 60 to 80%.
Mason and Todd prepared bis(dibenzyl phosphoryl) oxalate (VI)

\[
\text{(PhCH}_2\text{O)}_2\text{P}-\text{O}-\text{C}-\text{O}-\text{P(OCH}_2\text{Ph)}_2
\]

(VI)

from anhydrous dibenzyl phosphoric acid and excess oxyalyl chloride by heating it under reflux at ca. 60° (equation 27). The excess

\[
2(\text{PhCH}_2\text{O})_2\text{P}-\text{OH} + \text{Cl}_2\text{C}-\text{C}-\text{Cl} \rightarrow
\]

\[\text{(PhCH}_2\text{O)}_2\text{P}-\text{O}-\text{C}-\text{O}-\text{P(OCH}_2\text{Ph)}_2 + \text{HCl} \]

………(27)

Oxyalyl chloride and hydrogen chloride generated in the reaction were removed by vacuum evaporation at room temperature. The product was a crystalline solid that evolved carbon monoxide and dioxide on heating to 108° leaving a residue of tetrabenzyl pyrophosphate (equation 28).

\[
\text{(PhCH}_2\text{O)}_2\text{P}-\text{O}-\text{C}-\text{O}-\text{P(OCH}_2\text{Ph)}_2 \rightarrow
\]

\[\text{(PhCH}_2\text{O)}_2\text{P}-\text{O}-\text{P(OCH}_2\text{Ph)}_2 + \text{CO} + \text{CO}_2 \]

………(28)

Bis(dibenzylphosphoryl) oxalate reacted with anhydrous ammonia to yield predominantly oxamide (35%) but some phosphorylation took place, and dibenzyl phosphoramidate (5.5%) was also isolated (equation 29).

\[
\text{(PhCH}_2\text{O)}_2\text{P}-\text{O}-\text{C}=\text{O} + 4\text{NH}_3 \rightarrow \text{(NH}_2\text{CO)}_2 + 2(\text{PhCH}_2\text{O})_2\text{P-O})_2\text{NH}_4
\]

\[2(\text{PhCH}_2\text{O})_2\text{P-NH}_2 + (\text{CO}_2\text{NH})_2\]

………(29)
Mixed anhydrides derived from dibenzyl- or diphenylphosphoric acid and trifluoracetic anhydride have been described as mild phosphorylating reagents. These anhydrides were not isolated and all the evidence for their existence is indirect. Triethylammonium dibenzyl phosphate (2 mol.) and trifluoracetic anhydride (1 mol.) reacted to give a 75% yield of tetrabenzyl pyrophosphate. The reaction was assumed to proceed in two stages (equations 30, 31).

\[
\begin{align*}
\text{(PhCH}_2\text{O)}_2\text{P}^+ \text{-O}^- \text{+ (CF}_3\text{CO})_2\text{O} & \rightarrow \text{(PhCH}_2\text{O)}_2\text{P}^+ \text{-O}^- \text{+ CF}_3\text{CO}^- \text{+ CF}_3\text{CO}_2^- \quad \cdots \cdots \text{(30)} \\
\text{(PhCH}_2\text{O)}_2\text{P}^+ \text{-O}^- \text{+ CF}_3\text{CO}^- \text{+ (PhCH}_2\text{O})_2\text{P}^+ \text{-O}^- & \rightarrow \text{(PhCH}_2\text{O)}_2\text{P}^+ \text{-O}^- \text{+ (OCH}_2\text{Ph})_2 \text{+ CF}_3\text{CO}_2^- \quad \cdots \cdots \text{(31)}
\end{align*}
\]

Tetraphenylpyrophosphate was obtained in an analogous fashion but tetra(p-nitrophenyl) pyrophosphate was not formed from di(p-nitrophenyl) phosphate salts and trifluoracetic anhydride. The failure of the reaction in the latter case was attributed to the inability of the stable di(p-nitrophenyl) phosphate anion to take part in the exchange reactions.

The product from the reaction of dibenzyl phosphate with trifluoracetic anhydride (equation 30) yielded no phosphoramidate with cyclohexylamine. However, if the crude product was first allowed to react with a diphenylphosphate salt and subsequently this reaction mixture treated with cyclohexylamine, a good yield of 0,0 dibenzyl N, cyclohexylphosphoramidate was obtained. To account for these facts it was assumed that an exchange reaction...
had taken place between dibenzyl trifluoracetyl phosphate and the
diphenylphosphate ion yielding \( \text{Ph}^1 \text{P} \) dibenzyl \( \text{Ph}^2 \text{P} \) diphenyl pyro-
phosphate (equation 32) and that this then reacted with the amine
(equation 33).

\[
\begin{align*}
\text{(PhCH}_2\text{O)}_2\text{P}^+ - 0 - \text{CCF}_3 + (\text{PhO})_2\text{PO}^- & \rightarrow (\text{PhCH}_2\text{O})_2\text{P}^+ - 0 - \text{P(OPh)}_2 \\
+ \text{CF}_3\text{CO}^- & \quad \ldots(32)
\end{align*}
\]

\[
\begin{align*}
(\text{PhCH}_2\text{O})_2\text{P}^+ - 0 - \text{P(OPh)}_2 + \text{C}_6\text{H}_{11}\text{NH}_2 & \rightarrow (\text{PhCH}_2\text{O})_2\text{P}^+ \text{NHC}_6\text{H}_{11} \\
+ (\text{PhO})_2\text{P}^+ - 0^- & \quad \ldots(33)
\end{align*}
\]

The characterisation of trifluoracetyl dibenzyl phosphate
as an acylating agent rather than a phosphorylating agent would
better suit the facts reported above. It is unlikely that a mixed
anhydride derived from two such strong acids as trifluoracetic
and dibenzylphosphoric acid would fail to react with a strongly
basic nucleophile like cyclohexylamine. If trifluoracetyl di-
benzyl phosphate is an acylating agent, the non-ionic product of
the reaction with cyclohexylamine would be \( N \)-cyclohexyl trifluor-
acetamide (equation 34). It was reported that no \( N \)-cyclohexyl

\[
\begin{align*}
(\text{PhCH}_2\text{O})_2\text{P}^+ - 0 - \text{CCF}_3 + 2\text{C}_6\text{H}_{12}\text{NH}_2 & \rightarrow \\
\text{CF}_3\text{CONHC}_6\text{H}_{12} + (\text{PhCH}_2\text{O})_2\text{POO.NH}_3\text{C}_6\text{H}_{12} & \quad \ldots(34)
\end{align*}
\]

dibenzyl phosphoramidate was formed, but no attempt was made to
establish the presence or absence of the trifluoracetamide.
The exchange reactions that trifluoracetyl dibenzyl phosphate undergoes are in complete accord with those described earlier for carboxylic-carboxylic anhydrides and pyrophosphates. In both of these classes of anhydride, the reaction is reversible and thermodynamically controlled, the ionic product being derived predominantly from the stronger of the two constituent acids. There is no reason to believe that phosphoric carboxylic anhydrides would behave differently in an exchange reaction.

Petrov and Neimysheva claimed to have prepared a series of acyl dialkyl phosphates by allowing the silver salt of the carboxylic acid to react with dialkyl phosphorochloridates in refluxing ether. The reaction time was varied from 6 hours to several days. After filtration and evaporation of the ether, the products were not further purified. The compounds claimed were acetyl dimethyl phosphate (II; \( R = \text{Me}, R' = \text{Me} \)), acetyl diethyl phosphate (II; \( R = \text{Et}, R' = \text{Me} \)), trifluoracetyl diethyl phosphate (II; \( R = \text{Et}, R' = \text{CF}_3 \)) and benzoyl diethyl phosphate (II; \( R = \text{Et}, R' = \text{Ph} \)). These compounds were not characterised or adequately authenticated. They were described as almost clear colourless liquids readily soluble in organic solvents and easily hydrolysed to their constituent acids. With alcohols they yielded triesters of phosphoric acid but no experiments were described to support this claim. These mixed anhydrides were described as thermally unstable. All attempts at vacuum distillation resulted in quantitative decomposition to the symmetrical anhydrides. Indeed this reaction was described by the authors as a new method for the preparation of pyrophosphates.
When the work of Petrov and Neimysheva is compared with other published results described below, and particularly with results described in this thesis, it would seem to be most unlikely that they obtained more than a mixture of the acyl phosphate with the corresponding symmetrical anhydrides.

An elegant method for the synthesis of acyl diethyl phosphates was described by Cramer and Gartner\(^5\). These workers applied the enol phosphates diethyl (\(\alpha\)-ethoxy-\(\beta\)-dichlorovinyl) phosphate (\(\text{VII}\)) and diethyl (\(\alpha\)-ethoxy-\(\beta\)-carbethoxyvinyl) phosphate (\(\text{VIII}\)) to the phosphorylation of carboxylic acids (equations 35 and 36). The reactions were conducted with and without an inert solvent at a temperature not exceeding 37°. After removing the solvent and by-product, ethyl dichloroacetate or ethyl malonate by distillation, the residue was distilled under high vacuum yielding clear, colourless liquids that were well authenticated by boiling points, refractive indices and elemental analysis. The best yields (60–90\%) were obtained with diethyl \((\alpha\)-ethoxy-\(\beta\)-carbethoxyvinyl) phosphate (equation 36). The following mixed anhydrides were prepared and

\[
\begin{align*}
\frac{O}{\text{(EtO)\textsubscript{2}P- O- CCl\textsubscript{2}}} & \quad \frac{O}{\text{Et}} \quad \text{(EtO)\textsubscript{2}P- O- C- CH\textsubscript{2}CO\textsubscript{2}Et}} \\
\text{(VII)} & \quad \text{(VIII)}
\end{align*}
\]

\[
\begin{align*}
\frac{O}{\text{(EtO)\textsubscript{2}P- O- CCl\textsubscript{2}}} + \frac{O}{\text{HO-CR}} & \rightarrow \frac{O}{\text{(EtO)\textsubscript{2}P- O- CR} + \text{CHCl\textsubscript{2}CO\textsubscript{2}Et}} \quad \ldots \ldots (35) \\
\frac{O}{\text{(EtO)\textsubscript{2}P- O- C- CH\textsubscript{2}CO\textsubscript{2}Et}} + \frac{O}{\text{HO-CR}} & \rightarrow \frac{O}{\text{(EtO)\textsubscript{2}P- O- CR} + \text{CH\textsubscript{2}(CO\textsubscript{2}Et)\textsubscript{2}}} \quad \ldots \ldots (36)
\end{align*}
\]
purified by distillation, acetyl diethyl phosphate (II: \( R = Et, R' = Me \)), propionyl diethyl phosphate (II: \( R = Et, R' = Et \)), butyryl diethyl phosphate (II: \( R = Et, R' = nC_6H_{13} \)), valeryl diethyl phosphate (II: \( R = Et, R' = nC_6H_{13} \)) and benzoyl diethyl phosphate (II, \( R = Et, R' = Ph \)). The acetyl and propionyl compounds were miscible with water and immediately hydrolysed. The higher aliphatic compounds were immiscible with water and more slowly hydrolysed, while benzoyl diethyl phosphate could be shaken with aqueous sodium bicarbonate solution without obvious reaction. All of these mixed anhydrides reacted with aniline in inert solvents to yield anilides (equation 37). The aliphatic derivatives afforded yields according to the above equation of the order of 90%. No phosphoramidate was formed in any of these experiments. The corresponding reaction between aniline and benzoyl diethyl phosphate was only conducted with crude anhydride. The yield of benzanilide after recrystallisation was only 37% and benzoic acid (40%) was isolated by acidifying the aqueous washings of the reaction product. It could be construed therefore that some anilinium benzoate had been formed (equation 38)

\[
(EtO)_2P-O-CR' + 2PhNH_2 \rightarrow PhNCO\cdot+(EtO)_2POO\cdotH_3NPh \quad \cdots\cdots\cdots(37)
\]

although no \( \text{H-phosphoramidate, which should have been formed simultaneously, was isolated. Both acetyl and benzoyl diethyl phosphate were further characterised by their infra-red spectra.} \]
The high yields of anilides obtained when these anhydrides and aniline react proved conclusively that the distilled products were mixed anhydrides and not equimolar mixtures of the two symmetrical anhydrides.

As shown by earlier workers, these anhydrides were acylating agents. Cramer and Gartner concluded that these mixed anhydrides react with amines to yield the amide derived from the weaker acid moiety and the salt of the stronger acid. That is to say they follow the pattern of nucleophilic reactions shown by the pyrophosphates and not the carboxylic-carboxylic anhydrides.

Michalski and Dedro also obtained acyl phosphates by phosphorylating carboxylic acids. The phosphorylating agent used by these workers was tetrasteryl phosphoric-phosphorus anhydride (IX).

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \\
\text{P} & \quad \text{O} \\
\text{EtO}_2\text{P} & \quad \text{Et}
\end{align*}
\]

(IX)

This anhydride was allowed to react with an equimolar amount of a carboxylic acid at a temperature not exceeding 30°C (equation 39).

\[
\begin{align*}
0
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{Et} \\
\text{EtO}_2 & \quad \text{Et}
\end{align*}
\]

After removing the diethyl hydrogen phosphate by distillation, the residue was distilled under vacuum. By this method acetyl diethyl phosphate (II: R = Et, R' = Me), propionyl diethyl phosphate (II: R = Et, R' = Et) and trichloroacetyl diethyl phosphate (II: R = Et, R' = CCl3) were prepared. The boiling points and
refractive indices quoted by these workers for the first two compounds were in good agreement with those recorded by Cramer and Gartner. Benzoin acid failed to react with tetrachlorophosphoric phosphorus anhydride.

Michalski and Medro also experimented with the formation of acyl phosphates from simple acid components. Ethyl phosphoro-chloridate in benzene was allowed to react with acetic acid in the presence of pyridine. After removal of the pyridine hydrochloride, distillation gave a 70% yield of tetrachlorophosphoric acid. They compared their results with those of Petrov and Kaimisheva who used silver acetate and ethyl phosphoro-chloridate (p. 36). In order to ascertain whether acyl diethyl phosphate had been formed and disproportionated on distillation, they added the stoichiometric quantity of ethanol to the reaction mixture, prior to distillation. If acyl diethyl phosphate had been present ethyl acetate would have been formed (equation 40). However, tetrachlorophosphoric acid

\[
(\text{EtO})_2\text{OCOCCH}_3 + \text{EtOCH} \rightarrow (\text{EtO})_2\text{OCH} + \text{CH}_3\text{COOH} \quad \ldots \quad (40)
\]

was again produced in 70% yield. They concluded that the acetyl diethyl phosphate disproportionated as soon as it was formed, both in their experiments and those of Petrov and Kaimisheva. They also suggested that the disproportionation was catalysed by pyridine hydrochloride or silver chloride. A more probable explanation is advanced later in this thesis in the discussion of the experimental results.
Cramer and Winter\textsuperscript{43} showed that the dimethyl formamide complex with ethyl phosphorochloridate could react with carboxylate salts to form mixed anhydrides. Using sodium benzoate, distillable benzoyl diethyl phosphate was obtained in 54\% yield (equation 41).

\[
\text{EtO} \ 
\begin{array}{c}
\text{P} - \text{O} - \text{CH} = \text{NMe}_2
\end{array}
\] + \text{Cl} + \text{NaOCOPh} \rightarrow \text{(EtO)}_2\text{P} - \text{O} - \text{CPh} + \text{Me}_2\text{N} - \text{CHO} + \text{NaCl} \quad \cdots \cdots \cdots (41)

Finally, the preparation of bis(diethylphosphoryl) malonate (X)

\[
\text{(EtO)}_2\text{P} - \text{O} - \text{C} - \text{CH}_2 - \text{C} - \text{O} - \text{P(OEt)}_2
\]

was described as arising from the reaction of ethyl phosphorochloridate with malonic acid in the presence of excess pyridine in chloroform solution\textsuperscript{44}. The compound was claimed as an insecticide. As stated earlier the organophosphorus insecticides owe their toxicity to their ability to phosphorylate (p. 25). Thus the claim was tantamount to a statement that bis(diethyl phosphoryl) malonate was a phosphorylating agent. Yet the evidence above suggests that this compound should be an acylating agent. Further it has been shown that traces of tertiary bases cause acyl dialkyl phosphates to disproportionate into the symmetrical anhydrides (p. 30). In the light of these comments it would seem that the product, for which no data is given, was a mixture of symmetrical anhydrides, the insecticidal activity being due to the presence of tetraethyl pyrophosphate, a known powerful insecticide.
Owing to the paucity of reliable information on phosphoric carboxylic anhydrides, it is difficult to make a generalisation for them. It is evident that they undergo exchange reactions whereby the ion of the strongest acid of the system is present as the major ionic component. The majority of the compounds are acylating agents, but the possibility of phosphorylation exists. They are undoubtedly thermo-labile.
COMPARISON OF BIMOLECULAR NUCLEOPHILIC REACTIONS AT
CARBONYL AND PHOSPHORYL GROUPS

1) Introduction

It has been shown that pyrophosphates (p.23) and neutral carboxylic-carboxylic anhydride molecules (p.8) react with nucleophiles by bimolecular mechanisms. It is most probable that phosphoric-carboxylic anhydrides behave similarly. Therefore this discussion is restricted to bimolecular mechanisms.

Phosphoric-carboxylic anhydrides may react with a nucleophile at either of their two reaction centres. Depending upon the centre at which the reaction occurs, the compound will be acting either as a phosphorylating agent or an acylating agent. Where the two reaction centres are the same as in the pyrophosphates and carboxylic-carboxylic anhydrides, generalisations have been made for their nucleophilic reactions in cases where the steric effects are negligible. These may be reiterated as follows:— nucleophiles react predominantly at the most positive carbonyl group of carboxylic-carboxylic anhydrides and the least positive phosphoryl group of pyrophosphates. Obviously there must be considerable differences in mechanism and clearly with phosphoric-carboxylic anhydrides, which possess both carbonyl and phosphoryl groups, there must be some competition of mechanism. The evidence reviewed in the preceding section shows that phosphoric-carboxylic anhydrides are either predominantly or exclusively acylating agents. However, the number of compounds studied is very limited.
The difference in behaviour between carboxylic-carboxylic anhydrides and pyrophosphates must be due to the difference in the nucleophilic reactions that take place at the carbonyl and phosphoryl groups. It is cogent therefore to compare these reactions. This entails a consideration of the electronic and structural features of each group in the ground and transition state, and the mechanism of the reactions.

2) Structure of Carboxyl Compounds

In the ground state the carbon atom of the carboxyl group uses three planar \(s^2p^2\) bonding hybridized orbitals, the interbonding angles being 120°. The fourth orbital is a \(p\) orbital at right angles to the \(s^2p^2\) hybrids. The double bond of the carboxyl group is formed by the overlap of one \(s^2p^2\) hybrid orbital of the carbon and one \(p\) orbital of the oxygen together forming a \(\sigma\) bond; the remaining \(p\) orbitals of the oxygen and the \(p\) orbital of the carbon overlap to form a \(\pi\) bond. The oxygen atom has two pairs of non-bonding electrons \(2s^2\) and \(2p^2\), the latter pair are in a plane at right angles to the \(\pi\) bond. The \(\pi\) electrons of the carbonyl bond will be displaced towards the oxygen atom, because oxygen is more electronegative than carbon.

The electronic distribution of the carboxyl group is perturbed by the rest of the molecule, resonance and inductive effects being of importance. A carboxyl group conjugated with a double bond or an aromatic ring, is a resonance stabilized configuration and, as a consequence, is less reactive. This decrease in activity is
manifested by an increase in the activation energy. The importance of the inductive effect is revealed by the linear relationship between Taft's polar substituent constant $\delta$ of groups attached to the carbonyl group and the infra-red stretching frequency of that carbonyl group$^{47}$.

3) Bimolecular Nucleophilic Reactions at the Carbonyl Group

The most important property of the carbonyl group is its ability to form addition complexes via which the reactions take place. A typical example of a bimolecular nucleophilic reaction is the hydrolysis of benzoic anhydride described in detail earlier (p. 8).

As described above, the carbonyl group is planar with bonds at angles of 120° (XI). A nucleophilic reagent may attack the carbonyl carbon above or below the plane to form an addition intermediate (XII).

\[
\begin{align*}
\text{(XI)} & \quad \text{(XII)} \\
\text{with } & \quad \text{sp}^3 \text{ tetrahedral configuration}^{45} \text{ (equation 42). The intermediate}
\end{align*}
\]

\[
\begin{align*}
R-C-X + Y & \underset{\text{Y+}}{\overset{\text{Y-}}{\rightleftharpoons}} R-C-X \quad \overset{\text{Y+}}{\rightarrow} R-C-Y + X \quad \text{.................(42)}
\end{align*}
\]

complex partitions forward to the reaction products with the elimination of $X$ or back to the reactants. The facility with which $X$ is eliminated is in the sequence $\text{Cl} > \text{OCOR} > \text{OR} > \text{NH}_2$. This is the same order as the ease of ionization of the saturated compounds $\text{C-X}^\ominus$. It is also the order of the stability of the anion $X^\ominus$.
4) Structure of Phosphoryl Compounds

Phosphorus, unlike carbon, has available d- as well as p- and s-orbitals. In the last few years attention has been drawn to the importance of d-orbitals in chemical bonding\textsuperscript{48-52}. It is now established that in compounds such as phosphorus pentachloride and phosphorus pentafluoride, the bonds can be described as covalent \textit{sp}$^3$\textit{3p}$^3$d hybrids\textsuperscript{51,52}. The bonds are directed to the apices of a trigonal bipyramid.

In phosphorus compounds possessing the phosphoryl group, the central phosphorus atom is bonded to four atoms or groups (with the exception of metaphosphoric acid derivatives which are not considered here). It is now considered that there is an appreciable amount of d-character in the $\sigma$ bond hybrid of the phosphorus atom with the neighbouring ligands\textsuperscript{51,52}. However their geometry and many other properties correspond closely to those predicted for an $\textit{sp}^3$ hybrid\textsuperscript{53}. For example, they possess a tetrahedral configuration with bond angles close to 109°, i.e., similar to a saturated carbon atom. Phosphoryl compounds are therefore very different geometrically from the configuration of carbonyl compounds.

A second, and possibly greater difference, is the nature of the bond between the phosphorus and oxygen atoms on the one hand, and carbon and oxygen on the other. It has long been established that the carbon and oxygen atoms of a carbonyl are united by a double bond as described above. However the nature of the bond between phosphorus and oxygen atoms in the phosphoryl group has been the subject of much controversy.
Originally these compounds were formulated as pentovalent structures with a double bond between the phosphorus and oxygen atoms (XIII). Later, when the principle of the dative or coordinate bond was established, the structure was modified with a single bond in place of the double bond (XIV). It was argued that

\[
\begin{array}{cc}
  X \backslash & X \backslash \\
  Y - P = 0 & Y - P^+ - O^- \\
  X & Z \\
\end{array}
\]  

(XIII) (XIV)

the bond did not differ from a normal covalent bond except for the charge transfer resulting in the dipole as shown (XIV). Subsequent measurements of bond length and dipole moment suggested that the phosphoryl compounds were, in fact, more realistically formulated with a double bond between the phosphorus and oxygen\(^5\). Until recently the case for the existence of any double bond character in these compounds has rested on the analysis of bond characteristics such as lengths, mean energies, dipole moments and vibrational frequencies\(^5\). Wells\(^5\) in 1949 challenged this reasoning and concluded that there were insufficient data at the time to draw any definite conclusions. However Craig and co-workers in 1954\(^1\) and 1956\(^2\) have presented a convincing case for the existence of appreciable double bond character between the phosphorus and oxygen in phosphoryl compounds.

The concept involves the d-orbitals of phosphorus and differs considerably from the description of bonding between carbon and oxygen in the carbonyl group. Examination of the free-atom parameters
of the outer d-orbitals of phosphorus reveals that the overlap integrals are too weak and too diffuse to contribute to the bond energy of a compound. A type of polarization had therefore been proposed in which these diffuse orbitals are contracted, bringing the electrons closer to the atoms or groups with which bonds are to be formed, thus adapting them to stronger bonding. This contraction is brought about as a result of perturbation caused by the ligands attached to the central phosphorus atom. When the central atom is attached by a σ bond to a strongly electronegative atom like oxygen, the resulting σ bond confers some degree of positive charge on the phosphorus atom causing the d-orbital to contract. This increases the overlap of the d,π orbitals and renders the formation of a stable π bond possible. It has been calculated that the additional stability due to the double bond character of the phosphoryl bond amounts to between 13 and 38 k.cal/mole. The corresponding value for the O = O bond is 70-80 k.cal/mole.

The positive charge on the central phosphorus atom will vary from compound to compound depending directly on the electron attracting power of the ligands attached to it. Consequently it may be seen that the degree of overlap of the d-orbitals of phosphorus and the p-orbitals of oxygen will vary and, in turn, the amount of π or double bonding in a phosphoryl group will vary between compounds.
5) Bimolecular Nucleophilic Reactions at the Phosphoryl Group

The phosphoryl group has no ability to form addition complexes with the opening of the double bond. Unlike the carbonyl group, the double bond of the phosphoryl group does not open. Hudson and Keary consider that the mechanism of phosphorylation involves the tetrahedral $sp^3$ phosphorus compound utilizing its d-orbital to form the transition state with a nucleophile and adopting an $sp^3d$ trigonal bipyramidal configuration (equation 43). The $sp^3d$

\[ \begin{array}{c}
R \text{R'} \text{X} & \xrightarrow{Y} & Y - P - X & \xrightarrow{\text{SP}^3d} & Y \text{R} \text{R'} + X
\end{array} \]

hybrid bonds so formed are weaker than the $sp^3$ bonds. Therefore, a bond breaking is of more importance in this case than in the carbonyl reactions. This mechanism closely resembles one advanced by Gillespie for $S_n2$ reactions at saturated carbon atoms.

Earlier theories had postulated the reversible formation of an unstable quinquevalent phosphorus intermediate complex, but Halmann, who studied the acid, neutral and alkaline hydrolysis of a number of phosphoryl compounds, found no evidence for such an intermediate complex. The reactions were clearly shown to be bimolecular nucleophilic ($S_n2$) displacements.

Todd has discussed the mechanism of nucleophilic bimolecular reactions of phosphoric anhydrides including mixed phosphoric anhydrides. Both potential reaction centres of the neutral anhydride will carry a measure of positive charge but that belonging
to the stronger acid will be greater. The nucleophile will approach both centres; consequently two transition states are possible. This is shown for the generalised reaction between the anhydride \( R'R''O \equiv O \equiv O_X(0)_nR \), and a nucleophile \( YH \). The first step will be

\[
\begin{align*}
\text{step 1} & : R''P \equiv \equiv O_Y + \text{step 2} \quad R''P - Y + R \equiv \equiv (0)_nX^{-} + H^+ \\
\end{align*}
\]

\[
\begin{align*}
\text{step 1} & : R - X \equiv \equiv O + YH + \text{step 2} \quad R \equiv \equiv (0)_nX^{-} - Y + \text{step 2'} \quad R'P - O^{-} + H^+ \\
\end{align*}
\]

favoured by the measure of positive charge at the site of reaction. However if this step were rate controlling, the reaction would take place predominantly at the most positive centre, as indeed is the case with carboxylic anhydrides. Since this is not the case, some other controlling factor must be operating in the second step, namely bond breaking. It follows that bond breaking is more important than bond formation. This is in contrast to reactions at carbonyl groups, where bond formation to yield the intermediate complex is the rate limiting step (p. 6). The partial bonds \( P \equiv \equiv 0 \) or \( X \equiv \equiv 0 \) must be substantially polarized and weakened by the approach of the nucleophile, before bond formation \( P \equiv \equiv YH \) or \( X \equiv \equiv YH \) can commence. The second step will therefore be governed by the ease with which the partial bonds \( P \equiv \equiv 0 \) or \( X \equiv \equiv 0 \) break. The more
readily the partial bond breaks, the greater the reaction rate. It is an essential requirement of Todd's theory of the mechanism that the fission of these partial bonds shall be rate controlling. The facility with which these partial bonds break is directly related to the stability of the ion so produced; that is to say $R'R''\text{PCO}^-$ or $R-X(0)_n^-$. A grouping that will readily form a stable anion will be a very effective leaving-group. The stability of an ion is a measure of the strength of the corresponding acid and the stronger the acid, the more stable the ion. Therefore it follows that, with the mechanism depicted, the moiety derived from the stronger acid will occur as the anion in the reaction, and that the moiety derived from the weaker acid will acylate or phosphorylate the nucleophile.

This mechanism described above for phosphoric anhydrides could be applied to carboxylic-carboxylic anhydrides. However the characteristic that distinguishes a good leaving group, namely its ability to form a stable anion, also demands that the carbon of the carboxyl group shall have a relatively high positive charge. This characteristic also greatly facilitates the formation of the intermediate addition complex (XV). Indeed derivatives of trifluoroacetic acid,

$$
\begin{array}{c}
\text{O}^- \\
\text{R-C} \cdot \text{O}^- \cdot \text{CR'}
\end{array}
$$

(XV)

the strongest known carboxylic acid, very readily form addition complexes that are stable enough for isolation. Considering an unsymmetrical anhydride $R\cdot\text{CO} \cdot \text{O} \cdot \text{CO} \cdot R'$ where $R\cdot\text{COOH}$ is a stronger acid
than R'COOH, once the addition complex (XV) is formed, the positive charge on the carbon of the carbonyl group in R.CO- is eliminated depriving the stronger acid moiety of its potential as a leaving group. The stable ion must therefore arise from the weaker acid residue, fission occurring at $\Phi$. (XV).

A further point arises concerning phosphoric and phosphoryl compounds that is peculiar to the multiple bonding that may arise between phosphorus and oxygen atoms. Substituents on the phosphoryl group which increase the strength of the acid also increase the positive charge on the central phosphorus atom. This in turn causes the d-orbital of phosphorus to contract allowing greater overlap with the p-orbitals of oxygen and facilitating some $\sigma_{n-p^*}$ bonding between oxygen and phosphorus. The resulting multiple bonding between these two atoms strengthens the P-O link. The effect can be illustrated in a generalised anhydride (XVI) derived from (RO)$_2$POOH and (R'O)$_2$POOH where the former acid is the stronger.

The bond $a$ between the phosphorus and oxygen will be stronger than bond $b$ as a consequence of this multiple bonding, thereby favouring fission at $\Phi$ (XVI), the weaker bond.
6) Comparison of Steric Effects at Carbonyl and Phosphoryl Groups in Anhydrides

The steric effects occurring at the carbonyl group of unsymmetrical carboxylic-carboxylic anhydrides have been discussed earlier (p.14). Apart from the observation that isopropyl groups cause steric hindrance in unsymmetrical pyrophosphates (p.23) there is no other data on this subject in the literature. Two recent papers \(^{46, 60}\) have discussed steric effects at phosphoryl groups.

Hudson and Keary \(^{46}\) state that in comparison with carbonyl compounds the stereo-chemistry of the phosphoryl group leads to greater steric effects. They compare the \(S\_n\_2\) reactions at phosphoryl groups with the \(S\_n\_2\) reactions at saturated carbon atoms rather than with the addition elimination bimolecular reactions of carbonyl compounds. It is therefore interesting to compare the steric effect a methyl group, and a t-butyl group has on the three relevant types of reactions, namely an addition elimination reaction at a carbonyl group, an \(S\_n\_2\) reaction at a saturated carbon atom and an \(S\_n\_2\) reaction at a phosphoryl group (Table IV).
### Table IV
Comparison of Some Bimolecular Reactions

<table>
<thead>
<tr>
<th>Description of Reaction</th>
<th>Ratios of Reaction Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous hydrolysis of acetic anhydride and trimethylacetic anhydride&lt;sup&gt;61&lt;/sup&gt; at 25°.</td>
<td>33 : 1</td>
</tr>
</tbody>
</table>
| \[
\begin{align*}
\text{CH}_3\text{CO} \cdot \text{CO} \cdot \text{CH}_3 & : \text{CH}_3\text{CO} \cdot \text{CO} - \text{CH} - \text{CH}_3 \\
\text{CH}_3 & : \text{CH}_3
\end{align*}
\] | 240,000 : 1                  |
| Reaction of ethoxide ion in ethanol with ethyl bromide and with neopentyl bromide<sup>62</sup> at 55°. | 750 : 1                   |
| \[
\begin{align*}
\text{CH}_3\text{CH}_2\text{Br} & : \text{CH}_3 - \text{CH}_2\text{Br} \\
\text{CH}_3 & : \text{CH}_3
\end{align*}
\] | 750 : 1                   |
| Alkaline hydrolysis of ethyl p-nitrophenyl methyl phosphate and ethyl p-nitrophenyl t-butylphosphonate<sup>60</sup> at 37.5°. | 750 : 1                   |
| \[
\begin{align*}
\text{NO}_2\text{P} - \text{CH}_3 & : \text{NO}_2\text{P} - \text{CH}_3 \\
\text{NO}_2\text{P} - \text{CH}_3 & : \text{NO}_2\text{P} - \text{CH}_3
\end{align*}
\] | 750 : 1                   |

The extreme unreactivity of the neopentyl halides is well known and is attributed to the steric hindrance caused by the t-butyl group<sup>62</sup>. Butler and Gold<sup>61</sup> have pointed out how much less effect the t-butyl group had on the reactivity of trimethyl acetic anhydride compared with neopentyl halides. The steric effect of the t-butyl group at a phosphoryl group appears to be intermediate between the two cases stated above. However, the difference between the ratios

- 54 -
for the reactions at a carbonyl group (33 : 1) and a phosphoryl
group (750 : 1) is not sufficiently great to be conclusively attribut-
ted to greater steric hindrance without taking into account the
reaction temperatures and activation energies. Dostrovsky and Halmann have compared the Arrhenius parameters for the alcoholysis of a series
of chloroformate esters and phosphorochloridates at 25° and shown
that the activation energy for the phosphorus acid chlorides is
3-4 kcal/mol. less than in the case of the carboxylic acid chlorides.
If we assume from these data that the activation energies for the
hydrolysis reactions of carbonyl and phosphoryl compounds are of
very similar magnitude the ratios above support the argument that
similar reactions occurring at phosphoryl groups are subject to more
steric hindrance than those as carbonyl groups.

7) Conclusions

The difference between a carbonyl and a phosphoryl group which
may be expected to affect reactivity at these sites may be summarised
as follows. Phosphorus, being in a higher series than carbon in
the periodic system, will be more polarisable than carbon, possibly
leading to larger inductive effects than in carbon. The stereo-
chemistry of the phosphorus atom of a phosphoryl group will resemble
that of a saturated carbon atom. The steric effects will be some-
what mitigated as a consequence of the greater atomic radius of
phosphorus compared with carbon but, nevertheless, steric effects
will be greater at phosphoryl groups than at carbonyl groups. Unlike
carbonyl compounds the double bond does not open so that a stable
addition intermediate is never formed with phosphoryl compounds. In the S_N2 reactions with phosphoryl compounds synchronous bond formation and rupture takes place. The use of 3d-orbitals for \( \equiv \) bonding in phosphorus compounds leads to multiple bonding of a different type from the \( \equiv \) bonding of carbonyl compounds. Conjugation plays a very much smaller part. Thus there is no resonance between the Ph and P = O groups in benzene phosphonic, benzene phosphonous, and diphenyl phosphonic acids, or in triphenyl phosphine oxide\textsuperscript{46,63}. In the S_N2 reactions with phosphoryl compounds synchronous bond formation and rupture takes place, bond breaking being more important than bond formation.
From the foregoing discussion several unauthenticated and anomalous claims concerning the chemistry of diesters of phosphoric acids and carboxylic acids are apparent.

Cramer and Gartner have clearly shown that acyl diethyl phosphates derived from aliphatic carboxylic acids are acylating agents.\(^5\) Other workers have confirmed this to be so. However the behaviour of benzoyl diethyl phosphate is not unambiguously characterised. As mentioned earlier (p. 38), the results could be construed to indicate that benzoyl diethyl phosphate is a phosphorylating as well as a benzoylating agent. Since the carbonyl group of benzoyl compounds is deactivated by conjugation with the benzene nucleus, such an argument would be plausible. However it must be remembered that the reaction was conducted with crude benzoyl diethyl phosphate. Undoubtedly there is evidence that at least one acyl phosphate possesses some phosphorylating power, \(\text{viz.}\) bis (dibenzyl phosphoryl) oxalate yielded 5.5\% dibenzylphosphoramidate with ammonia (p. 33). It is one of the aims of this study to examine the products of the reaction between benzoyl diethyl phosphate and aniline.

It would appear from the difficulties experienced by earlier workers that the choice of acid derivatives used for the synthesis of acyl phosphates may be critical (pps. 32, 36 and 40). Acetyl diethyl phosphate and benzoyl diethyl phosphate appear to be attractive compounds for the investigation of this point.
The principal aim of the work recorded in this thesis is to apply data recorded in the preceding sections to the design of an acyl diethyl phosphate that is a phosphorylating agent.

It has been shown that phosphoric anhydrides react with nucleophiles by a mechanism that results in the ionic product arising from the stronger of the constituent acids (p. 27). If this reasoning can be applied to acyl phosphates, then a mixed anhydride of diethyl phosphoric acid and a carboxylic acid of greater acid strength should be a phosphorylating agent. Thus trifluoracetyl diethyl phosphate should phosphorylate, which is indeed the reasoning behind Todd's suggestion. However, on the evidence it seems more likely that the addition complex at the carbonyl is formed before the nucleophile can attack the phosphoryl group and displace the trifluoracetic ion (pp. 35 and 51). If pure trifluoracetyl diethyl phosphate can be isolated, the point can be established by examining the products of its reaction with aniline.

Another approach uses carboxylic acids with deactivated carbonyl groups (cf. unsymmetrical anhydrides with ethyl carbonic acid and amino acids and acetic benzoic anhydride, p. 17). The intention of studying benzoyl diethyl phosphate has already been noted. In addition ethoxycarbonyl diethyl phosphate appears to have merit in this connection. If it could be obtained and proved to be a phosphorylating agent it would provide an elegant reagent (equation 45).

\[
\begin{align*}
\text{EtO} \quad \overset{\ominus}{\text{C}} - \overset{\ominus}{\text{O}} - \overset{\ominus}{\text{CHt}} + \overset{\ominus}{\text{H}} \overset{\ominus}{\text{NR}} & \rightarrow \quad \text{EtO} \quad \overset{\ominus}{\text{P}} - \overset{\ominus}{\text{HNR}} + \overset{\ominus}{\text{EtCH}} + \overset{\ominus}{\text{CO}}_2 \\
\end{align*}
\]
The by-products would be ethanol and carbon dioxide.

If the nucleophile could be prevented from forming the addition complex with the carbonyl group, it may then react at the phosphoryl group. Thus mixed anhydrides with sterically hindered carboxylic acids and diethyl phosphoric acids might prove to be phosphorylating agents. Two such acids are trimethyl acetic and triphenylacetic acids.

Probably the greatest promise is afforded by the combination of all three of the above theories. That is to say, the use of a carboxylic acid that possesses a deactivated, heavily hindered carbonyl group. It should be a strong acid thereby affording a good leaving group. Three acids that conform to these requirements are 2,3,5-trichlorobenzoic, 2,3,5,6-tetrachlorobenzoic and 2,3,4,5,6-pentachlorobenzoic acids. The mixed anhydrides of these acids and diethyl phosphoric acid should possess considerable phosphorylating ability.
DISCUSSION OF EXPERIMENTAL WORK

1) Introduction

Nine acyl diethyl phosphates have been prepared and isolated as pure compounds, namely: acetyl diethyl phosphate (XVII), trifluoroacetyl diethyl phosphate (XVIII), trimethylacetyl diethyl phosphate (XIX), triphenylacetyl diethyl phosphate (XX), benzoyl diethyl phosphate (XXI), 2,3,5-trichlorobenzoyl diethyl phosphate (XXII), 2,3,5,6-tetrachlorobenzoyl diethyl phosphate (XXIII), 2,3,4,5,6-pentachlorobenzoyl diethyl phosphate (XXIV) and ethoxy carbonyl diethyl phosphate (XXV).
With the exception of acetyl diethyl phosphate (XVII) and benzyl diethyl phosphate (XXI), all the compounds are new. Petrov and Neizycheva\textsuperscript{41} (p. 35) claimed to have prepared trifluoracetyl diethyl phosphate (XVIII). However, as will be made clear later they cannot have obtained more than a trace of the compound.

In theory these anhydrides may undergo phosphorylation or acetylation reactions, or both simultaneously. The model reaction chosen to establish the mode of reaction was the interaction between two moles of aniline and one mole of the anhydride in ether. The possible products were the respective anilides and diethyl N-phenyl phosphoramidate. All were readily characterised crystalline compounds with sharp melting points. Quantitative analysis for phosphorus of the crude products after removal of the anilinium salts gave an indication of the amount of phosphorylated material present. Where possible isolation of N-phenyl diethyl phosphoramidate confirmed this estimation.

2) General Method of Preparation

The method selected for the preparation of these mixed anhydrides was the reaction between a salt and an acid chloride. It will be shown later that it is critical which moiety is present as the salt or acid chloride. This method has been applied for the preparation of phosphoric-carboxylic anhydrides by several other workers (p. 33 at end).

The use of silver, lead and sodium salts of diethyl phosphoric acid was investigated. The use of tertiary amines was deliberately
avoided, since it has been shown that catalytic quantities cause
disproportionation of acyl dialkyl phosphates (p. 31). Unless a
deficiency of tertiary base was used the possibility existed of a
trace of it remaining. Further the resulting hydrochlorides of these
amines are soluble in the reaction mixture and may possibly dealkylate
the acyl phosphates. Trisubstituted phosphates are dealkylated by
solutions of tertiary amine hydrohalides 55 (equation 46).

$$\text{Alkali metal salts that are soluble in organic solvents, e.g. sodium}$$
$$\text{iodide and lithium chloride, behave similarly}^{66} \text{ (equation 47).}$$

$$\text{Rigorously anhydrous conditions for the reactions between the salts}$$
$$\text{and acid chlorides were maintained. The acid chlorides being freshly}$$
$$\text{distilled and the salts dried at 100°/15 mm.}$$

3) **Diethyl Phosphoric Acid Intermediates**

Diethyl phosphorochloridate was prepared by the general method
of Cook et al. 67 for the preparation of phosphorochloridates. Rather
surprisingly data on the preparation of salts of diethyl phosphoric
acid are sparse and incomplete. Consequently the work is dealt with
in some detail. Silver diethyl phosphate was first described by
Lessen and Kohler 68. Barium diethyl phosphate, obtained from the
hydrolysis of triethyl phosphate with aqueous barium hydroxide was
interacted with sulphuric acid yielding diethyl phosphoric acid which,
with silver oxide yielded the silver salt. Scanlon and Collier mention that silver diethyl phosphate may be obtained from the interaction of silver oxide with ethyl phosphorochloridate (equation 43).

\[
\text{Ag}_2\text{O} + (\text{EtO})_2\text{P(O)Cl} \rightarrow (\text{EtO})_2\text{P(O)Ag} + \text{AgCl} \quad \text{(43)}
\]
The writer found that freshly prepared hydrated silver oxide gave a
cleaner product. The salt was light-sensitive. It could be crystallised from hot methanol but some reduction of the salt took place and the yields were poor.

Lead diethyl phosphate is not well authenticated in the literature. It is mentioned by Zervas and Biliris although the preparation was not given. Vogeli in 1849, interacted white lead with the product of the reaction between phosphorus pentoxide and ethanol. He isolated two salts, one readily soluble in water, m.p. 180°, which was probably \[\left[(\text{EtO})_2\text{P(O)Cl}\right]_2\text{Pb},\] the other sparingly soluble in water of no stated melting point or structure. Vogeli's work was repeated by van Hove who isolated a salt crystallisable from alcohol to which he assigned the structure \[\left((\text{EtO})_2\text{P(O)Cl}\right)_2\text{Pb}\] on the basis of the lead content. No melting point was quoted.

In the present work two methods of preparation of lead diethyl phosphate were investigated. The first was the metathesis of a
soluble lead salt and sodium diethyl phosphate, and the second the interaction of lead hydroxide and ethyl phosphorochloridate.
The main product of the reaction between aqueous solutions of lead nitrate and sodium diethyl phosphate was a salt, sparingly soluble in water and insoluble in alcohol of m.p. 235-40°. The properties and phosphorus content were consistent with those of a hydrated basic phosphate of the formula \((\text{NH}_4)_2\text{P(O)}\text{O}\text{P}(\text{OH})\text{H}_2\text{O}\). This salt may be the same as that obtained by Vogeli of unstated melting point. Its insolubility in ethanol permitted its separation from the soluble lead diethyl phosphate \([(\text{NH}_4)_2\text{P(O)}\text{O}\text{P}\text{O}]_2\text{Pb}, \text{m.p. 130°}\), simultaneously formed in poor yield. When lead nitrate was replaced by lead acetate in this reaction a very poor yield of lead salt, m.p. 100°, was obtained, but no basic salt separated, the main product being an uncrystallizable gum.

Good yields of lead diethyl phosphate were obtained from the reaction between lead hydroxide in water and ethyl phosphorochloridate. However, the product had the disadvantage that it was contaminated with lead chloride. Partial purification could be effected by crystallization from methanol or ethanol. About 1.5% lead chloride remained after recrystallizing repeatedly from ethanol, despite the reported insolubility of lead chloride in ethanol \(^{72}\) (0.002% in absolute ethanol). The product contained less than 0.1% lead chloride after recrystallizing from methanol. The small amount of lead chloride in the lead diethyl phosphate had no adverse effect on the subsequent reactions described in this work.

The trihydrate of sodium diethyl phosphate was described by Bailly \(^{73}\), who isolated it in very poor yield from the products of the reaction between trisodium phosphate and ethyl halides or ethyl
sulphate. Pascal mentions sodium diethyl phosphate but does not describe its preparation. Zervas and Bilocic showed that sodium diethyl phosphate is formed when triethyl phosphate was dealkylated with sodium iodide (equation 49). In the writer's experience this

\[(\text{EtO})_2\text{P(0)OEt} + \text{NaI} \rightarrow (\text{EtO})_2\text{P(0)ONa} + \text{EtI}\]  \hspace{1cm} \text{(49)}

reaction was unpromising. It yielded a product contaminated with sodium iodide, an impurity which was not easily removed.

McIver et al. describe the preparation of anhydrous sodium diethyl phosphate. Triethyl phosphate was hydrolysed with aqueous alcoholic sodium hydroxide solution at room temperature followed by the removal of the water and alcohol by azeotropic distillation with benzene. This method has been modified by the use of boiling aqueous sodium hydroxide, and improved by recrystallising the product from ethanolic acetone. The anhydrous salt was extremely deliquescent, very soluble in water, alcohols and chloroform.

The sodium salt of diethyl phosphoric acid was preferred for the synthesis of the mixed anhydrides. It could be prepared pure more easily than the silver or the lead salt and reacted more rapidly than either of the latter with acid chlorides. The relative ease of reaction of these three salts was revealed by the experiments relating to the synthesis of ethoxycarbonyl diethyl phosphate. The only disadvantage of the sodium salt was its extremely deliquescent nature and the consequent difficulty of maintaining anhydrous conditions. Although not deliquescent, the silver and lead salts afforded poor yields and the latter especially reacted very slowly with acid chlorides.
4) Carbonylic Acid Intermediates

Good quality commercial samples of acetyl chloride, benzyol chloride, ethyl chloroformate, sodium acetate and sodium benzoate were used after drying or redistilling as applicable.

Pure anhydrous sodium triphenylacetate was obtained from a commercial sample of the anhydrous acid and sodium methoxide solution; care being taken to ensure that excess acid was present before evaporation, otherwise decarboxylation took place and the salt was contaminated with sodium carbonate. Triphenylacetic acid was prepared via the Grignard method\(^7\) and from this the sodium salt. Hydrated sodium triphenylacetate has been described by Bittner\(^5\) as a crystalline product separating from a highly alkaline solution of the salt. The anhydrous sodium triphenyl acetate was prepared in this work by exact neutralisation of the acid in aqueous media followed by the isolation of the salt in an anhydrous organic solvent. Triphenylacetyl chloride was prepared by the method of Adams et al.\(^7\). Tri-N-methylacetyl chloride was prepared from commercial triacetyl chloride and thionyl chloride.

A new method for the synthesis of the polychloro benzoic acids was developed. 2,3,5-Trichlorobenzoic acid and 2,3,4,5,6-pentachlorobenzoic acid are reported in the literature, but 2,3,5,6-tetrachlorobenzoic acid is not. Earlier literature describing 2,3,6-trichlorobenzoic acid is not without ambiguity. However, Brincker and collaborator\(^7\) have adequately authenticated the acid. They prepared it by nitric acid oxidation of 2,3,6-trichloro tolune or 2,3,6-trichloro- benzaldehyde. The oxidation of the latter with aqueous potassium...
permanaganate also offered a suitable method. Lastly, they prepared it from 3,5'-dichloroanthranilic acid via the diammonium compound and cupric chloride.

Pentachlorobenzoic acid has been prepared by nitric acid oxidation of pentachlorotoluene and from the benzenaldehyde with aqueous alkaline permanganate. Hais and Keil hydroylysed pentachlorobenzene-nitrile with ethyl alcohol sodium hydride but did not isolate the acid. A mixture of isomeric tetrachlorobenzoic acids and pentachlorobenzoic acid was obtained by the action of hydrochloric acid and manganese dioxide on 2,3-dichloro, or 2,6-dichlorobenzoic acid, but no yields were recorded. Finally, a small amount of pentachlorobenzoic acid arises from the action of antimony pentachloride on benzophenone.

Although these polychlorobenzoic acids may be obtained from the corresponding toluene or benzenaldehyde in good yields, the methods described require either nitric acid oxidation in a sealed tube or the oxidation of the benzenaldehyde with large volumes of aqueous potassium permanganate solutions. Both methods are convenient only for the preparation of small amounts of the acid.

Kermic and Bours prepared 2,6-dichlorobenzoic acid by brominating 2,6-dichlorotoluene to give the benzylic bromide followed by hydrolysis to the benzylic alcohol with aqueous sodium hydride and subsequent oxidisation of the alcohol with aqueous potassium permanganate, obtaining a yield of 83% of 2,6-dichlorobenzoic acid. Cohen and Ruben reported failure for this method. A similar method was used by Lehmstedt and Schneider. However their workers
interacted 2,6-dichlorobenzyl chloride with sodium acetate to form 2,6-dichlorobenzyl acetate which was hydrolyzed to the alcohol. Oxidation of the latter gave 2,6-dichlorobenzoic acid in 92% yield. This last method avoids the possible formation of di(2,6-dichlorobenzyl) ether, which would account for the failure of the method in Cohen and Bokin's hands and the poor yield reported by Norris and Seers.

The following reaction sequence (59) therefore appeared attractive provided the toluenes were available. 2,3,6-Trichloro toluene

\[
\begin{align*}
\text{Cl} & \quad \text{CH}_3 \quad \text{Cl} \quad \text{Cl} \quad \text{CH}_2\text{Br} \quad \text{Cl} \\
\text{CH}_3 & \quad \text{Cl} \quad \text{Cl} & \quad \text{CH}_2\text{OH} \quad \text{Cl} \\
\text{Cl} & \quad \text{COOH} \quad \text{Cl} \quad \text{COOH} & \quad \text{Cl} \quad \text{COOH}
\end{align*}
\]

and 2,3,5,6-tetrachloro toluene were obtained from Mears Pest Control, Horston, having been made by the method of Bricker et al.,\textsuperscript{78} namely by the chlorination of tertiary p-methylphenyl chloride, followed by hydrolysis, acetylation and vacuum fractionation to yield 2,3,6-trichloro toluene b.p. 112-122\(^\circ\) C (lit.\textsuperscript{76} b.p. 110\(^\circ\) C) 60% and 2,3,5,6-tetrachloro toluene b.p. 142-152\(^\circ\) C, m.p. 93-94\(^\circ\) C, 27%. Cohen and Haper\textsuperscript{57} reported m.p. 93-94\(^\circ\) C for the latter compound.

2,3,4,5,6-Pentachloro toluene was obtained by the method of Wilhkim.\textsuperscript{66} Addition of bromine to the polychloro toluenes irradiated with ultraviolet light afforded the benzyl bromides. 2,3,6-Trichlorobenzyl bromide first described in 1935\textsuperscript{69} was obtained by the addition of
bromine to 2,3,6-trichloro toluene. This method was improved by the
use of ultra-violet light whereby the yield was increased from 77 to
87%. 2,3,5,6-Tetrachlorobenzyl bromide and pentachlorobenzyl bromide
are now compounds. The polychlorobenzyl bromides reacted with potassium
acetate in ethanol to yield the corresponding benzyl acetates. Penta-
chlorobenzyl acetate has been prepared from the benzyl chloride and
potassium acetate90. 2,3,6-Triehlorobenzyl acetate and 2,3,5,6-
tetrachlorobenzyl acetate are not mentioned in the literature. These
acetates were readily hydrolyzed with alcoholic potassium hydroxide
to the corresponding benzyl alcohol. Indeed water alone will hydrolyze
pentachlorobenzyl acetate to pentachlorobenzyl alcohol91. 2,3,5,6-
Tetrachlorobenzyl alcohol has not been described before. 2,3,6-Tri-
chlorobenzyl alcohol has been prepared by the action of sodium nitrite
on the benzylamine92. Direct replacement of bromine with hydroxyl by
allowing the benzyl bromide to react with alcoholic potash either
failed, or gave very poor yields. Pentachlorobenzyl chloride and
alcoholic potash have been reported to react to give di(pentachloro-
benzyl) ether93. However it was not necessary to isolate the acetate.
Good yields were obtained by adding alkali to the alcoholic acetate
reaction mixture. The use of alkaline potassium persulfate as
described by Norman and others94 for the preparation of dichlorobenzoic
acid was very satisfactory for 2,3,6-trichlorobenzoic acid. However
neither 2,3,5,6-tetrachlorobenzyl alcohol nor pentachlorobenzyl
alcohol were sufficiently soluble and were recovered unchanged from
the attempted reaction. This difficulty was readily overcome by the
use of aqueous pyridine potassium persulfate solution, although
this solvent was less satisfactory than water alone for 2,3,6-trichlorobenzoic acid.

Direct oxidation of 2,3,5,6-tetrachloro toluene with pyridine/potassium permanganate gave a very poor yield of 2,3,5,6-tetrachlorobenzoic acid therefore this method was rejected.

The sodium salts of these polychlorobenzoic acids were obtained by the incomplete neutralisation of an alcoholic solution of the acids with aqueous sodium hydroxide. Excess acid was then removed with chloroform or carbon tetrachloride.

5) **Compounds Required for the Authentication of Reaction Products**

A number of anilides and N-phenyl phosphoramidate were required to confirm the identity of the products of reaction between the mixed anhydrides and aniline. Where these were not commercially available they were prepared from aniline and the appropriate acid chloride or anhydride. 2,3,6-Trichlorobenzanilide, one of the compounds required, has not been described previously.

Similarly the anilinium salts of 2,3,6-trichlorobenzoic acid, 2,3,5,6-tetrachlorobenzoic acid and 2,3,4,5,6-pentachlorobenzoic acid were required. None of these appear in the literature. They were prepared by dissolving the stoichiometric quantities of acid and aniline in alcohol and mixing the solutions. The anilinium salt of 2,3,6-trichlorobenzoic acid was unusual in that it always appeared to separate as the acid salt, i.e., one mol of aniline to two mols of 2,3,6-trichlorobenzoic acid.
An improved method has been found for the preparation of tetraethylpyrophosphate, a recurring contaminant in preparations of the anhydrides. The sample was required as a reference in the spectrographic work. The reaction between a salt of diethyl phosphoric acid and ethylphosphorochloridate has been utilized by other workers for the preparation of tetraethylpyrophosphate²⁵. By conducting the reaction in chloroform in which the sodium diethyl phosphate is soluble - a property of the anhydrous sodium salt hitherto unremarked - a good yield of very pure tetraethylpyrophosphate was readily obtained.

When tetraethylpyrophosphate was present in the crude reaction mixtures of phosphoric-carboxylic anhydrides the symmetrical carboxylic anhydride was always concurrently formed. Reference samples of 2,3,6-trichlorobenzoic anhydride and triphenylacetic anhydride were prepared. The former is a new compound, an improved method for the preparation of the latter was evolved.

Many phosphodiesters have been isolated and characterised by their cyclohexylamine salts. Where diethylphosphate salts were formed the possibility of using cyclohexylammonium diethyl phosphate for this purpose was examined. It proved to be a deliquescent crystalline compound quite unsuitable for characterisation purposes.

6) Diethyl Phosphoric-Carboxylic Anhydrides (Acyl Diethyl Phosphates)

The preparative methods used by other workers have been reviewed earlier (p. 29). A particularly confusing aspect of this earlier work is the variation in results reported by these workers when using
simple acid components such as the acid chlorides and salts. Sheehan and Frank \(^3\) obtained phosphoric-carboxylic anhydrides using the silver salt of the phosphodiester and the carboxylic acid chloride, but only a mixture of symmetrical anhydrides when the functional characteristic of the components was reversed, i.e., if phosphoric acid chloride and silver carboxylate was used in place of the carboxylic acid chloride and silver dialkyl phosphate. Sheehan and Frank also claimed that the triethylammonium salt of the phosphodiester could not be used in place of the silver salt. Cosmatos \(^3\) and collaborators however, were successful using the phosphoric acid chloride and carboxylic acids in the presence of pyridine. Although the mixed anhydrides were not isolated, the products of the reaction of the crude reaction mixture with aniline leave no doubt that a substantial amount of acyl phosphate was present. The claims of Petrov and Neimysheva \(^4\) are far more open to doubt and they contradict Sheehan and Frank. Petrov and Neimysheva used the phosphoric acid chloride and silver carboxylates for their preparations, which were conducted in boiling ether. They gave no evidence in support of their claim that acyl phosphates were prepared by this method. Distillation of their reaction mixtures gave the symmetrical anhydrides, and, in this respect, they agree with Sheehan and Frank. The results reported by Michalski and Modro \(^5\) confuse this issue further. Using similar conditions to those of Cosmatos and collaborators above, namely the phosphoric acid chloride, carboxylic and pyridine, they showed that only symmetrical anhydrides were formed in significant quantity. Their examination of the crude reaction
mixture prior to distillation revealed that the phosphoric compound was largely pyrophosphate. Thus this conflicts directly with the work of Cosmatos. Michalski and Modro state that in their reactions, and those of Petrov and Neimysheva, the mixed anhydrides disproportionate immediately they are formed. Thus they reject the claim of the last mentioned workers to have prepared acyl phosphates.

In recent years acetyl diethyl phosphate and benzoyl diethyl phosphate have been prepared by several methods. They are therefore well authenticated, and the simple acid derivatives required for their preparation are readily available. These two compounds are thus well suited for the investigation of the general conditions for the preparation of acyl phosphates.

The dealkylation of tertiary phosphates by soluble halide salts has already been mentioned (p. 62). It is obviously desirable, therefore, that the chloride salt formed from the reaction between the acid chloride and salt of the phosphoric or carboxylic acid should be insoluble in the reaction media. While it is also preferable that the salt of the phosphoric acid or carboxylic acid should dissolve to some extent. Salts of tertiary bases are inclined to be soluble in many organic solvents. In addition, any free base would cause disproportionation of the mixed anhydride present. For this reason tertiary bases were avoided, and the sodium salts utilized in most cases. In some cases excess acid chloride served as a suitable solvent, in others, where excess acid chloride was undesirable, or its physical properties rendered it unsuitable, acetone or methyl ethyl ketone proved satisfactory.
Ethoxyl carbonyl diethyl phosphate (XXV) proved to be a very stable mixed anhydride. It therefore served as a suitable model compound for the study of the reactivity of the lead, silver and sodium salts of diethyl phosphoric acid where in some cases prolonged refluxing was necessary. Disproportionation under these conditions would have vitiated the experiments. All the chlorides of these metals were insoluble in the reaction media used.

Acetyl Diethyl Phosphate (XVII). Sodium diethyl phosphate reacted smoothly with boiling acetyl chloride giving good yields of acetyl diethyl phosphate of high purity, excess acetyl chloride being used as solvent. The physical properties and infra-red spectrum were in complete accord with those published by Cramer and Gartner. When sodium acetate was allowed to react with excess ethyl phosphorochloridate no acyl phosphate could be isolated. A volatile liquid, identified as acetyl chloride, was first obtained on fractional distillation of the reaction mixture (cf. corresponding reactions using sodium benzoate, p. 76). After removal of the excess ethyl phosphorochloridate, a colourless liquid distilled over a wide temperature range. The latter was collected in two fractions. Continued heating caused the residue to decompose. The infra-red spectra of the two fractions were very similar and it was concluded from these that they were a mixture of triethyl phosphate and tetraethyl pyrophosphate. Triethyl phosphate was present in larger quantity in the first fraction. This conclusion is consistent with the boiling points of triethyl phosphate and tetraethyl pyrophosphate.
Acetyl diethyl phosphate is a mobile pungent colourless liquid, miscible with water and rapidly hydrolysed with the evolution of heat. On standing for several months at room temperature it undergoes considerable disproportionation to acetic anhydride and tetraethyl pyrophosphate.

**Benzoyl Diethyl Phosphate (XXI).** Sodium diethyl phosphate reacted smoothly with excess benzoyl chloride at 100°, the latter also serving as the solvent. It was difficult to obtain pure benzoyl diethyl phosphate although the boiling point, refractive index and infra-red spectrum were in very close agreement with those found by Cramer and Gartner. However, neither the analytical figures for this product nor of those of Cramer and Gartner were good. Further it was suspected that the weak band at 1795 cm⁻¹ in the carbonyl region occurring in Cramer and Gartner's spectrum and the one recorded in this work, might be due to an impurity. Careful fractionation of the product, which boiled over a 1° range, into three fractions confirmed this view. In the first fraction the band at 1795 cm⁻¹ was almost absent, becoming increasingly strong in the second and third fractions. Benzoic anhydride has a carbonyl doublet at 1795 and 1735 cm⁻¹. It was concluded that the band at 1795 cm⁻¹ was due to contamination by benzoic anhydride. The second band of the carbonyl doublet at 1735 cm⁻¹ was masked by the strong carbonyl absorption at 1755 cm⁻¹ of benzoyl diethyl phosphate. The analytical results support this conclusion. It was not found possible to free completely the product of benzoic anhydride.
by distillation, since it was probably formed by thermal dis-
proportionation of the unsymmetrical anhydride (equation 51).

\[ 2(\text{EtO})_2\text{P(0)OCOPh} \rightarrow (\text{EtO})_2\text{PO.0.PO(0Et)}_2 + \text{PhCO.0.COPh} \] (51)

When the acid chloride of diethyl phosphoric acid was allowed
to react with sodium benzoate, no benzoyl phosphate could be iso-
lated. Moreover, the products of the reaction varied as the ratio
of acid chloride to salt was varied. When equimolecular amounts
of sodium benzoate and ethyl phosphorochloridate were allowed to
react spontaneously and the infra-red spectrum of the product
examined, it was evident that benzoic anhydride, tetraethyl pyro-
phosphate and benzoyl diethyl phosphate were present. It was not
possible to achieve any appreciable separation of these products
by distillation. The following sequence of reactions is advanced
to explain the presence of the above products. Benzoyl diethyl
phosphate initially formed (equation 52) undergoes an exchange
reaction with benzoate ions (equation 53). Todd and collaborators
\[ (\text{EtO})_2\text{P(O)Cl} + \text{PhCO}^- \rightarrow (\text{EtO})_2\text{P(O).OCOPh} + \text{Cl}^- \] (52)

\[ (\text{EtO})_2\text{P(O).0.COPh} + \text{PhCOO}^- \rightarrow (\text{PhCO})_2\text{O} + (\text{EtO})_2\text{P(O)O}^- \] (53)

have shown that mixed phosphoric anhydrides undergo exchange re-
actions with anions such that the ion of the stronger acid of the
system is in solution (p. 26). Indeed this is also consistent with
the behaviour of unsymmetrical carboxylic anhydrides (p. 19). Di-
ethyl phosphoric acid (pK 1.39) is stronger than benzoic acid
therefore the benzoate ion displaces the diethyl phosphate ion thereby forming benzoic anhydride. Finally, the diethyl phosphate ion interacts with ethyl phosphorochloridate (equation 54) yielding tetraethyl pyrophosphate.

\[(\text{Et}_0)_2\text{P(O)}\text{O}^- + (\text{Et}_0)_2\text{P(O)}\text{Cl} \rightarrow (\text{Et}_0)_2\text{P(O).O.P(O)(OEt)}_2 \quad \ldots \ldots (54)\]

When ethyl phosphorochloridate was present in excess and the reaction conducted at 100°, the products of the reaction were different. The infra-red and ultra-violet spectra of the products revealed the presence of benzoyl chloride which could be co-distilled with the excess ethyl phosphorochloridate. The two compounds could not be separated effectively because of the closeness of their boiling points. It was thought that benzoyl chloride was produced by the action of ethyl phosphorochloridate on the benzoic anhydride formed initially (equation 55), (cf. corresponding reaction using sodium acetate, p. 74).

\[2(\text{Et}_0)_2\text{P(O)}\text{Cl} + (\text{PhCO})_2\text{O} \rightarrow (\text{Et}_0)_2\text{P(O).O.P(O)(OEt)}_2 + 2\text{PhCOCl} \quad \ldots \ldots (55)\]

The latter reaction is comparable with that between benzoyl chloride and acetic anhydride, where Zetzsche and collaborators have shown that acetyl chloride and benzoic anhydride are formed (equation 56).

\[2\text{PhCO.Cl} + (\text{MeCO})_2\text{O} \rightarrow (\text{PhCO})_2\text{O} + 2\text{MeCOCl} \quad \ldots \ldots \ldots (56)\]

However after removal of the excess ethyl phosphorochloridate and benzoyl chloride, the infra-red spectrum of the residue did not indicate the presence of tetraethyl pyrophosphate. Notably the
bands at 1290 and 940 cm\(^{-1}\) were absent. On attempting to distil
this residue it decomposed yielding triethyl phosphate; therefore
equation 55 is inadequate. However the presence of tetraethyl
pyrophosphate has been shown in products from the comparable re-
action with sodium acetate and ethyl phosphorochloridate above (p.74).

These experiments are in agreement with all the results reported
by other workers. Acyl phosphates are formed when either the salt
of the phosphoric acid and the carboxylic acid chloride or the salt
of the carboxylic acid and the alkyl phosphorochloride interact.
However, in the examples reported so far the acyl phosphates can be
isolated by distillation only when salt of the phosphoric acid is used.
In these cases this is the salt of the stronger acid component. Under
the alternative conditions an exchange reaction occurs between the
acyl phosphate already formed and the unreacted salt (equation 53)
concurrently with the continued formation of the acyl phosphate
(equation 52). The increased temperature required for distillation
of the products apparently effects the completion of the exchange
reaction or the disproportionation of the remaining acyl phosphate.

Benzoyl diethyl phosphate is a colourless, mobile, almost
odourless liquid, soluble in most organic solvents, insoluble in
water, and only slowly hydrolysed when allowed to stand with water.

From the argument presented here the following generalisation
is made and tested in subsequent preparations. In the preparation
of phosphoric–carboxylic anhydrides from a salt and acid chloride,
the stronger acid moiety must be present in the salt or ionized
form, while the weaker must be present as the acid chloride.
Ethoxycarbonyl Diethyl Phosphate (XXV). This compound was found to be stable up to 150° therefore it proved to be a very suitable compound for investigating the reaction conditions required for the three diethyl phosphoric acid salts described earlier (p. 65).

Equimolar quantities of ethyl chloroformate and silver diethyl phosphate in acetone gave a 40% yield after heating for 16 hours under reflux. The use of methyl ethyl ketone in place of acetone gave a 38% yield after 4 hours. A yield of 48% was obtained when excess ethyl chloroformate was used as solvent and the reaction conducted for 1/2 hour under reflux. When sodium diethyl phosphate replaced the silver salt in this last mentioned experiment, the yield was increased to 71%. The same percentage yield was obtained from lead diethyl phosphate and excess refluxing ethyl chloroformate after heating for 10 hours. Under similar conditions the basic lead salt gave a 63% yield of ethoxycarbonyl diethyl phosphate and an appreciable amount of tetraethyl pyrophosphate. Although it is probable that improved yields could be obtained with the silver salt, it is evident that the sodium salt is by far the most reactive and was therefore used for all subsequent preparations involving salts of diethyl phosphoric acid. Provided the acid chloride is a liquid at a temperature above 90° there appears to be no advantage in using acetone or methyl ethyl ketone as solvents. Indeed the reaction proceeds more slowly under these conditions.

Recent work on carboxylic-carbonic anhydrides has shown that contrary to earlier statements these compounds are stable\textsuperscript{95,96}, and
do not disproportionate unless heated to about 150°. The thermal stability of these anhydrides was investigated by Windholtz who found it to be markedly influenced by the strength of the carboxylic acid. The stability decreased with increase in acid strength. The following paths of decomposition were demonstrated (equations 57, 58).

\[
R'\text{CO}\cdot\text{O}\cdot\text{CO}\cdot\text{OR} \rightarrow R'\text{CO}\cdot\text{OR} + \text{CO}_2 \quad \text{.................}(57)
\]

\[
2R'\text{CO}\cdot\text{O}\cdot\text{CO}\cdot\text{OR} \rightarrow (R'\text{CO})_2\text{O} + (\text{RO})_2\text{CO} + \text{CO}_2 \quad \text{.................}(58)
\]

Ethoxycarbonyl diethyl phosphate was found to be stable up to 150° when decomposition began, carbon dioxide being evolved. Triethyl phosphate was isolated from the residue (equation 59).

\[
(\text{EtO})_2\text{P(O)}\cdot\text{CO}\cdot\text{OEt} \rightarrow (\text{EtO})_3\text{PO} + \text{CO}_2 \quad \text{.................}(59)
\]

This reaction compares with the decomposition of carboxylic-carbonic anhydrides to the carboxylic ester and carbon dioxide (equation 57). However the decomposition of ethoxycarbonyl diethyl phosphate must be more complicated than shown here (equation 59) as some undistillable residue remained. No evidence was found for a reaction (equation 60)

\[
2(\text{EtO})_2\text{P(O)}\cdot\text{CO}\cdot\text{OEt} \rightarrow (\text{EtO})_2\text{P(O)}\cdot\text{O}\cdot\text{P(O)}(\text{OEt})_2 + (\text{EtO})_2\text{CO} + \text{CO}_2 \quad \text{......}(60)
\]

analogous to the decomposition of carboxylic-carbonic anhydride to dialkyl carbonates, carboxylic-carboxylic anhydrides and carbon dioxide (equation 58).

The possibility that ethoxycarbonyl diethyl phosphate may phosphorylate carboxylic acids in a similar way to tetraethyl phosphoric phosphorus anhydride (IX, p. 39) was investigated. With benzoic acid a quantitative yield of ethyl benzoate was produced.
Ethoxycarbonyl diethyl phosphate is a mobile, colourless, odourless liquid, soluble in organic solvents, insoluble in water. It is very slowly hydrolysed on standing with water, and is the most stable anhydride of the series reported in this thesis.

Trifluoracetyl Diethyl Phosphate (XVIII). This anhydride was the most difficult to prepare and the least stable of the series. It was prepared by interacting sodium trifluoracetate with ethyl phosphorochloridate. Care had to be taken to ensure that at no stage in the preparation and isolation the temperature exceeded 30°, otherwise disproportionation to tetraethyl pyrophosphate and trifluoroacetic anhydride occurred. The yield was poor and a considerable amount of tetraethyl pyrophosphate remained after distillation.

Trifluoracetyl diethyl phosphate was isolated from the reaction mixture by distillation at 30°/0.01 mm. in a specially designed short-path still. The condensing surface was a cold finger at -70°. The product collected as a crystalline solid on the latter. On warming, it melted at -10° to a colourless pungent liquid, soluble in all organic solvents and immediately hydrolysed by water with the evolution of considerable heat. After standing for 24 hours at 15° it had largely disproportionated.

Petrov and Neimysheva\(^1\) (p. 36) claimed to have obtained trifluoracetyl diethyl phosphate by the interaction of silver trifluoracetate with ethyl phosphorochloridate for 6 hours in refluxing ether, but there was no evidence to support their claim. In view of the obvious thermal instability of this compound, Petrov and Neimysheva's work should be disregarded.
As was to be expected sodium trifluoracetate and ethyl phosphorochloridate when allowed to react at 100° gave only trifluoracetic anhydride and tetraethyl pyrophosphate.

Trimethylacetyl Diethyl Phosphate (XIX). Sodium diethyl phosphate and boiling trimethylacetyl chloride afforded pure trimethylacetyl diethyl phosphate. This is the first example of the series where the carbonyl group is subject to steric hindrance. It did not show any sign of disproportionation after standing for two months in the laboratory. However its behaviour resembles acetyl diethyl phosphate very closely. This is perhaps not surprising in view of the recent work by Butler and Gold on trimethylacetic anhydride (p. 54). They showed that the tertiary butyl group had a very small retarding effect on the rate of spontaneous hydrolysis as compared with acetic anhydride.

Trimethylacetyl diethyl phosphate is a colourless, pungent, mobile liquid, soluble in most organic solvents, miscible with water. It is hydrolysed by water but the reaction is less obviously exothermic than in the case of acetyl diethyl phosphate.

Triphenylacetyl Diethyl Phosphate (XX). The steric hindrance due to the triphenylmethyl group in triphenylacetic acid is known to be far greater than that of the tertiary butyl group in trimethylacetic acid. Triphenylacetyl chloride is so unreactive that only 60% is hydrolysed after boiling for 2 hours with 10% aqueous alkali. This is a consequence of the severe steric hindrance at
the carbonyl group. No reaction was observed between triphenyl-
acetyl chloride and sodium diethyl phosphate in solvents at 100°.
The mildest conditions under which reaction would take place were
when the mixture of acid chloride and sodium salt was heated to the
point of fusion (135–140°). The melt was then allowed to stand on
a steam bath for a prolonged period. Under these conditions tri-
phenylacetyl diethyl phosphate was formed slowly, but the rate of
thermal disproportionation was evidently greater than that of the
initial rate of formation. The infra-red spectrum of the product
showed the presence of a small amount of the triphenylacetyl diethyl
phosphate but only triphenylacetic anhydride and tetraethyl pyro-
phosphate were actually isolated.

Good yields of triphenylacetyl diethyl phosphate were obtained
by allowing ethyl phosphorochloridate to react with sodium triphenyl-
acetate for 3 hours. However if the reaction time was increased to
8 hours triphenylacetic anhydride was formed in 95% yield. This
divergence from the generalisation (p. 78) can be interpreted in
terms of steric hindrance. As triphenylacetic acid is a weaker acid
then diethyl phosphoric acid, it would be expected that after the
initial formation of triphenylacetyl diethyl phosphate (equation 61)
and exchange reaction (equation 62) would occur. However, the

\[
\text{Ph}_3\text{C.COONa} + (\text{EtO})_2\text{P(0)Cl} \rightarrow \text{Ph}_3\text{C.CO.O(0Et)_2} + \text{NaCl} \quad \ldots \ldots \ldots \ldots \ldots \ldots (61)
\]

\[
\text{Ph}_3\text{C.CO.O(0Et)_2} + \text{Ph}_3\text{C.CO}^- \rightarrow (\text{Ph}_3\text{CO})_2\text{O} + (\text{EtO}_2\text{POO}^-) \quad \ldots \ldots \ldots \ldots \ldots \ldots (62)
\]

exchange reaction involves a nucleophilic attack of the triphenyl
acetyl anion on the carbonyl group of the triphenylacetyl diethyl
phosphate molecule. As already mentioned, this carbonyl group is subject to considerable steric hindrance. Thus the formation of the acyl phosphate (equation 61), which does not involve a reaction at the hindered carbonyl group, proceeds faster than its destruction (equation 62). When the reaction time was prolonged, this exchange reaction took place to completion.

The reaction conditions examined for the preparation of triphenylacetyl diethyl phosphate from sodium triphenylacetate and ethyl phosphorochloridate included the use of excess ethyl phosphorochloridate, and of acetone as solvent. The best results were achieved with acetone. If appreciable amounts of triphenylacetic anhydride were formed through prolonged reaction time (i.e. greater than 3 hours), considerable losses were incurred during crystallisation to obtain a pure sample.

Triphenylacetyl diethyl phosphate is a solid, readily soluble in organic solvents, insoluble in water which is apparently without effect on it in the cold. It is stable at room temperature.

2,3,6-Trichlorobenzoyl Diethyl Phosphate (XXII). Sodium 2,3,6-trichlorobenzoate and ethyl phosphorochloridate reacted together in boiling acetone to form the mixed anhydride. The isolation of the latter proved difficult because it is a high boiling liquid. Ordinary vacuum distillation techniques proved useless. The boiling point of 2,3,6-trichlorobenzoyl diethyl phosphate was greater than 140°/0.05 mm. at which temperature extensive disproportionation took place. The anhydride was obtained pure and in moderate yield by subjecting the
crude product to molecular distillation at 80°. The fore-runnings which distilled over at a pressure range of 0.01 to 0.003 mm. contained an appreciable amount of tetraethyl pyrophosphate. 2,3,6-Trichlorobenzoyl diethyl phosphate distilled at 81°/0.004 mm. After distilling all the liquid products, a crystalline solid remained in the still-pot. This was shown to be 2,3,6-trichlorobenzoic anhydride. The considerable difference in molecular weights of tetraethyl pyrophosphate, 2,3,6-trichlorobenzoyl diethyl phosphate and 2,3,6-trichlorobenzoic anhydride, allowed good separation under the conditions of molecular distillation.

2,3,6-Trichlorobenzoyl diethyl phosphate is a colourless viscous liquid, miscible with most organic solvents and insoluble in water. When allowed to stand under water for a number of days it is slowly hydrolysed. On standing at room temperature for several months some disproportionation may be detected.

2,3,5,6-Tetrachlorobenzoyl Diethyl Phosphate (XXIII). This anhydride was obtained in good yield from sodium 2,3,5,6-tetrachlorobenzoate and excess ethyl phosphorochloridate in refluxing acetone. It is a solid difficult to crystallise without seed crystals, readily soluble in most organic solvents and insoluble in water. It is slowly hydrolysed by prolonged contact with the latter. 2,3,5,6-Tetrachlorobenzoyl diethyl phosphate is stable at room temperature.

2,3,4,5,6-Pentachlorobenzoyl Diethyl Phosphate (XXIV). Unlike 2,3,5,6-tetrachlorobenzoyl diethyl phosphate the preparation of this anhydride required stoichiometric quantities of sodium pentachloro-
benzoate and ethyl phosphorochloridate. Excess of the latter resulted in poor yields. 2,3,4,5,6-Pentachlorobenzoyl diethyl phosphate is a solid with very similar properties to the tetrachloro analogue above.

It is now desirable to review the generalisation made earlier (p. 78). Namely that when a salt and an acid chloride are used to prepare these phosphoric-carboxylic anhydrides the stronger acid moiety must be present in the salt or ionized form, while the weaker must be present as the acid chloride.

It is germane at this point to consider the strengths of the acids from which the mixed anhydrides (XVII to XXV) are derived. The relevant data is summarised in Table V. The value of \( \alpha \) for the hypothetical ethyl carbonic acid EtO\( \cdot \)COOH has been extrapolated from the plot of the ionization constants of carboxylic acids R\( \cdot \)COOH against Taft's polar substituent constant \( \sigma^+ \). The value of \(-0.18\) has been used for \( \sigma^+ \) for the EtO group.\(^{98}\)

<table>
<thead>
<tr>
<th>Acid</th>
<th>( \alpha )</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethylacetic</td>
<td>5.05</td>
<td>93</td>
</tr>
<tr>
<td>Ethylcarboxylic</td>
<td>4.92</td>
<td>93</td>
</tr>
<tr>
<td>Acetic</td>
<td>4.76</td>
<td>93</td>
</tr>
<tr>
<td>Benzoic</td>
<td>4.20</td>
<td>93</td>
</tr>
<tr>
<td>Triphenylacetic</td>
<td>3.96</td>
<td>93</td>
</tr>
<tr>
<td>Diethylphosphoric</td>
<td>1.39</td>
<td>53</td>
</tr>
<tr>
<td>2,3,6-Trichlorobenzoic</td>
<td>1.28</td>
<td>100</td>
</tr>
<tr>
<td>2,3,5,6-Tetrachlorobenzoic</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2,3,4,5,6-Pentachlorobenzoic</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Trifluoracetic</td>
<td>0.23</td>
<td>101</td>
</tr>
</tbody>
</table>

- 86 -
By applying the above generalisation to the data in Table V, it may be predicted that sodium diethyl phosphate should react with the acid chlorides of the first five carboxylic acids to yield the corresponding phosphoric-carboxylic anhydrides. The analogous acyl phosphates from the polychlorobenzoic and trifluoracetic acids should be formed by the interaction of the salts of these acids with ethyl phosphorochloridate. In the event, this prediction proved to be correct, except in the case of the reaction between triphenylacetyl chloride and sodium diethyl phosphate.

This exception does not invalidate the generalisation of the reaction of acid chlorides and salts, for it can be clearly attributed to steric hindrance as explained earlier (p. 84).

7) Acylating and Phosphorylating Reactions of Phosphoric-Carboxylic Anhydrides

The anomalous and inadequately authenticated reactions of phosphoric-carboxylic anhydrides have been discussed earlier (p. 57 et seq.). The anhydrides (XVII to XXV) were allowed to react with two moles of aniline in ether and the products examined. In cases where the reactions were very rapid and highly exothermic, they were conducted at 0°. At the other extreme the reaction mixture was heated for 50 hours under reflux. In the reactions where the anilinium salt was water soluble it could be removed by extracting the solid with water after evaporating the ether. All the anilides and N-phenyl diethyl phosphoramidate are insoluble in water, while anilinium diethyl phosphate is very soluble. Therefore quantitative analysis of the crude water insoluble products from the reactions
gave a figure from which the amount of N-phenyl diethyl phosphoramidate present could be calculated. This in turn could be used to derive the amount of phosphorylation that had taken place. A value of less than 0.1% for phosphorus was ignored.

Acetyl diethyl phosphate (XVII) reacted with aniline in ether at 0° to give a 92% yield of pure acetanilide. There was no evidence of any phosphorylation having taken place.

Trimethylacetyl diethyl phosphate (XIX) behaved in a very similar fashion to the acetyl compound above, with the exception that it required heating under reflux to complete the reaction with aniline, when a 95% yield of trimethylacetanilide was produced.

Trifluoracetyl diethyl phosphate (XVIII) was the most reactive mixed anhydride of the series. It reacted vigourously with aniline in ether at 0°. Although the crude trifluoracetanilide contained a significant amount of phosphorus, indicating that perhaps as much as 2% of the aniline had been phosphorylated, trifluoracetyl diethyl phosphate is clearly an acylating, rather than a phosphorylating agent. The phosphorylation that had occurred could be due to either the presence of tetraethyl pyrophosphate, formed by disproportionation of the mixed anhydride, or alternatively, the anhydride reacting to a small extent as predicted by Todd.

Triphenylacetyl diethyl phosphate (XX) and aniline reacted very slowly. After heating for 48 hours under reflux a mixture of triphenylacetanilide and N-phenyl diethyl phosphoramidate was produced.
Calculation from the phosphorus content of the crude anilide and phosphoramidate mixture, revealed that it has phosphorylated 29% of the aniline, but the amount of phosphoramidate actually isolated corresponded to only 14.7% phosphorylation having taken place. This discrepancy is accounted for by the considerable losses incurred in the separation of the anilide and phosphoramidate.

Ethoxycarbonyl diethyl phosphate (XXV) and aniline reacted to form primarily N-phenylurethane. The yield of the latter was greater when the reaction was conducted in boiling dioxan rather than in ether at room temperature. In the former case the fate of the diethyl phosphoryl moiety was investigated and, as expected, it was present in the reaction products as the diethyl phosphate ion (equation 63). Calculations from the quantity of phosphorus present

\[
(EtO)_2PO.OCOEt + 2PhNH_2 \rightarrow PhNHCO_2Et + \left[\left(EtO\right)_2PO\right]^\cdot \quad PhNH_3^+ \]...

in the crude N-phenylurethane showed that approximately 5% of the aniline was phosphorylated.

The use of the cyclohexylammonium salt for the characterisation of the diethyl phosphoric acid fragment was demonstrated in this experiment. Cyclohexylammonium diethyl phosphate proved to be an unsatisfactory compound for the purpose, because although it separated readily from benzene in easily filterable crystals, its extremely deliquescent nature vitiated its use.
Benzoyl diethyl phosphate (XXI) was clearly shown to be a benzoylating agent, there being no evidence of any phosphorylation having taken place. Pure benzanilide was isolated in 91% yield. The reaction conditions were identical to those for acetyl diethyl phosphate and aniline.

2,3,6-Trichlorobenzoyl diethyl phosphate (XXII) was shown to be a moderately effective phosphorylating agent. The only products isolated from its reaction with aniline were N-phenyl diethyl phosphoramidate in 83% yield and the anilinium 2,3,6-trichlorobenzoate complex. The reaction was complete after 18 hours heating under reflux. The amount of phosphorus present in the crude reaction product indicated 84% phosphorylated aniline in close agreement with the amount of crude phosphoramidate isolated.

2,3,5,6-Tetrachlorobenzoyl diethyl phosphate (XXIII) and aniline interacted very slowly in boiling ether. Only one half of the theoretical amount of anilinium 2,3,5,6-tetrachlorobenzoate had separated after 6 hours heating. After 28 hours the reaction was complete. Anilinium 2,3,5,6-tetrachlorobenzoate was found to be less soluble in water than in ether, and difficulty was experienced in the quantitative separation of it from the N-phenyl diethyl phosphoramidate. There was no evidence that any 2,3,5,6-tetrachlorobenanilide was formed in the reaction. The crude phosphoramidate contained about 10% of the anilinium tetrachlorobenzoate. 2,3,5,6-Tetrachlorobenzoyl diethyl phosphate was shown to phosphorylate aniline quantitatively.
2,3,4,5,6-Pentachlorobenzoyl diethyl phosphate (XXIV) reacted even more slowly with aniline in boiling ether than the tetrachlorobenzoyl analogue above. The half life for the reactions (assessed from the amount of anilinium pentachlorobenzoate formed) was about 12 hours. After 50 hours the reaction was substantially complete. As in the case of 2,3,5,6-tetrachlorobenzoyl diethyl phosphate, it was difficult to separate the anilinium 2,3,4,5,6-pentachlorobenzoate from the N-phenyl diethyl phosphate, due to the insolubility of the former in water and its appreciable solubility in ether. The amount of the impure N-phenyl diethyl phosphoramidate isolated was greater than the theoretical quantity as a consequence. In this example, and the example with the corresponding tetrachlorobenzoyl compound, the infra-red spectrum of the phosphoramidate showed the presence of the anilinium salt as an impurity. 2,3,4,5,6-Pentachlorobenzoyl diethyl phosphate effected quantitative phosphorylation of the aniline.

The results of the reactions between these mixed anhydrides and aniline are tabulated below (Table VI). An explanation of them undoubtedly rests with the steric properties of the carboxylic acid moiety.

It is perhaps cogent to refer to the projected lines of investigation discussed earlier (pps. 57 and 58) and the existing anomalies at the time this work was commenced. As expected the acylating properties of acetyl diethyl phosphate have been confirmed. It has been established by this work that benzoyl diethyl phosphate
### Table VI

Summary of Results of Reactions Between Carboxylic-Phosphoric Anhydrides and Aniline

<table>
<thead>
<tr>
<th>Anhydride R = (EtO)₂P(0)-</th>
<th>Principal product</th>
<th>Yield of crude anilide</th>
<th>M.p.</th>
<th>Authentic anilide m.p.</th>
<th>Mixed m.p.</th>
<th>F content of crude product %</th>
<th>% Phosphorylation</th>
</tr>
</thead>
<tbody>
<tr>
<td>R.O.COCl₂</td>
<td>Acetanilide</td>
<td>92%</td>
<td>111-5°</td>
<td>114-5°</td>
<td>112-5°</td>
<td>0.09</td>
<td>-</td>
</tr>
<tr>
<td>R.O.COC(CH₃)₃</td>
<td>Trimethyl acetonilide</td>
<td>95%</td>
<td>132-5°</td>
<td>136-7°</td>
<td>133-6°</td>
<td>0.06</td>
<td>-</td>
</tr>
<tr>
<td>R.O.COClF</td>
<td>Trifluoroacetonilide</td>
<td>91%</td>
<td>85-9°</td>
<td>90-1°</td>
<td>89-91°</td>
<td>0.28</td>
<td>2</td>
</tr>
<tr>
<td>R.O.CO.OEt</td>
<td>N-phenyl-anilide</td>
<td>78%</td>
<td>45-9°</td>
<td>50-1°</td>
<td>46-50°</td>
<td>1.05</td>
<td>4.7</td>
</tr>
<tr>
<td>R.O.COMe</td>
<td>Benzilidene</td>
<td>93%</td>
<td>163-4°</td>
<td>163-4°</td>
<td>163-4°</td>
<td>0.05</td>
<td>-</td>
</tr>
<tr>
<td>R.O.COCl₂</td>
<td>Triphenyl acetonilide</td>
<td>57%</td>
<td>110-4°</td>
<td>171-2°</td>
<td>-</td>
<td>1.80</td>
<td>29</td>
</tr>
<tr>
<td>R.O.COCl₂</td>
<td>N-phenyl dibutyl phosphorimidate</td>
<td>84%</td>
<td>50.5°</td>
<td>95°</td>
<td>70-85°</td>
<td>5.76</td>
<td>63</td>
</tr>
<tr>
<td>R.O.COCl₂</td>
<td>N-phenyl dibutyl phosphorimidate</td>
<td>100%</td>
<td>78-85°</td>
<td>95°</td>
<td>86-90°</td>
<td>11.2</td>
<td>36</td>
</tr>
<tr>
<td>R.O.COCl₂</td>
<td>N-phenyl dibutyl phosphorimidate</td>
<td>94%</td>
<td>92-96°</td>
<td>95°</td>
<td>94-95°</td>
<td>9.02</td>
<td>94</td>
</tr>
</tbody>
</table>

* Corrected for phosphorimidate present.

* Calculated from phosphorus content.
has no phosphorylating power. The benzoic acid isolated by Cramer and Gartner (p. 38) cannot have arisen from a phosphorylation reaction in which benzoyl diethyl phosphate had taken part (equation 38). It was either present as benzoic acid in the crude anhydride or alternatively, and more probably, it arose from a reaction involving benzoic anhydride that had been formed by disproportionation of the mixed anhydride. Trifluoracetyl diethyl phosphate has now been shown to be an acylating agent.

Clearly, for an acyl phosphate to possess phosphorylating properties some characteristic in its structure is required, other than that the carboxylic acid should be stronger than the phosphoric acid. The writer's prediction of the behaviour of trifluoracetyl diethyl phosphate (p. 58) and the ideas advanced to explain the behaviour of trifluoracetyl dibenzyl phosphate (p. 35), are supported by this work. Although trifluoracetic acid is a stronger acid than diethyl phosphoric acid, and therefore its ion is a better leaving group, this property is paralleled by another and apparently more important one. Namely the increased facility with which strong carboxylic acids form the tetrahedral addition complex (p. 51) which has been established as the rate limiting step for reactions with carboxylic derivatives (p. 8).

Continuing this line of reasoning further, it follows that the factor which decides whether an acyl phosphate will acylate or phosphorylate, will be the relative rates of bond formation at the carboxyl groups (XXVI) to the breaking of the P-O bond (a) of the
anhydride bridge (XXVII). It is known that sterically hindered

\[
\begin{align*}
\text{XXVI} & \quad \text{XXVII} \\
\begin{align*}
\text{RO} & \quad \text{P} \quad \text{O} \quad \text{C} \quad \text{R} \\
\text{X} & \quad \text{X} \\
\end{align*}
\end{align*}
\]

carboxylic acids undergo the normal carbonyl reactions more slowly\(^{45}\), presumably through the hindrance to the formation of the addition complex. The degree of hindrance can be assessed from comparative rates of esterification or of reactions of acid chlorides and other typical reactions of carbonyl functions.

The choice of trimethylacetyl, triphenylacetyl and 2,3,6-trichlorobenzoyl residues for the acyl group of the phosphoric-carboxylic anhydrides used to demonstrate the effect of steric hindrance on reactivity, rests upon esterification and hydrolysis data. Smith and Burn\(^{102}\) found the rates of esterification of trimethylacetic acid and acetic acid by methanolic hydrochloric acid at 25° to be \(1.94 \times 10^{-3}\) and \(5.93 \times 10^{-2} \text{min}^{-1}\) respectively, while the rate for triphenylacetic acid was too slow for measurement. It may be concluded that trimethylacetyl derivatives are hindered to a moderate degree and that triphenylacetyl derivatives are very considerably hindered. Finally, Hughes\(^{100}\) found that the alkaline hydrolysis rates of the methyl esters of benzoic and 2,3,6-trichlorobenzoic acids in 50% aqueous acetone at 50° were \(6.3 \times 10^{-1}\) and \(5.3 \times 10^{-3}\) \(\text{l} \cdot \text{mol}^{-1} \cdot \text{min}^{-1}\) respectively. As 2,3,6-trichlorobenzoic acid is a stronger acid than benzoic acid, this indicates that there must be considerable steric
hindrance of the carbonyl group of 2,3,6-trichlorobenzoic acid since the hydrolysis rate normally increases with increasing acid strength. There is no kinetic data available for any derivative of 2,3,5,6-tetrachlorobenzoic acid as it has not been reported before. However, its carbonyl group would be expected to be subjected to greater steric hindrance than that of 2,3,6-trichlorobenzoic acid, because the 5 chloro group would buttress the 6 chloro group. There is no quantitative data on any 2,3,4,5,6-pentachlorobenzoyl compound, but an indication of the extreme nature of the hindrance is given by the following facts. Pentachlorobenzoyl chloride may be crystallised from boiling alcohol, while the methyl ester is formed by refluxing the acid chloride in methanol for 30 hours.

It is clear from the results described in this thesis that the ability of an acyl phosphate to phosphorylate aniline increases with the increase in steric hindrance at the carbonyl group. The most effective phosphorylating agents of this series, 2,3,5,6-tetrachlorobenzoyl and 2,3,4,5,6-pentachlorobenzoyl diethyl phosphate, embody carboxylic acid residues that in addition to being subject to very considerable steric hindrance, are also stronger acids than diethyl phosphoric acid.

Finally, the third point discussed in the projected lines of research (p. 58) , the use of carboxylic acids possessing carbonyl groups deactivated by conjugation, has shown very little promise. Benzoyl diethyl phosphate does not phosphorylate at all and ethoxy-carbonyl diethyl phosphate is a very weak phosphorylating agent.
The extent to which the carbonyl groups of the polychlorobenzoic acids are deactivated by conjugation is difficult to assess. The crowding effect of the chlorine atoms will force the carbonyl group out of the plane of the ring and thereby decrease or perhaps eliminate the conjugation.

8) Conclusions

(1) Acyl dialkyl phosphates may be prepared from carboxylic acid chlorides and dialkyl phosphate salts or from dialkyl phosphoro-chloridates and carboxylate salts. The choice of which moiety should be in the salt form is critical.

(2) This choice is dependent upon two factors, (a) the relative acid strength of the constituent acids and (b) the degree of steric hindrance existing at the carbonyl group of the carboxylic acid.

(3) In the absence of steric hindrance the salt should be derived from the stronger constituent acids.

(4) When the carbonyl group is seriously hindered the acid chloride is insufficiently reactive. Therefore the dialkyl phosphoric acid chloride must be used irrespective of acid strengths.

(5) In the absence of steric hindrance, the use of the salt of the weaker acid results in an exchange between the anion of the latter and the acyl phosphate. One of the products of this exchange reaction is the anion of the stronger acid, which may react further with the acid chloride present to form some symmetrical anhydride of the stronger acid. The other product of the exchange reaction
is the symmetrical anhydride of the weaker acid.

(6) The factors that decide the mode of action of acyl phosphates are the relative rates of bond formation at the carbonyl group to give the addition complex, and bond breaking of the phosphorus-oxygen bond with the expulsion of a carboxylate ion.

(7) By varying the degree of steric hindrance at the carbonyl group of these anhydrides it is possible to obtain compounds that at one extreme are exclusively acylating agents, progressing through compounds that react by a dual mechanism being both phosphorylating and acylating agents to those that are exclusively phosphorylating agents.
EXPERIMENTAL

Diethyl Phosphorochloridate (EtO)$_2$P(O)Cl

Ethanol (183 g., dried over metallic calcium) was added with mechanical stirring from a dropping funnel to a solution of phosphorus trichloride (174 g.) in carbon tetrachloride (900 ml.). The temperature was maintained between 25-35° by external cooling. When the addition of ethanol was complete the solution was allowed to stand for 1/3 hour then chlorine passed in, the temperature not being allowed to rise above 30°. The chlorination was continued until a pale yellow colour was produced which lasted 2 or 3 minutes. The hydrochloric acid gas and solvent were removed from the product by passing a stream of dry nitrogen through the solution while evacuating the flask on the water pump. No external heating was used. The residue was distilled, b.p. 62-3°/2 mm. (lit. 105 b.p. 61-3°/2.5 mm.). Yield 165 g. (70% theory).

Silver Diethyl Phosphate (EtO)$_2$P(O)OAg

(a) A stirred mixture of silver oxide (121.5 g.), water (125 ml.) and ethyl phosphorochloridate (86.5 g.) was heated on a steam bath for 1 hour. After filtration, the aqueous solution of silver diethyl phosphate was evaporated to dryness yielding a black crystalline mass. The latter was redissolved in methanol (250 ml.) at 60° and, after being treated with decolourising charcoal, precipitated with ether (500 ml.). The solid was recrystallised from the minimum amount of hot methanol to give straw coloured needles, yield 50 g. (45%).
(b) Hydrated silver oxide, produced by mixing aqueous solutions of silver nitrate (187 g.) and sodium hydroxide (46 g.) was digested for two hours on a steam bath. After collection and washing with water, the moist silver oxide was resuspended in water. Ethyl phosphorochloridate (86.5 g.) was added to the stirred solution and the product worked up as described in (a). Yield of colourless needles was 55 g. (43%).

Lead Diethyl Phosphate \([\text{(EtO)}_2\text{P(O)}\text{O}]_2\text{Pb}\) and Basic Salt

(a) Boiling solutions of lead nitrate (83 g.) in water (200 ml.) and sodium diethyl phosphate (90 g.) in water (100 ml.) were mixed with stirring. Crystallisation began immediately and after cooling the needles were collected. A second crop was obtained from the mother liquor after concentration to ca. 100 ml. Total yield 97.5 g. This product was extracted with boiling ethanol (750 ml.) and filtered. The residual microcrystalline powder was basic lead phosphate 63.0 g. (63%), m.p. 235-40° decomp. and remained unchanged after recrystallisation from water. Found P, 7.80%; \(\text{C}_4\text{H}_{13}\text{O}_6\text{Pb}\) requires P, 7.85%. The ethanolic filtrate on evaporation to dryness afforded lead diethyl phosphate m.p. 184-5°, yield 31.3 g. (24%). After recrystallisation from boiling methanol, fine needles were obtained m.p. 179-81° (lit. 180°). Found P, 11.6%; \(\text{C}_6\text{H}_{20}\text{O}_6\text{P}_2\text{Pb}\) requires P, 12.1%.

(b) Lead acetate trihydrate (96 g.) in boiling water (50 ml.) was added to solid sodium diethyl phosphate (95 g.). After standing at
0° for three days, the crystalline product was collected and re-
crystallised from boiling ethanol to give lead diethyl phosphate
needles, m.p. 179-81°, yield 19.5 g. (15%). Found P, 11.7%;
C₆H₂₀O₅P₂Pb requires P, 12.0%. The syrupy mother liquor gave no
further crystalline material.

(c) Lead hydroxide prepared from solution of lead nitrate (414 g.)
and sodium hydroxide (100 g.) in water (800 ml.) was digested on a
steam bath for 2 hours, filtered, washed with water and resuspended
in water. Diethyl phosphorochloridate (172.5 g.) was added, with
stirring, and the mixture boiled and filtered hot. Crystalline lead
chloride was filtered from the cold solution and the filtrate eva-
porated to 200-250 ml. After cooling, the solution deposited lead
diethyl phosphate, m.p. 167-70°. Yield 200 g. (78%), which after
recrystallisation from methanol formed needles, m.p. 174-7°. Found
P, 11.6%; C₆H₂₀O₅P₂Pb requires P, 12.0%. (A solution of the product
gave a slight turbidity of silver chloride when treated with silver
nitrate.)

Sodium Diethyl Phosphate (EtO)₂P(O)ONa

(a) A stirred mixture of triethyl phosphate (320 g.), sodium
hydroxide (64 g.) and water was heated under reflux and the liberated
ethanol continuously removed via a McIntyre reflux ratio head until
the still head temperature was 100°, and the pot temperature 108°.
The reaction mixture was concentrated to minimum volume on a steam
bath at reduced pressure. The semi-crystalline residue was dissolved
in ethanol (500 ml.) and again evaporated to dryness. The crystalline
solid was redissolved in boiling ethanol, filtered and the filtrate diluted with acetone (1500 ml.). When cold, the crystalline mass of sodium diethyl phosphate was collected. Yield of very deliquescent needles 264 g. (85%). Found P, 17.3% ; C₄H₁₀NaP₂O₄ requires P, 17.6%.

(b) Sodium iodide (82.5 g.) and triethyl phosphate (91 g.) were heated together in refluxing acetone (400 ml.) for 5 hours. The solution was concentrated to a gum at reduced pressure and set aside to crystallise. The solid collected was washed with acetone, yield of prisms 30.5 g. (When this product was treated with concentrated sulphuric acid much iodine was liberated.)

**Triphenylacetic Acid Ph₃C·COOH**

Triphenylacetic acid was prepared in 93% yield by the action of carbon dioxide on triphenylmethylmagnesium chloride¹⁰⁶,¹⁰⁷ and was recrystallised from glacial acetic acid, m.p. 271-3° (lit.¹⁰⁸ m.p. 271°).

**2,3,6-Trichlorobenzyl Bromide C₆H₃Cl₃·CH₂Br**

Bromine (168 g.) was added dropwise to a stirred melt of 2,3,6-trichlorotoluene (210 g.) at 170°. The reaction mixture was irradiated with ultra-violet light during the bromination. Distillation of the crude product gave a liquid, b.p. 152° at 12 mm. (lit.¹⁰⁹ b.p. 140-3° at 10 mm.). Yield 247 g. (87%).

**2,3,6-Trichlorobenzyl Alcohol C₆H₃Cl₃·CH₂OH**

2,3,6-Trichlorobenzyl bromide (151 g.) and potassium acetate
(132 g.) in ethanol (950 ml.) were stirred together under reflux for 2 hours. After removal of the precipitated potassium bromide, and evaporation of the ethanol at diminished pressure, the residue was washed with water. The oil — crude 2,3,6-trichlorobenzyl acetate — was separated, and hydrolysed by boiling for 4½ hours with a solution of ethanol (600 ml.), water (100 ml.) and sodium hydroxide (35 g.). The reaction mixture was concentrated to about 300 ml. and poured into water (3 l.), when the separated yellow oil slowly crystallised; it was dried and distilled and the fraction boiling 96-100°/0.1 mm. collected. The distillate crystallised, and separated, from light petroleum (400 ml., boiling range 60-80°) in small prisms, m.p. 67-70° (lit. 78 m.p. 73°). Yield 98 g. (84%).

2,3,6-Trichlorobenzoic Acid C₆H₄Cl₃·COOH

Potassium permanganate (150 g.) was added in portions of 2-3 g. to a stirred suspension of 2,3,6-trichlorobenzyl alcohol (106 g.) in a solution of sodium hydroxide (40 g.) in water (400 ml.) maintained at 40-45°. After 24 hours the precipitated manganese dioxide was removed, washed with water and the combined filtrate and washing decolourised with sulphur dioxide. Addition of concentrated hydrochloric acid (100 ml.) precipitated 2,3,6-trichlorobenzoic acid as an oil that slowly solidified. Yield 109 g. (98%), m.p. 110-15°. Recrystallisation from carbon tetrachloride (220 ml.) gave irregular prisms, m.p. 124-6° (lit. 78 m.p. 124-6°). Yield 88 g.
2,3,6-Trichlorobenzoic Acid \( \text{C}_6\text{H}_2\text{Cl}_3\text{COOH} \) (Pyridine potassium permanganate method)

Trichlorobenzyl alcohol (31.8 g.) was dissolved in pyridine (170 ml.) and water (30 ml.) by heating it on a steam bath. Finely ground potassium permanganate (48 g.) was added to the hot stirred solution over a period of 3-4 hours. After heating on the steam bath for a further 2 hours the mixture was filtered, washed with water. Sodium hydroxide solution (50 ml., 10%) was added to the filtrate and the mixture evaporated to dryness. The crude sodium trichlorobenzoate was extracted with benzene (50 ml.) and filtered to remove unreacted trichlorobenzyl alcohol. The sodium salt was dissolved in the minimum of boiling water, and acidified with hydrochloric acid (50 ml. S.G. 1.16). The crude 2,3,6-trichlorobenzoic acid separated as an oil that crystallised slowly. After drying in vacuo over phosphorus pentoxide the yield was 23.6 g. (70%), m.p. 124-6°. Recrystallisation from carbon tetrachloride (1 g. in 2 ml.) yielded needles, m.p. 126-7°. Found C, 37.2; H, 1.37; Cl, 46.6%; \( \text{C}_7\text{H}_3\text{Cl}_3\text{O}_2 \) requires C, 37.2; H, 1.37; Cl, 47.2%.

2,3,5,6-Tetrachlorobenzyl Bromide \( \text{C}_6\text{HCl}_4\text{CH}_2\text{Br} \)

2,3,5,6-Tetrachlorotoluene (23 g.) was heated to 185° and the stirred melt irradiated with an ultra-violet lamp while bromine (16 g.) was added dropwise. The rate of addition was adjusted so that there was no appreciable amount of bromine vapour in the reaction flask above the melt and so that the temperature did not exceed 190°. When all the bromine had been added, the temperature was maintained at 185° with irradiation for 15 minutes. When cold, the product
solidified yielding crude 2,3,5,6-tetrachlorobenzyl bromide, 29.6 g.
This crude product was crystallised from 140 ml. boiling ethanol.

Yield 21.6 g. (70%) m.p. 91-2°C. Recrystallisation from ethyl acetate gave glistening plates, m.p. 92-3°C. Found C, 27.3; H, 0.97;
Cl, 45.6; Br, 25.6% ; C\textsubscript{7}H\textsubscript{3}Cl\textsubscript{4}Br requires C, 27.2; H, 0.98;
Cl, 45.9; Br, 25.9%.

2,3,5,6-Tetrachlorobenzyl Acetate C\textsubscript{6}H\textsubscript{4}Cl\textsubscript{4}CH\textsubscript{2}O.CO.CH\textsubscript{3}

2,3,5,6-Tetrachlorobenzyl bromide (15.4 g) was dissolved in a solution of potassium acetate (10 g.) in ethanol (100 ml.) and heated under reflux with stirring for 2 hours. The potassium bromide was removed by filtration and the alcohol evaporated until the volume of solution was ca. 25 ml. Water (100 ml.) was added and, when cold, the product was collected and dried in vacuo yielding crude 2,3,5,6-
tetrachlorobenzyl acetate 13.3 g. (92%), m.p. 72-76°C, which was recrystallised from isopropyl ether, ethanol and finally methanol, m.p. 103-4°C. Found C, 37.5; H, 2.18; Cl, 49.2%; C\textsubscript{9}H\textsubscript{6}Cl\textsubscript{4}O\textsubscript{2} requires C, 37.5; H, 2.10; Cl, 49.3%.

2,3,5,6-Tetrachlorobenzyl Alcohol C\textsubscript{6}H\textsubscript{4}Cl\textsubscript{4}CH\textsubscript{2}OH

2,3,5,6-Tetrachlorobenzyl acetate (27.6 g.) was dissolved in a solution of potassium hydroxide (25 g.) in ethanol (150 ml.) and heated under reflux with stirring for 6 hours. The mixture was evaporated to dryness at 15 mm. pressure on the water bath and the residue triturated with water then filtered and dried in vacuo. Yield of crude 2,3,5,6-tetrachlorobenzyl alcohol was 22.4 g. (91%) m.p. 111-3°C. The crude product was crystallised from 75% aqueous
ethanol. The yield was 17.2 g. and m.p. 120-21° unchanged by recrystallisation from carbon tetrachloride. Found C, 34.6; H, 1.70; Cl, 57.4%; C₇H₄Cl₀ requires C, 34.2; H, 1.64; Cl, 57.7%.

2,3,5,6-Tetrachlorobenzoic Acid C₇HCl₄COOH

2,3,5,6-Tetrachlorobenzyl alcohol (12.3 g.) was dissolved in a mixture of "Analar" pyridine (60 ml.) and water (10 ml.) and heated on a water bath. Finely ground potassium permanganate (17 g.) was added to the stirred solution in portions of about 2 g. at a time over a period of about 1½ hours. After the final addition of potassium permanganate, the reaction mixture was heated for 5 hours on a steam bath. The precipitated manganese dioxide was removed by filtration, and the clear almost colourless filtrate, evaporated to dryness at 15 mm. pressure. The solid product was treated with 50 ml. water and filtered from an insoluble residue, weight 1.5 g., m.p. 115-6° which was undepressed when mixed with starting material. The filtrate was acidified with concentrated hydrochloric acid, precipitating 2,3,5,6-tetrachlorobenzoic acid as a white powder which was dried in vacuo. Yield 10.3 g. (79%, or allowing for recovered alcohol, 90% theory), m.p. 182-3°. Found C, 32.1; H, 0.85; Cl, 54.3%; C₇H₂Cl₄O₂ requires C, 32.3; H, 0.78; Cl, 54.6%.

2,3,5,6-Tetrachlorobenzoic Acid C₇HCl₄COOH (Potassium permanganate oxidation of tetrachlorotoluene)

2,3,5,6-Tetrachlorotoluene (11.5 g.) was dissolved in a solution of pyridine (60 ml.) and water (10 ml.). Finely ground potassium permanganate (17.0 g.) was added in portions over six hours to a
stirred solution heated on a steam bath. When the addition was complete the mixture was stirred, and heated for a further 18 hours. The manganese dioxide was removed by filtration, and washed with pyridine (50 ml.). The filtrate was evaporated to dryness after the addition of 10% sodium hydroxide solution (30 ml.). The residue was boiled with water (100 ml.) and filtered from insoluble material. Acidification of the filtrate yielded a white microcrystalline powder, m.p. 174-6° mixed with 2,3,5,6-tetrachlorobenzoic acid, m.p. 179-82°. Yield 1.3 g. (10%).

2,3,5,6-Tetrachlorobenzoic Acid C₆H₄Cl₄COOH (from 2,3,5,6-Tetrachlorobenzyl alcohol and aqueous potassium permanganate)

2,3,5,6-Tetrachlorobenzyl alcohol (5.3 g.) was stirred with a solution of sodium hydroxide (2 g.) in water (20 ml.) and heated on a steam bath. Potassium permanganate (12 g.) was added over 2 hours and the mixture heated for 6 hours. Manganese dioxide was removed and the aqueous solution was decolourised with sulphur dioxide. 2,3,5,6-Tetrachlorobenzoic acid was precipitated with hydrochloric acid (10 ml. S.G. 1.16) to give a white microcrystalline precipitate, m.p. 180° which gave no depression when mixed with product of the previous experiment. Yield 0.8 g. (14%). The manganese dioxide residue was mixed with an appreciable amount of material which was soluble in carbon tetrachloride.

2,3,4,5,6-Pentachlorotoluene C₆Cl₄CH₃

Aluminium chloride (5 g.) was added to toluene (92 g.) and the stirred mixture heated to ca. 60°. Silberads reagent (482 mls.
sulphury chloride and 4.8 mls. sulphur: monochloride) was added dropwise at a rate that maintained a vigorous reaction. The mixture was heated on the steam bath for a further hour during which time it solidified. The crude pentachlorotoluene was ground and washed with water, then recrystallised from benzene (1.5 l.) to give needles, m.p. 211-14°, yield 116 g. Concentration of the mother liquor afforded a second crop, m.p. 182-6°, yield 70 g., which, after recrystallisation from 1:1 benzene:ethanol mixture (1400 ml.), had m.p. 216-19°. Total yield of recrystallised material 156 g. (59%). Further recrystallisation from alcohol gave long needles, m.p. 220-1° (lit. 109 m.p. 218°). Found Cl, 67.0%; C_7H_3Cl_5 requires Cl, 67.1%.

2,3,4,5,6-Pentachlorobenzyl Bromide C_6Cl_5CH_2Br

Bromine (58.6 g.) was added dropwise under the surface of a stirred melt of 2,3,4,5,6-pentachlorotoluene (90 g.) at 225°. The reaction mixture was irradiated with ultra-violet light during the addition. On cooling, the crude product (109 g.) was dissolved in boiling carbon tetrachloride (220 ml.) and decolourised with charcoal. Pentachlorobenzyl bromide separated as plates, m.p. 114-16°. Yield 55.5 g. A second crop, yield 25 g., m.p. 102-5°, was obtained from the mother liquor after concentration (70%). Recrystallisation from dioxan gave needles, m.p. 115-6°. Found C, 24.7; H, 0.55; Cl, 51.4; Br, 23.5%; C_7H_2Cl_5Br requires C, 24.5; H, 0.59; Cl, 51.6; Br, 23.3%.
2,3,4,5,6-Pentachlorobenzyl Acetate $\text{C}_9\text{H}_5\text{Cl}_5\cdot\text{CH}_2\text{OCOCCH}_3$

2,3,4,5,6-Pentachlorobenzyl bromide (8.6 g.), potassium acetate (5 g.) and ethanol (50 ml.) were heated together under reflux with stirring for 3 hours. After removing the potassium bromide, the ethanolic solution was evaporated, and the residue washed with water affording a buff crystalline product (weight 7 g.). Crystallisation of this crude product from hot carbon tetrachloride (50 ml.) gave needles, m.p. 195-6° (lit. 90 m.p. 198°). Yield 1.7 g. (24%). The melting point was not raised by further recrystallisation from ethanol.

Found C, 29.9; H, 1.20; Cl, 63.3%; pentachlorobenzyl alcohol $\text{C}_7\text{H}_7\text{Cl}_5\text{O}$ requires C, 30.0; H, 1.08; Cl, 63.2%. This compound had no absorption in the carbonyl region of the infra-red spectrum. The carbon tetrachloride filtrate was evaporated and the residue (4.7 g.) crystallised from ethanol, needles, m.p. 87° (lit. 90 m.p. 87-90°).

Yield of 2,3,4,5,6-pentachlorobenzyl acetate was 3.7 g. (46%). The melting point was unchanged by recrystallisation from cyclohexane.

This compound has a carbonyl band at 1740 cm$^{-1}$ in the infra-red spectrum. Found C, 33.6; H, 1.60; Cl, 54.9%; $\text{C}_9\text{H}_5\text{Cl}_5\text{O}_2$ requires C, 33.5; H, 1.56; Cl, 55.0%.

2,3,4,5,6-Pentachlorobenzyl Alcohol $\text{C}_9\text{H}_5\text{Cl}_5\cdot\text{CH}_2\text{CH}$

2,3,4,5,6-Pentachlorobenzyl acetate (6.4 g.), ethanol (30 ml.) and potassium hydroxide (5.0 g.) were heated under reflux for 1½ hours and the mixture filtered. The filtrate was evaporated to dryness and the residue washed with water. Yield of crude pentachlorobenzyl alcohol 4.3 g., m.p. 163-8°. Recrystallisation from chloroform and
then ethanol raised the melting point to 195\(^{\circ}\) which was undepressed when mixed with the sample of pentachlorobenzyl alcohol obtained in the proceeding experiment.

**2,3,4,5,6-Pentachlorobenzyl Alcohol** \(\text{C}_6\text{Cl}_6\text{CH}_2\text{OH}\) (without isolating the acetate)

2,3,4,5,6-Pentachlorobenzyl bromide (24 g.), potassium acetate (14 g.) and ethanol (120 ml.) were heated under reflux with stirring for 3 hours. Potassium hydroxide (7 g.) in ethanol (100 ml.) was added and the mixture heated for a further two hours. After filtration and evaporation to dryness the residue was washed with water. Yield of buff coloured, crystalline, crude pentachlorobenzyl alcohol was 19.3 g. (98%), m.p. 184-9\(^{\circ}\); recrystallised from methyl isobutyl ketone (190 ml.) gave needles, m.p. 193-5\(^{\circ}\), yield 16.2 g.

**2,3,4,5,6-Pentachlorobenzoic Acid** \(\text{C}_6\text{Cl}_6\text{COOH}\)

2,3,4,5,6-Pentachlorobenzyl alcohol (20 g.) was dissolved in a solution of pyridine (150 ml.) and water (20 ml.) by heating on a steam bath. Finely ground potassium permanganate (35 g.) was added in portions to the hot stirred solution over 4-5 hours. After heating on a steam bath for a further 3 hours the mixture was filtered, the manganese dioxide precipitate washed first with pyridine (50 ml.) then water (100 ml.) and the filtrate evaporated to a small bulk under reduced pressure. Sodium hydroxide (15 ml. 30\% solution) was added and the mixture evaporated to dryness under reduced pressure. The residue of crude sodium pentachlorobenzoic acid was digested with boiling carbon tetrachloride (100 ml.) and filtered. Yield of crude
sodium pentachlorobenzoate was 22.4 g. The latter was dissolved in boiling water (200 ml.) and filtered from a small amount of insoluble material. The filtrate was acidified with hydrochloric acid (20 ml. S.G. 1.16) and the precipitate of crude pentachlorobenzoic acid collected. Yield 16.4 g. (76%), m.p. 200-206°. Recrystallisation from boiling carbon tetrachloride gave pentachlorobenzoic acid, needles, m.p. 205-7° (lit. m.p. 208°). Yield 15.0 g. Found C, 28.7; H, 0.40; Cl, 60.1%; C7HCl5O2 requires C, 28.6; H, 0.34; Cl, 60.2%.

Sodium Trifluoracetate CF3COONa

Trifluoracetic acid (84 g.) was dissolved at 0° in a solution of sodium (15 g.) in methanol (180 ml.). The resulting solution of pH 4 was evaporated to dryness yielding deliquescent prisms 90.5 g. (102%). Found F, 41.3%; C2F3NaO2 requires F, 41.9%.

Sodium Triphenylacetate Ph.C6COONa

A solution of triphenylacetic acid (29 g.) in aqueous sodium hydroxide (4 g. in 250 ml.) was evaporated to dryness and the anhydrous residue digested with boiling chloroform. The solid was collected, and washed with acetone, yielding hygroscopic needles 30.0 g. (97%). Found Na, 7.20%; C26H15NaO requires Na, 7.41%.

Sodium 2,3,6-Trichlorobenzoate Cl2C6H3COONa

2,3,6-Trichlorobenzoic acid (17.3 g.) was dissolved in ethanol (60 ml.) containing sodium hydroxide (3.1 g.) by warming. The clear solution was evaporated to dryness on the steam bath at
15 mm. pressure, the dry residue dissolved in hot acetone (70 ml.) and filtered hot. Chloroform (150 ml.) was added to the hot filtrate, initiating crystallisation. The microcrystalline, white precipitate was collected and dried in vacuo at 120°. Yield of sodium 2,3,6-trichlorobenzoate 15.5 g. (80%) microcrystalline, hygroscopic powder. Found Na, 9.50%; C_7H_2Cl_3O_2Na requires Na, 9.29%.

**Sodium 2,3,5,6-Tetrachlorobenzoate C_6HCl_4COONa**

2,3,5,6-Tetrachlorobenzoic acid (20 g.) was dissolved in hot ethanol (25 ml.) and 10% sodium hydroxide solution (30 ml.) added. Crystals began separating immediately. The solution was evaporated almost to dryness and the crystalline slurry digested with carbon tetrachloride (50 ml.) to remove excess tetrachlorobenzoic acid. Yield of glistening plates was 20 g. (98%). Found Na, 7.95%; C_7HCl_4O_2Na requires Na, 8.16%.

**Sodium 2,3,4,5,6-Pentachlorobenzoate C_6Cl_5COONa**

2,3,4,5,6-Pentachlorobenzoic acid (11.1 g.) was dissolved in boiling ethanol (20 ml.) and sodium hydroxide (1.5 g.) in water (10 ml.) added. Crystals began to separate immediately. The solvent was evaporated and the residue washed with boiling carbon tetrachloride. Yield of sodium 2,3,4,5,6-pentachlorobenzoate 11.5 g. (99%) plates. Found Na, 7.35%; C_7Cl_5NaO_2 requires Na, 7.27%.

**Trifluoracetanilide C_6H_NH.CO.CF_3**

Trifluoroacetic anhydride (13.4 g.) in ether (25 ml.) was added during 15 minutes with stirring to a solution of aniline (12 g.)
in ether (15 ml.) at 0° to -10°. After 1 hour, the ether was evaporated under reduced pressure and the solid residue triturated with water (50 ml.) then collected, yield 10.9 g. (91%), m.p. 88-90°. After recrystallisation from petroleum (b.p. 60-80°, 100 ml.) it formed needles m.p. 90-91° (lit. 89.5-90.5°).

**Trimethylacetanilide Me$_3$CCONHPh**

A solution of trimethylacetyl chloride (24.1 g.) in ether (50 ml.) was added dropwise to aniline (37.3 g.) in ether (125 ml.) at such a rate as to maintain gentle reflux and the mixture stirred for an extra ½ hour. The resulting trimethylacetanilide separated from 50% aqueous alcohol (300 ml.) in fine needles, m.p. 136° (lit. m.p. 132°). Found N, 7.83%; $C_{11}H_{15}NO$ requires N, 7.90%.

**Triphenylacetanilide Ph$_3$CCONHPh**

Triphenylacetic anhydride (5.6 g.), aniline (1.9 g.) and dioxan (30 ml.) were heated under reflux for 5 hours. The dioxan was evaporated at diminished pressure leaving an oil which solidified on washing with dilute hydrochloric acid, yield 6.0 g., m.p. 163-73°. After recrystallising successively from cyclohexane, ethanol and finally propanol, minute plates formed m.p. 171-2° (lit. m.p. 170°). Found N, 3.93%; $C_{26}H_{21}NO$ requires N, 3.86%.

**2,3,6-Trichlorobenzanilide $C_6H_2Cl_3$CONHPh**

2,3,6-Trichlorobenzoyl chloride (6.1 g.) and aniline (4.6 g.) were heated together under reflux in ether (50 ml.) for 5 hours. After evaporating the ether, the solid residue was washed with
water and recrystallised from benzene giving small needles, m.p. 183-4°C, 7.1 g. (94%). Found N, 4.83%; \( \text{C}_{13}\text{H}_{20}\text{Cl}_{3}\text{NO} \) requires N, 4.66%.

**N-Phenyl Diethyl Phosphoramidate \((\text{C}_{2}\text{H}_{5}\text{O})_{2}\text{P(O)NHCH}_{2}\text{CH}_{2}\text{H}_{2}\)**

Ethyl phosphorochloridate (60.3 g.) was added to a solution of aniline (65.0 g.) in dry ether (320 ml.) with stirring. The temperature of the solution was maintained at 20°C by external cooling. When the addition of the phosphorochloridate was complete, the mixture was stirred for \( \frac{1}{2} \) hour and then filtered from the aniline hydrochloride. The ether was evaporated under diminished pressure and the residual dark oil chilled, when it solidified to a buff-coloured, crystalline mass. After drying in vacuo over phosphorus pentoxide the yield was 76 g. The solid was dissolved in boiling ethanol (60 ml.) and, while boiling, water (90 ml.) was added. The solution was allowed to cool slowly. Yield of fine off-white needles was 63.5 g. (78.5%). m.p. 93-95°C; (lit.\(^{11}\) m.p. 95.5-96.5°C).

**Trimethylacetyl Chloride \( \text{Me}_{3}\text{C.COCI} \)**

Trimethylacetyl chloride was obtained in 65% yield from trimethylacetic acid and thionyl chloride and had b.p. 105°C, \( n_{D}^{22} \) 1.4110. Found Cl, 29.3%; \( \text{C}_{5}\text{H}_{9}\text{OCl} \) requires Cl, 29.4%. (Constants quoted in the literature\(^{114}\) are variable, b.p. varies from 103.4 to 107°C and \( n_{D}^{22} \) from 1.4126 to 1.4118.)

**Triphenylacetyl Chloride \( \text{Ph}_{3}\text{C.COCI} \)**

Triphenylacetic acid (22.4 g.), thionyl chloride (31.0 g.), benzene (100 ml.) and pyridine (0.35 ml.) were heated under reflux for 4 hours. After removal of benzene and excess thionyl chloride by
distillation, the residue was recrystallised from light petroleum 
(boiling range 100-120°) giving yellow needles, m.p. 126-8° 
(lit. 108 m.p. 128-9°). Yield 18.0 g. (74%).

2,3,6-Trichlorobenzoyl Chloride C₆H₄Cl₃CO.Cl

2,3,6-Trichlorobenzoic acid (20.2 g.) and thionyl chloride 
(9 ml.) were heated under reflux for 1½ hours. The reaction mixture 
was fractionated and the fraction b.p. 145-8°/20 mm. was collected, 
yield 19.0 g. (85%), colourless liquid, nD²⁵ 1.5766. Found C, 34.3 ; 
H, 0.85 ; Cl, 57.4% ; C₁₇H₂₁₂Cl₄O requires C, 34.3 ; H, 0.83 ; Cl, 58.1%.

2,3,6-Trichlorobenzoic Anhydride C₆H₄Cl₃CO.CO.CO.C₆H₄Cl₃

Trichlorobenzoyl chloride (6.1 g.) and sodium trichloro-
benzoate (10 g.) were heated together on an oil bath at 200° for 2 
hours. The solid product was crystallised from carbon tetrachloride 
(300 ml.), yield was 8.1 g. (75%), m.p. 181°. Recrystallisation 
from toluene gave prisms, m.p. 183°. Found C, 38.6 ; H, 0.96 ; 
Cl, 48.9% ; C₁₇H₂₁₂Cl₄O requires C, 38.8 ; H, 0.93 ; Cl, 49.1%.

Triphenylacetic Anhydride Ph₃CCO.OCCOPh₃

Triphenylacetic acid (2.9 g.), triphenylacetyl chloride (3.2 g.), 
pyridine (0.8 g.) and acetonitrile were heated under reflux for 10 
hours. Triphenylacetic anhydride slowly crystallised from the boiling 
reaction mixture during the course of the refluxing, yield 5.5 g. (98%), 
m.p. 174-5°. After recrystallising from carbon tetrachloride and 
then cyclohexane, prisms were obtained with a m.p. 183-4° (lit. 115 
m.p. 163°). Found C, 86.1 ; H, 5.50% ; C₆₀H₃₁O₃ requires C, 86.0 ; 
H, 5.41%.

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Tetraethylpyrophosphate \((\text{EtO})_2\text{PO.CPO(OEt)}_2\)

Ethyl phosphorochloridate (43.2 g.) in chloroform (100 ml.) was added to a solution of sodium diethyl phosphate (44 g.) in hot chloroform (250 ml.). After heating under reflux for 24 hours, the sodium chloride was removed and the chloroform evaporated leaving a colourless liquid, b.p. 118-9°C/0.3 mm. Yield 56.0 g. (77%) \(n_D^{21} 1.4190\) (lit. \(n_D^{28} 1.32-30^\circ/0.5 \text{ mm., } n_D^{25} 1.4182\)). Found P, 21.2%; 
\(\text{C}_8\text{H}_{20}\text{O}_7\text{P}_2\) requires P, 21.2%.

Anilinium 2,3,6-Trichlorobenzoate Complex \(\text{PhNH}_2\text{C}_6\text{H}_2\text{Cl}_3\text{CO}_2\text{H}\)_2

Aniline hydrochloride (6.5 g.) in water (30 ml.) was added to sodium 2,3,6-trichlorobenzoate (12.4 g.) in water (30 ml.) and the precipitate collected and washed with water, yield 11.9 g. (75%), m.p. 120-25°C. After sublimation and recrystallising from aqueous alcohol the complex separated as needles, m.p. 150°C. Found C, 43.8; H, 2.30; Cl, 39.8; N, 2.73; O, 11.7%; \(\text{C}_{20}\text{H}_{13}\text{O}_4\text{NCl}_6\) requires C, 44.1; H, 2.41; Cl, 39.1; N, 2.58; O, 11.8%.

Cyclohexylammonium Diethyl Phosphate \((\text{EtO})_2\text{PO(OEt)}_2\text{NH}_2\text{C}_6\text{H}_{11}\)

An aqueous solution of sulphuric acid (10 ml. S.G. 1.84 in 30 ml. water) was added, at 0°C, to a solution of sodium diethyl phosphate (24.5 g.) in chloroform (100 ml.) and the mixture was stirred for 1/2 hour. The chloroform layer was separated and evaporated leaving a colourless syrup of diethylphosphoric acid. The latter was dissolved in benzene (25 ml.) and cyclohexylamine (14 g.) added. The crystalline product was collected and washed with benzene, yield 39.9 g. (104%) of deliquescent needles, m.p. 71-3°C which was unchanged after recrystallisation from ethyl acetate. Found P, 12.0%; \(\text{C}_{10}\text{H}_{24}\text{NO}_4\text{P}\) requires P, 12.2%. 

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Acetyl Diethyl Phosphate (EtO)$_2$P(O)COMe

Acetyl chloride (170 ml.) was added with stirring and cooling to sodium diethyl phosphate (37.3 g.). The stirred mixture was heated under reflux for 4 hours, filtered and the excess acetyl chloride evaporated at diminished pressure. The residue was distilled and the fraction b.p. 70°/0.2 mm. was collected, yielding 32.0 g. (82%) of colourless liquid $n_D^{25}$ 1.4114 (lit. $^5$ b.p. 70°/0.2 mm., $n_D^{25}$ 1.4115). Found C, 36.8; H, 6.72; P, 15.8%; $C_5H_{13}O_5P$ requires C, 36.7; H, 6.68; P, 15.8%.

Reaction Between Sodium Acetate and Ethyl Phosphorochloridate

Sodium acetate (16.4 g.) and diethyl phosphorochloridate (100 ml.) were heated together at 100° for 3 hours; after filtration the filtrate was evaporated first at 15°/20 mm. The vapour was condensed in a cold trap at -80° yielding a pungent, fuming liquid (5.7 g.) that had a boiling range 40-53°, the majority boiling at 46-51°. (Acetyl chloride b.p. 51-2°). Found C, 31.3; H, 4.35; Cl, 41.9%; Acetyl chloride, $C_2H_3OCl$ requires C, 30.6; H, 3.85; Cl, 45.2%. The infra-red spectrum of this material was identical to that of acetyl chloride. The remainder of the reaction mixture was stripped of the excess ethyl phosphorochloridate by distillation at 15 mm. from a steam bath. The almost colourless residual liquid had an infra-red absorption spectrum identical in all the principal bands to that obtained from the similar reaction with sodium benzoate and ethyl phosphorochloridate. The carbonyl band was completely absent. The principal bands in the spectrum were at 1310, 1165, 1040 and 940 cm$^{-1}$. There was a shoulder at 980-990 cm$^{-1}$. Distillation
of this material gave a first fraction boiling 50-100°/0.5 mm. and a second fraction 100-115°/0.5 mm. The remaining material in the distillation flask decomposed. The infra-red spectrum of each fraction indicated that they were mixtures of triethyl phosphate and tetraethyl pyrophosphate, the former being present in greater amount in the first fraction than in the second.

**Benzoyl Diethyl Phosphate (EtO)₂P(O)OOCPh**

A stirred mixture of benzoyl chloride (60 ml.) and sodium diethyl phosphate (17.6 g.) was heated on a steam bath for 5 hours, then diluted with carbon tetrachloride and filtered to remove the sodium chloride. Carbon tetrachloride and the excess benzoyl chloride were distilled from the filtrate at 15 mm. and the residue fractionated. The first fraction b.p. 100-115°/0.05 mm. (2.5 g.) had an infra-red spectrum with a strong band at 940 cm⁻¹, characteristic of tetraethyl pyrophosphate, the carbonyl band at 1755 cm⁻¹ was not very strong. The second fraction, benzoyl diethyl phosphate, b.p. 115-6°/0.05 mm. was collected yielding 20.6 g. (80%) n_D²⁵ 1.4915. Found C, 52.0 ; H, 5.94 ; P, 11.5% ; C₁₁H₁₅O₅P requires C, 51.2 ; H, 5.86 ; P, 12.0%. (lit,⁵ b.p. 110-111°/0.01 mm., n_D²⁵ 1.4922).

**Reaction Between Sodium Benzoate and Diethyl Phosphorochloridate**

(a) In the presence of excess diethyl phosphorochloridate. A stirred suspension of sodium benzoate (14.4 g.) in diethyl phosphorochloridate (75 ml.) was heated on a steam bath for 5 hours. The sodium chloride was removed by filtration and all material volatile below 100° at 15 mm. distilled from the filtrate, giving a colourless
distillate (48.5 g.) and a straw-coloured residue (36.5 g.). The infra-red spectrum of the former revealed a doublet in the carbonyl region at 1775 cm$^{-1}$ and 1755 cm$^{-1}$, characteristic of benzoyl chloride, superimposed on the spectrum of diethyl phosphorochloridate. The ultra-violet absorption spectra of the above distillate and benzoyl chloride, each in isooctane, were qualitatively identical. Extinctions at 240 nm and 281.5 nm indicated the presence of 12 ± 1% benzoyl chloride corresponding to a total yield of ca. 6 g. benzoyl chloride. It was not possible to separate the benzoyl chloride from the ethyl phosphorochloridate by distillation. The straw-coloured residue had the following principal bands in the infra-red spectrum, 1310, 1165, 1040 and 940 cm$^{-1}$. There was no absorption in the carbonyl region. On attempting to distil the material it decomposed, giving a relatively low boiling product, b.p. 50-60°/0.5 mm., yield 8.5 g. and leaving an involatile residue. Redistillation of the product gave a colourless liquid b.p. 213-219°. Found P, 16.7%; triethyl phosphate b.p. 216°, C$_3$H$_5$O$_3$P requires P, 17.0%. The infra-red spectrum of the redistilled liquid was identical to that of authentic triethyl phosphate.

(b) With an equimolar quantity of diethyl phosphorochloridate.
Sodium benzoate (14.4 g.) and diethyl phosphorochloridate (17.3 g.) were mixed at room temperature to form a dough-like mass that rapidly warmed up to 70° and became fluid. After 2 hours it was diluted with dry carbon tetrachloride, filtered and the solvent evaporated at diminished pressure leaving a colourless liquid, the infra-red spectrum of which had three bands in the carbonyl region, 1795, 1755 and 1735 cm$^{-1}$. The band at 1755 cm$^{-1}$ is characteristic of benzoyl
diethyl phosphate, while the doublet 1795 and 1735 cm\(^{-1}\) is characteristic of benzoic anhydride. There were strong bands at 1290, 980 and 940 cm\(^{-1}\) characteristic of tetraethyl pyrophosphate. The mixture was fractionated, and ignoring the fore-runnings boiling below 120°, four fractions were collected at 0.15 mm. (i) b.p. 120-130° ca. 5 g., (ii) b.p. 130-136° ca. 5 g., (iii) b.p. 136° ca. 5 g. and (iv) b.p. 136-140° ca. 6 g. In all fractions, the infra-red spectrum had the characteristic doublet of benzoic anhydride at 1795 and 1735 cm\(^{-1}\) and the carbonyl vibration frequency 1753 cm\(^{-1}\) of benzoyl diethyl phosphate. The intensity of these bands increased from fraction (i) to fraction (iv) whilst that of the P-O-P link at 940 cm\(^{-1}\) for tetraethyl pyrophosphate decreased. However, no clear separation of the components was achieved by distillation.

(c) Equimolecular quantities of sodium benzoate and diethyl phosphorochloridate in the presence of benzene. The previous experiment (b) was repeated with the difference that refluxing benzene was used as a solvent. After filtration, and removal of benzene, the residual liquid had an identical infra-red spectrum to that of the crude reaction mixture obtained in (b).

**Ethoxycarbonyl Diethyl Phosphate \((\text{EtO})_2\text{P(O)OCOOEt}\)**

(a) Via the silver salt with acetone as solvent. Ethyl chloroformate (10.8 g.) and silver diethyl phosphate (26.2 g.) in acetone (250 ml.) were heated together under reflux with stirring for 16 hours. The silver chloride was removed by filtration and the acetone by distillation at diminished pressure. The residue of crude
Ethoxycarbonyl diethyl phosphate was distilled, b.p. 86-80/0.05 mm.
Yield 9.1 g. (40%). Colourless liquid, $n_D^{24} 1.4108$. Found C, 37.8; H, 6.96; P, 14.1%; $C_2H_5O_6P$ requires C, 37.2; H, 6.69; P, 13.7%.

(b) Via the silver salt with ethyl chloroformate as solvent. Ethyl chloroformate (50 ml.) and silver diethyl phosphate (26.2 g.) were heated under reflux with stirring for 1 hour. After removing the silver chloride by filtration and the excess ethyl phosphoro­chloridate at diminished pressure, the residue was distilled, b.p. 96-80/2 mm. Yield 10.9 g. (48%). Colourless liquid, $n_D^{24} 1.4108$. Found C, 37.4; H, 6.78; P, 13.6%; $C_2H_5O_6P$ requires C, 37.2; H, 6.69; P, 13.7%.

(c) Via the silver salt with methyl ethyl ketone as solvent. The reaction described in (a) was repeated replacing the solvent acetone by ethyl methyl ketone. The time of reflux was reduced to 4 hours. Yield 8.5 g. (37%), b.p. 98-90/2 mm., $n_D^{24} 1.4109$.

(d) Via the sodium salt. Anhydrous sodium diethyl phosphate (123.5 g.) was added, with stirring, to ethyl chloroformate (370 ml.) at room temperature. The glutinous reaction mixture changed gradually to a mobile suspension of finely divided sodium chloride. When the temperature of the reaction mixture ceased to rise, external heat was applied and the mixture was refluxed for 1 hour. After removal of the sodium chloride and ethyl chloroformate, the pale straw-coloured residue was distilled, b.p. 89-900/0.02 mm. Yield 113 g. (71%), $n_D^{24.5} 1.4106$. Found C, 37.4; H, 6.88; P, 13.3%; $C_7H_{15}O_6P$ requires C, 37.2; H, 5.69; P, 13.7%.
(e) Via the lead salt. Lead diethyl phosphate (38.5 g.) was added to ethyl chloroformate (100 ml.) at room temperature and the mixture heated under reflux with stirring for 10 hours, and then filtered. The product, ethoxycarbonyl diethyl phosphate, was isolated as described in the previous experiment, b.p. 91°/0.1 mm.

Yield 23.3 g. (71%), $n_D^{25} 1.4101$. Found C, 37.2; H, 6.75; P, 13.8%; $C_7H_{15}O_6P$ requires C, 37.2; H, 6.69; P, 13.7%.

(f) Via the basic lead salt. Basic lead diethyl phosphate (51.3 g.) and ethyl chloroformate were heated together under reflux, with stirring, for 9 hours. The lead chloride and ethyl chloroformate were removed, and the residue was fractionated by vacuum distillation.

The first fraction, less than 1 g., distilled below 91°/0.03 mm. The second fraction boiled at 91-92°/0.03 mm., yield 18.5 g. (63%), $n_D^{24} 1.4100$. The third fraction distilled at 92-116°/0.03 mm., yield 4.6 g., $n_D^{24} 1.4130$. Infra-red absorption spectrum showed that this was substantially tetraethyl pyrophosphate. (Tetraethyl pyrophosphate b.p. 104-106°/0.08 mm., $n_D^{25} 1.4182$).

Thermal Stability of Ethoxycarbonyl Diethyl Phosphate

The temperature of ethoxycarbonyl diethyl phosphate (22.6 g.) was raised from 25° to 200° during 1½ hour, and maintained at 200° for 2 hours. Evolution of carbon dioxide began at 150° and was complete after 1½ hours. The contents of the flask were distilled, b.p. 215°, yield 11.3 g. (62% theory of triethylphosphate) $n_D^{22.5} 1.4038$. Found P, 17.0%; triethylphosphate, $C_6H_{15}O_4P$ requires P, 17.0%, b.p. 215-6°, $n_D^{25} 1.4039$. The residue (4.3 g.) decomposed on further heating.
Reaction Between Ethoxycarbonyl Diethyl Phosphate and Benzoic Acid

A solution of benzoic acid (12.2 g.) in ethoxycarbonyl diethyl phosphate (50 ml.) was heated on an oil bath at 150° for 2 hours, and the product distilled. Yield 16.0 g., b.p. 108°/28 mm. (107% of theoretical amount of ethyl benzoate). Undistillable residue 11.1 g. The distillate was redistilled, b.p. 211-13°. Yield 14.8 g. (99%). Found C, 69.0; H, 6.82; P, 1.3%. Ethyl benzoate, C₇H₈O₂ requires C, 72.0; H, 6.71; b.p. 212°. The distillate was washed with water, dried over anhydrous calcium sulphate and redistilled, b.p. 211-13°, yield 11.7 g. Found C, 70.4; H, 6.65; P, 0.22%.

Trifluoracetyl Diethyl Phosphate (EtO)₂P(O)O·CO·CF₃

Diethyl phosphorochloridate (41 g.) was cooled to -30° in a flask protected from atmospheric moisture and equipped with a thermometer, stirrer and a bent side arm with a conical flask attached. Sodium trifluoracetate (32.5 g.) was added from the conical flask and the mixture was allowed to warm up. The suspension was easily stirred and at 15° complete solution was obtained. The viscosity of the reaction mixture increased until at 25° it gelled and became opaque. The temperature was not allowed to exceed 30°, external cooling being used when necessary. After standing at 15° for 18 hours, ether (70 ml.) was added and the sodium chloride filtered off. The residue (46.5 g.) was distilled at 30°/0.01 mm. in a specially designed short-path still. The trifluoracetyl diethyl phosphate was collected on a cold finger at -70° as a crystalline solid, m.p. -9 to -10°, Yield 14.7 g. (25%). At room temperature it was a colourless liquid dissolving in water with the evolution of heat.
Found C, 28.8 ; H, 4.09 ; P, 12.3% ; C_6H_{10}F_3O_P requires C, 28.8 ; H, 4.03 ; P, 12.4%. The undistilled residue (19.1 g.) had only slight carbonyl absorption and a strong P–O–P peak (940 cm\(^{-1}\)). When chloroform replaced ether in the above experiment, the material isolated from the reaction product had identical physical properties and infra-red absorption spectrum to that above. Yield 18.1 g. (30%).

**Reaction Between Diethyl Phosphorochloridate and Sodium Trifluoroacetate at 100°**

A stirred mixture of sodium trifluoroacetate (21.8 g., 1 mol.) and diethyl phosphorochloridate (27.5 g., 1 mol.) was heated on a steam bath under reflux for 4\(\frac{1}{2}\) hours. The reaction mixture was stripped of volatile material at 20\(^\circ\)/15 mm. and the vapour condensed in a cold trap at -70\(^\circ\). A colourless, fuming, volatile liquid, yield 4.6 g., was collected, its infra-red spectrum being identical to that of trifluoroacetic anhydride. After filtering the sodium chloride from the undistilled residue of the reaction mixture, the resultant liquid had b.p. 128\(^\circ\)/0.3 mm. Yield 12.5 g. It had an infra-red spectrum identical to that of tetraethyl pyrophosphate (lit. b.p. 125-130\(^\circ\)/0.5 mm.).

**Trimethylacetyl Diethyl Phosphate (EtO)\(_2\)P(O)O.COC(CH\(_3\))\(_3\)**

Sodium diethyl phosphate (35.2 g.) and trimethyl acetyl chloride (75 ml.) were mixed with cooling and subsequently were refluxed with stirring for \(\frac{1}{2}\) hour. After filtering and removing the excess of trimethylacetyl chloride, the residue was fractionated at low pressure. The fraction b.p. 66-83\(^\circ\)/0.05 mm. was redistilled.
yielding trimethylacetyl diethyl phosphate, b.p. 64-65°/0.05 mm.,
36.2 g. (76%). Colourless liquid, \( n_D^{25} = 1.4144 \). Found C, 45.6;
H, 8.10; P, 13.0% ; \( \text{C}_9\text{H}_{19}\text{O}_2\text{P} \) requires C, 45.4; H, 8.04; P, 13.0%.

**Triphenylacetyl Diethyl Phosphate (EtO)\(_2\)P(O)OCOCPh\(_3\)**

(a) **Using excess diethyl phosphorochloridate.** Sodium triphenyl acetate (10.3 g.) was added with stirring to diethyl phosphorochloridate (15 ml.) at room temperature. After the initial reaction had subsided the stirred mixture was heated on a steam bath for 6 hours then diluted with carbon tetrachloride and washed with water. The carbon tetrachloride solution was dried over calcium sulphate. The solvent and excess diethyl phosphorochloridate were removed by distillation at reduced pressure from a steam bath, leaving an oil that solidified overnight. Yield 7.9 g. (56%). The crude product was crystallised from cyclohexane (25 ml.) giving triphenylacetyl diethyl phosphate 5 g., small cubic crystals, m.p. 60-65°. Two further recrystallisations raised the m.p. to 71-2°. Found C, 67.5; H, 6.05; P, 7.40%; \( \text{C}_{24}\text{H}_{25}\text{O}_2\text{P} \) requires C, 67.9; H, 5.94; P, 7.30%.

(b) **Using acetone as solvent.** Sodium triphenylacetate (28.8 g.), diethyl phosphorochloridate (16.0 g.) and acetone (125 ml.) were heated under reflux and stirred for 3 hours. After filtration, the acetone solution was concentrated to about 50 ml., cooled and diluted with water (200 ml.). By cooling and scratching, the oil was encouraged to solidify and, after grinding with water, the solid was collected, yield 33.5 g. (82%), m.p. 69-72°. Recrystallisation from cyclohexane/petrol gave a micro-crystalline powder, m.p. 71-2°, yield 33.3 g. (76.5%). Found C, 68.2; H, 6.05; P, 7.40%; \( \text{C}_{24}\text{H}_{25}\text{O}_2\text{P} \) requires C, 67.9; H, 5.94; P, 7.30%.
(c) When the reflux time of (b) was increased to 8 hours, triphenylacetic anhydride, m.p. 165-70°, yield 23.1 g. (95%) was isolated. After recrystallising from cyclohexane, small prisms were obtained, m.p. 182-3° alone and with authentic triphenylacetic anhydride.

Reaction Between Triphenylacetyl Chloride and Sodium Dibutyl Phosphate

A mixture of triphenyl acetyl chloride (15.3 g.) and sodium dibutyl phosphate (8.8 g.) was heated in an oil bath at 140° until the contents of the flask just melted forming an almost clear solution. The mixture was heated for 24 hours at 100° during which time it slowly solidified. The infra-red spectrum of the crude product had bands at 1815, 1775 and 1755 cm⁻¹ in the carbonyl region. The band at 1775 cm⁻¹ was weak indicating the presence of only a small amount of triphenylacetyl dibutyl phosphate. The strong bands at 1815 and 1775 cm⁻¹ are attributable to triphenylacetic anhydride. The solid was dissolved in boiling carbon tetrachloride and filtered. On cooling this solution deposited small, cubic crystals 12.9 g., m.p. 168-70°, which after recrystallisation from cyclohexane had m.p. 184-5° which was undepressed when mixed with triphenylacetic anhydride. The infra-red spectrum of the filtrate of the reaction mixture showed only a very weak broad band in the carbonyl region. After removal of the solvent, the residue was distilled and the fraction b.p. 120°/0.1 mm. collected. Yield 2.6 g. Found P, 19.2%; tetraethyl pyrophosphate C₆H₂O₇P₂ requires P, 21.2%. The infra-red spectrum of this material was identical to that of tetraethyl pyrophosphate.
2,3,6-Trichlorobenzoyl Diethyl Phosphate \((\text{EtO})_2\text{P(O)}\text{COC}_6\text{H}_2\text{Cl}_3\)

Sodium 2,3,6-trichlorobenzoate (28.6 g.) and diethyl phosphorochloridate (21.7 g.) in acetone were heated under reflux with stirring for 5 hours. After filtration and evaporation of the acetone, the residual oil was washed with aqueous sodium bicarbonate, and then dissolved in carbon tetrachloride. The solution was dried over calcium sulphate, the carbon tetrachloride evaporated, and the residue submitted to molecular distillation. The fore-runnings distilled at 80° over a pressure range of 0.01 to 0.003 mm., yield 4.4 g. The infra-red spectrum of the latter had strong bands at 1785, 990 and 940 cm\(^{-1}\) revealing the presence of tetraethyl pyrophosphate together with the expected 2,3,6-trichlorobenzoyl diethyl phosphate. The latter distilled at 81°/0.004 mm. as a colourless viscous liquid, \(n_D^{25} 1.5139\), yield 19.6 g. (47%). Found C, 36.2; H, 3.40; Cl, 29.7; P, 8.65%; \(\text{C}_{11}\text{H}_{12}\text{Cl}_3\text{O}_5\text{P}\) requires C, 36.5; H, 3.35; Cl, 29.4; P, 8.57%. A solid residue, weight 2.5 g., m.p. 145-170° remained, which after re-crystallising from carbon tetrachloride had m.p. 175-6° undepressed when mixed with an authentic sample of 2,3,6-trichlorobenzoic anhydride.

2,3,5,6-Tetrachlorobenzoyl Diethyl Phosphate \((\text{EtO})_2\text{P(O)}\text{COC}_6\text{H}_2\text{Cl}_4\)

Sodium tetrachlorobenzoate (14.1 g.), diethyl phosphorochloridate (26.5 g.) and acetone (75 ml.) were heated together under reflux for 3 hours. The precipitated sodium chloride was removed by filtration, and the filtrate was evaporated on a steam bath first at 15 mm. then at 0.1 mm. to remove solvent and excess diethyl phosphorochloridate. The residual oil crystallised on standing overnight. It was
recrystallised from cyclohexane (15 ml.). Yield of crude 2,3,5,6-
tetrachlorobenzoyl diethyl phosphate 13.9 g., m.p. 58-68°. Further
recrystallisations from ether and then cyclohexane, gave needles,
m.p. 76-8°. Found C, 33.4; H, 2.8; Cl, 35.7; P, 7.9%;
C_{11}H_{11}Cl_{14}O_{5}P requires C, 33.4; H, 2.8; Cl, 35.8; P, 7.8%.

2,3,4,5,6-Pentachlorobenzoyl Diethyl Phosphate C_{11}Cl_{5}C=CH.CO.OPO(OCC_{2}H_{5})_{2}

Sodium 2,3,4,5,6-pentachlorobenzoate (10.5 g.), diethyl phospho-
phorochloridate (5.75 g.) and acetone (40 ml.) were heated under
reflux for 4½ hours with stirring. The sodium chloride was removed
and the acetone solution evaporated on a water bath at 15 mm. The
residual oil solidified on cooling and seeding, yield 13.9 g. (91%),
m.p. 60-65°. Crystallisation from cyclohexane (40 ml.) gave irregular
prisms, yield 10.8 g., m.p. 72-4° unchanged by further recrystallisa-
tion from ether. Found C, 30.9; H, 2.45; Cl, 40.7; P, 7.30%;
C_{11}H_{10}Cl_{5}O_{5}P requires C, 30.7; H, 2.34; Cl, 41.2; P, 7.20%.

Reaction Between Ethoxycarbonyl Diethyl Phosphate and Aniline

(a) In dioxan. Aniline (18.6 g.) was added carefully to a solu-
tion of ethoxycarbonyl diethyl phosphate (22.6 g.) in dioxan (60 ml.)
when the temperature of the reaction mixture rose to 70°. After
leaving on a steam bath overnight, the resulting clear, brown solu-
tion was stripped of dioxan and washed with water. The crystalline
solid 16.0 g. (97%) had m.p. 44-46°, when mixed with an authentic
sample of N-phenyl urethane m.p. was 47-50°. The product was re-
crystallised from 60% aqueous ethanol (32 ml.). Yield of white,
crystalline needles was 12.0 g., m.p. 49-50°. The aqueous filtrate
and washings from the crude reaction product were basified with 40% aqueous sodium hydroxide solution and extracted twice with benzene (2 x 25 ml.) to remove the liberated aniline. The aqueous alkaline solution was saturated with carbon dioxide, and then evaporated to dryness. The residue was extracted with boiling ethanol, filtered from the insoluble sodium carbonate and the filtrate evaporated to dryness. The residue was finally dried in vacuo over phosphorus pentoxide. Yield of crystalline sodium diethyl phosphate 16.2 g. (92%).

The latter was dissolved in chloroform (50 ml.) and 50% aqueous sulphuric acid (20 ml.) added carefully. When cold, the crystalline hydrated sodium sulphate was removed by filtration and the chloroform solution dried with anhydrous calcium sulphate. The chloroform was removed and the residual diethyl phosphoric acid dissolved in dry benzene (25 ml.) and cyclohexylamine (10 g.) was added. The cold mixture was diluted with 60-80° petroleum ether and the crystals were collected, washed with light petroleum and dried in vacuo over phosphorus pentoxide. Yield of deliquescent, white needles of cyclohexylammonium diethyl phosphate was 20.5 g. (82%), m.p. 71-3° alone and also when mixed with an authentic sample of cyclohexylammonium diethyl phosphate.

(b) In ether. Ethoxycarbonyl diethyl phosphate (22.6 g.) and aniline (18.6 g.) were mixed in ethereal solution and left overnight. After evaporation of the ether, the residual oil was washed with water, and left at 0° overnight when it crystallised. The buff needles were collected and dried in vacuo, yield 13.9 g. (84%).
m.p. 45-9°; when mixed with authentic N-phenyl urethane the m.p. was 47-9°. Analysis showed the product contained 1.05% phosphorus.

Reaction Between Acetyl Diethyl Phosphate and Aniline

Acetyl diethyl phosphate (19.6 g) in ether (75 ml) was added to aniline (18.6 g) in ether (100 ml) at 0°. After standing for 1 hour the ether was evaporated at room temperature leaving a solid, which after triturating with water, was filtered and washed. The product (12.4 g, 92% calc. for acetanilide) had m.p. 111-15°, when mixed with acetanilide m.p. 112-15°, it contained 0.09% phosphorus.

Reaction Between Benzoyl Diethyl Phosphate and Aniline

Benzoyl diethyl phosphate (10.6 g) and aniline (7.7 g) were allowed to react in ether (75 ml) as described for the corresponding acetyl derivative. The product (7.4 g, 91% calc. for benzanilide) was isolated in the same way, as in the previous experiment had m.p. 163-4° alone or, when mixed with benzanilide. It contained 0.05% phosphorus.

Reaction Between Trifluoracetyl Diethyl Phosphate and Aniline

Trifluoracetyl diethyl phosphate (10.7 g) was allowed to react with aniline (8.0 g) in ether (60 ml) as described for the acetyl derivative. The product (7.1 g, 91% calc. for trifluoracetanilide) was isolated as described for the acetyl derivative, and had m.p. 88-90°, undepressed when mixed with trifluoracetanilide of m.p. 90-91°, and contained 0.28% phosphorus.

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Reaction Between Trimethylacetyl Diethyl Phosphate and Aniline

Trimethylacetyl diethyl phosphate (23.8 g.), ether (200 ml.) and aniline (18.6 g.) were mixed together. There was no apparent heat of reaction. The solution was heated under reflux for 6 hours and the product was isolated as described in the previous experiments (16.7 g., 95% calc. for trimethylacetanilide). It contained 0.06% phosphorus and had m.p. 132-35° undepressed when mixed with trimethylacetanilide of m.p. 136-7°.

Reaction Between Triphenylacetyl Diethyl Phosphate and Aniline

Triphenylacetyl diethyl phosphate (10.6 g.), aniline (4.2 g.) and ether (50 ml.) were heated under reflux for 48 hours. After removing the ether the residual oil was triturated with water until it solidified (8.9 g.) m.p. 110-14°. This crude product containing 1.80% phosphorus was crystallised from carbon tetrachloride, yield 5.3 g. (57%), small plates m.p. 144-50°. Recrystallisation from cyclohexane, and finally aqueous alcohol, raised the m.p. to 168-71° undepressed when mixed with authentic triphenylacetanilide of m.p. 171-2°. The carbon tetrachloride filtrate from the crystallisation of the crude product was evaporated to dryness, extracted with ether (5 ml.), filtered and again evaporated, leaving a gum (0.6 g., 14.7%) whose infra-red spectrum possessed bands at 1600, 1500, 1420, 1390, 1300, 1290, 1230, 1165, 1040, 985 and 690 cm⁻¹ which were also present in the spectrum of a reference sample of N-phenyl diethyl phosphoramidate.

Reaction Between 2,3,6-Trichlorobenzoyl Diethyl Phosphate and Aniline

2,3,6-Trichlorobenzoyl diethyl phosphate (12.0 g.), aniline (6.2 g.) and ether (75 ml.) were heated under reflux for 18 hours.
After removal of the ether the residual gum was triturated with water and then allowed to crystallise in vacuo. The buff, sticky product (14.8 g.) which contained 5.78% phosphorus, was extracted with boiling carbon tetrachloride (100 ml.) and filtered from an insoluble residue (7.1 g.) m.p. 124-30°. The latter was recrystallised successively from benzene and aqueous alcohol to give needles m.p. 150°. The infra-red spectrum of this product and that of the anilinium 2,3,6-trichlorobenzoate complex were identical. When the two were mixed, there was no depression of m.p. The carbon tetrachloride filtrate was evaporated to dryness, and the residue dissolved in a little ether (discarding the small amount of insoluble residue) and again evaporated to dryness, leaving a gum that solidified after washing with 3N hydrochloric acid, yield 6.4 g., m.p. 50-65° (84%). When mixed with N-phenyl diethyl phosphoramidate of m.p. 92°, it had m.p. 70-85°. The crude product was recrystallised from aqueous alcohol and then ether yielding prisms m.p. 89-91° alone and with N-phenyl diethyl phosphoramidate.

Reaction Between 2,3,5,6-Tetrachlorobenzoyl Diethyl Phosphate and Aniline

2,3,5,6-Tetrachlorobenzoyl diethyl phosphate (4.0 g.), aniline (1.9 g.) in ether (40 ml.) were heated under reflux for 28 hours. Crystals separated during this period; these were removed by filtration. Yield 3.1 g. (91%), m.p. 182-6° undepressed when mixed with an authentic sample of anilinium 2,3,4,6-tetrachlorobenzoate. The infra-red spectrum was also identical to the above anilinium salt. Spontaneous evaporation of the ethereal filtrate afforded prisms. After washing with water yield 2.9 g., m.p. 78-85°, mixed with N-phenyl
diethyl phosphoramidate m.p. 85-90°. Found P, 11.2% ; C_{10}H_{16}NO_{3}P requires P, 13.5%. The infra-red spectrum of this was superimposable on that of an authentic sample of N-phenyl diethyl phosphoramidate apart from a weak, broad band in the carbonyl region, due to anilinium 2,3,5,6-tetrachlorobenzoate. Two recrystallisations of the crude N-phenyl diethyl phosphoramidate from ether gave needles, m.p. 92-95°, undepressed when mixed with an authentic sample of N-phenyl diethyl phosphoramidate m.p. 95-96°.

Reaction Between 2,3,4,5,6-Pentaohlorobenzoyl Diethyl Phosphate and Aniline

2,3,4,5,6-Pentaohlorobenzoyl diethyl phosphate (4.3 g.), aniline (1.86 g.) and ether (50 ml.) were heated under reflux for 48 hours. The ether was evaporated and the solid extracted with hot cyclohexane (50 ml.) and filtered from the anilinium salt, yield 2.7 g. (70%). The needles had m.p. 208-12°, undepressed when mixed with authentic anilinium 2,3,4,5,6-tetrachlorobenzoate. The infra-red spectrum of the latter was identical to the by-product from the reaction. When cold the cyclohexane filtrate deposited crystals, and after washing with water gave 0.9 g., m.p. 92-96° (melting to turbid liquid). The mother liquor was evaporated to dryness, and washed with water to give a second crop 2.3 g., m.p. 92-96° (melting to turbid liquid). Total yield 3.2 g. The infra-red spectrum showed this to be N-phenyl diethyl phosphoramidate, contaminated with anilinium 2,3,4,5,6-pentaohlorobenzoate. Found P, 9.05% ; C_{10}H_{16}NO_{3}P requires P, 13.5%. Recrystallisation from carbon tetrachloride gave prisms m.p. 96° undepressed when mixed with an authentic sample of N-phenyl diethyl phosphoramidate. Yield 1.1 g.
The anhydrides XVII to XXV have in common the structure $(\text{EtO})_2\text{P(O)O(C)}_0$. The important features of this structure, clearly revealed by infra-red spectroscopy, are the phosphoryl and carbonyl groups and the P-O-C unit, of which the P-O-Et grouping is a special case.

The Phosphoryl Group. The absorption of this group sometimes appears as a doublet$^{116,117}$ and it may occur over a very wide range, 1310-1170 cm$^{-1}$, apparently depending neither upon the type of compound nor on the size of the substituents. There is however a definite correlation between $\nu\text{P}=\text{O}$ and the total electronegativity of the substituents$^{118,119}$. The absorption shifts to higher frequencies with increase in the electronegativity of the substituent groups.

The Carbonyl Group. The absorption of this group, when part of a carboxylic acid residue, may occur over the range 1850-1740 cm$^{-1}$. As in the case of the phosphoryl group $\nu\text{C}=\text{O}$ is directly related to the electronegativity of the groups attached to it. Strong electronegative groups increase the absorption frequency of the band$^{47,120}$. 

- 133 -
The P-O-C Group. Alkyl esters of orthophosphoric acid possess a characteristically strong absorption band at about 1050 cm\(^{-1}\) due to the P-O-C bonding. The ethyl esters possessing the structure P-O-CH\(_2\)CH\(_3\) appear to be special cases. They show a sharp band of medium intensity at 1165 cm\(^{-1}\), while the -CH\(_3\) of the ethyl group absorbs in two weak bands at about 1390 and 1370 cm\(^{-1}\). Many organo-phosphorus compounds show a very intense absorption band near 980 cm\(^{-1}\). Bellamy and Beecher have very tentatively associated this with the P-O stretching of the P-O-C linkage.

The infra-red absorption spectrographs of the anhydrides XVII to XXV are recorded and the frequencies of the principal bands tabulated below. The spectra were obtained using a Unicam S.P.500 recording spectrophotometer with a rock salt prism. The compounds were examined in 5% solution in carbon tetrachloride, the path length of the cell being 0.1 mm.
### Principal Absorption Bands

<table>
<thead>
<tr>
<th>Band (cm⁻¹)</th>
<th>Structural Correlations</th>
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</thead>
<tbody>
<tr>
<td>1780</td>
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</tr>
<tr>
<td>1390</td>
<td>Me of EtO-P group</td>
</tr>
<tr>
<td>1370</td>
<td>Me of EtO-P group</td>
</tr>
<tr>
<td>1290</td>
<td></td>
</tr>
<tr>
<td>1200</td>
<td></td>
</tr>
<tr>
<td>1165</td>
<td>P-O-Et</td>
</tr>
<tr>
<td>1100</td>
<td></td>
</tr>
<tr>
<td>1040</td>
<td>P-O-C</td>
</tr>
<tr>
<td>990</td>
<td></td>
</tr>
<tr>
<td>960</td>
<td></td>
</tr>
<tr>
<td>925</td>
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<tr>
<td>825</td>
<td>No (?)</td>
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### Principal Absorption Bands

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<tr>
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<td>Me of EtO–P group</td>
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<tr>
<td>1305</td>
<td>C–F</td>
</tr>
<tr>
<td>1240</td>
<td>C–F</td>
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<td>1180</td>
<td>C–F</td>
</tr>
<tr>
<td>1140</td>
<td>C–F(?)</td>
</tr>
<tr>
<td>1040</td>
<td>P–O–C</td>
</tr>
<tr>
<td>990</td>
<td></td>
</tr>
<tr>
<td>965</td>
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</tr>
<tr>
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<td>820</td>
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### Principal Absorption Bands

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</tr>
<tr>
<td>1470</td>
<td>Me of t-Bu group</td>
</tr>
<tr>
<td>1390</td>
<td>Me of EtO-P group</td>
</tr>
<tr>
<td>1365</td>
<td>Me of EtO-P group</td>
</tr>
<tr>
<td>1285</td>
<td>P=O</td>
</tr>
<tr>
<td>1165</td>
<td>P-O-Et</td>
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<td>1120</td>
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<td>P-O-C</td>
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<td></td>
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<tr>
<td>950</td>
<td></td>
</tr>
<tr>
<td>890</td>
<td>Me of t-Bu group (?)</td>
</tr>
<tr>
<td>825</td>
<td>Me of t-Bu group (?)</td>
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---

*Trimethylacetyl Diethyl Phosphate XIX*
Triphenylacetyl Diethyl Phosphate

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<tr>
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</tr>
<tr>
<td>1600 &quot;</td>
<td>Aromatic C=O stretching</td>
</tr>
<tr>
<td>1500 &quot;</td>
<td>Aromatic C=O stretching</td>
</tr>
<tr>
<td>1450 &quot;</td>
<td></td>
</tr>
<tr>
<td>1395 &quot;</td>
<td>Me of EtO-P group</td>
</tr>
<tr>
<td>1370 &quot;</td>
<td>Me of EtO-P group</td>
</tr>
<tr>
<td>1295 &quot;</td>
<td>P=O</td>
</tr>
<tr>
<td>1165 &quot; (shoulder)</td>
<td>P-O-Et</td>
</tr>
<tr>
<td>1150 &quot;</td>
<td></td>
</tr>
<tr>
<td>1040 &quot;</td>
<td>P-O-C</td>
</tr>
<tr>
<td>985 &quot;</td>
<td></td>
</tr>
<tr>
<td>955 &quot;</td>
<td></td>
</tr>
<tr>
<td>945 &quot;</td>
<td></td>
</tr>
<tr>
<td>830 &quot;</td>
<td>C-H aromatic</td>
</tr>
<tr>
<td>700 &quot;</td>
<td>C-H aromatic</td>
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### Benzoyl Diethyl Phosphate XXI

**Principal Absorption Bands**

<table>
<thead>
<tr>
<th>Frequency (cm⁻¹)</th>
<th>Structural Correlations</th>
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<tr>
<td>1755</td>
<td>C=O</td>
</tr>
<tr>
<td>1600</td>
<td>Aromatic C=C stretching</td>
</tr>
<tr>
<td>1480</td>
<td>Aromatic C=C stretching</td>
</tr>
<tr>
<td>1395</td>
<td>Me of EtO-P group</td>
</tr>
<tr>
<td>1370</td>
<td>Me of EtO-P group</td>
</tr>
<tr>
<td>1295</td>
<td>P=O</td>
</tr>
<tr>
<td>1260</td>
<td></td>
</tr>
<tr>
<td>1245</td>
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</tr>
<tr>
<td>1210</td>
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</tr>
<tr>
<td>1165</td>
<td>P=O-Et</td>
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<tr>
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<td>P=O-C</td>
</tr>
<tr>
<td>990</td>
<td></td>
</tr>
<tr>
<td>960</td>
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</tr>
<tr>
<td>860</td>
<td>C-H aromatic</td>
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<tr>
<td>700</td>
<td>C-H aromatic</td>
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**2,3,6-Trichlorobenzoyl Diethyl Phosphate XXII**

<table>
<thead>
<tr>
<th>Principal Absorption Bands</th>
<th>Structural Correlations</th>
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<tbody>
<tr>
<td>1785 cm&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>C=O</td>
</tr>
<tr>
<td>1440 &quot;</td>
<td>C=C aromatic</td>
</tr>
<tr>
<td>1390 &quot;</td>
<td>Me of EtO-P group</td>
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<td>1370 &quot;</td>
<td>Me of EtO-P group</td>
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<tr>
<td>1300 &quot;</td>
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<tr>
<td>1230 &quot;</td>
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<tr>
<td>1180 &quot;</td>
<td></td>
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<tr>
<td>1165 &quot; (shoulder)</td>
<td>P-O-Et</td>
</tr>
<tr>
<td>1150 &quot;</td>
<td></td>
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<tr>
<td>1040 &quot;</td>
<td>P-O-C</td>
</tr>
<tr>
<td>990 &quot;</td>
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<tr>
<td>960 &quot;</td>
<td></td>
</tr>
<tr>
<td>885 &quot;</td>
<td>C-H aromatic</td>
</tr>
<tr>
<td>825 &quot;</td>
<td>C-H aromatic</td>
</tr>
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</table>
2,3,5,6-Tetrachlorobenzoyl Diethyl Phosphate XXIII

Principal Absorption Bands | Structural Correlations
--- | ---
1780 cm\(^{-1}\) | C=O
1410  | Me of Et-O-P group
1380  | P=O
1305  | P-O-Et
1240  | P-O-C
1175  | (shoulder)
1165  | P-O-Et
1040  | P-O-C
905   |
### Principal Absorption Bands

<table>
<thead>
<tr>
<th>Wavenumber (cm$^{-1}$)</th>
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<td>1775</td>
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<tr>
<td>1370</td>
<td>Me of P-O-Et group</td>
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<tr>
<td>1350</td>
<td>Me of P-O-Et group</td>
</tr>
<tr>
<td>1295</td>
<td>P=O</td>
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<tr>
<td>1245</td>
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<td>(shoulder)</td>
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<td>P-O-C</td>
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<td>820</td>
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<tr>
<td>Principal Absorption Bands</td>
<td>Structural Correlations</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>1775 cm⁻¹</td>
<td>C=O</td>
</tr>
<tr>
<td>1390 &quot;</td>
<td>Me of EtO-P group</td>
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<tr>
<td>1365 &quot;</td>
<td>Me of EtO-P group</td>
</tr>
<tr>
<td>1290 &quot;</td>
<td>P=O</td>
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<td>P-O-Et</td>
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<td>P-O-C</td>
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<tr>
<td>1000 &quot;</td>
<td></td>
</tr>
<tr>
<td>970 &quot;</td>
<td></td>
</tr>
<tr>
<td>830 &quot;</td>
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</table>
Transmission across the oxygen bridge of the inductive effects operating at carboxylic anhydrides and pyrophosphates was discussed earlier (p. 24). The absorption frequencies of the carbonyl and phosphoryl groups of the anhydrides XVII to XXV are obviously related to the acid strength of the carboxylic acid (Table VI). As stated above (p. 133) this is to be expected for the value of $\nu \text{C} = \text{O}$, but, unless the inductive effect operating at the carbonyl group is transmitted across the oxygen bridge to the phosphoryl group, $\nu \text{P} = \text{O}$ should be constant. This is manifestly not the case.

Table VI

<table>
<thead>
<tr>
<th>$pK_\alpha$</th>
<th>$-R$</th>
<th>$\text{C}=\text{O}$</th>
<th>$\text{P}=\text{O}$</th>
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<tbody>
<tr>
<td>5.05</td>
<td>$-\text{CMe}_3$</td>
<td>1760 cm$^{-1}$</td>
<td>1285 cm$^{-1}$</td>
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<tr>
<td>4.92</td>
<td>$-\text{OEt}$</td>
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<td>1290 &quot;</td>
</tr>
<tr>
<td>4.76</td>
<td>$-\text{Me}$</td>
<td>1780 &quot;</td>
<td>1290 &quot;</td>
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<td>4.20</td>
<td>$-\text{Ph}$</td>
<td>1755 &quot;</td>
<td>1295 &quot;</td>
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<td>3.96</td>
<td>$-\text{CPh}_3$</td>
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<td>1295 &quot;</td>
</tr>
<tr>
<td>1.28</td>
<td>$-2,3,6-\text{Cl}_3\text{C}_6\text{H}_2$</td>
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<td>1300 &quot;</td>
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<td>-</td>
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<td>-</td>
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<td>$-\text{CF}_3$</td>
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<td>1305 &quot;</td>
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</table>

The values of $pK_\alpha$ for the tetrachloro- and pentachloro-benzoic acids are not available. They would be expected to be about the same order, or slightly less than that for 2,3,6-trichloro-benzoic acid. However the absorption frequencies for the carbonyl
and phosphoryl groups for tetrachloro- and pentachloro- benzoic acids are not quite consistent; $\nu C=O$ for the tetrachloro compound at $1780 \text{ cm}^{-1}$ being lower than that for 2,3,6-trichlorobenzoyl diethyl phosphate and yet, $\nu P=O$ at $1805 \text{ cm}^{-1}$ is as high as that for trifluoracetyl diethyl phosphate. In the case of pentachlorobenzoyl diethyl phosphate $\nu C=O$ has fallen further with increased chlorine substitution to $1775 \text{ cm}^{-1}$ but there is a parallel decrease in $\nu P=O$ to $1295 \text{ cm}^{-1}$. The position of the carbonyl and phosphoryl frequencies in these compounds would suggest that the tetrachloro- and pentachlorobenzoic acids are weaker acids than 2,3,6-trichlorobenzoic acid. It may be added that the correlation of carboxylic acid strength with $\nu P=O$ adds authenticity to the structure assigned to the anhydrides of this series. Further support for the structure assigned to these compounds is afforded by the bands that are specific for the different R- groups.

Trimethylacetyl diethyl phosphate possesses a tertiary butyl group. Sheppard identified bands at about $1460, 1370, 1240, 1160, 1030, 910$ and $810 \text{ cm}^{-1}$ with the tertiary butyl group. The bands at $1470, 900$ and $825 \text{ cm}^{-1}$ that occur in the spectrum of trimethyl acetyl diethyl phosphate have been assigned to the tertiary butyl group. The remainder, if present, are masked by stronger bands arising from the $(\text{EtO})_2\text{PO}=O$ structure.

The $C=O-C$ band that must be present in the spectrum of ethoxy carbonyl diethyl phosphate is masked by the very strong $P=O-C$ band. In this compound the phosphoryl group absorbs as a doublet at $1290$ and $1260 \text{ cm}^{-1}$. 

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Both benzoyl and 2,3,6-trichlorobenzoyl diethyl phosphate have three strong bands in the phosphoryl region, 1295, 1260 and 1245 cm\(^{-1}\) for the former and 1300, 1260 and 1230 cm\(^{-1}\) for the latter. There is no record of the phosphoryl absorption appearing as a triplet. This phenomenon may be due to a doublet stemming from the phosphoryl group and an aromatic absorption band. However it is interesting to note that this region is not so complex in the case of triphenylacetyl diethyl phosphate.

The last mentioned compound has a strong band at 1150 cm\(^{-1}\) which is also common to the spectrum of 2,3,6-trichlorobenzoyl diethyl phosphate. This band masks the 1165 cm\(^{-1}\) band of the P-O-Et grouping. Pinchas and Samuel\(^{123}\) examined a series of triphenylmethyl compounds and assigned the bands occurring at 1290-1270 cm\(^{-1}\) and 1190-1175 cm\(^{-1}\) to the Ph\(_3\)C- group. In triphenylacetyl diethyl phosphate, the former is masked by the strong P-O band at 1295 cm\(^{-1}\), the latter by the 1165 cm\(^{-1}\) P-O-Et band and the band at 1150 cm\(^{-1}\).

Organofluorine compounds\(^{124}\) are characterised by a series of strong bands over the range 1400-1000 cm\(^{-1}\). The bands at 1244 and 1182 cm\(^{-1}\) in the spectrum of trifluoroacetic acid have been assigned to the C-F bond\(^{125}\). The band at 1140 cm\(^{-1}\) probably arises from the same source. The bands in trifluoroacetyl diethyl phosphate at 1240, 1180 and 1140 cm\(^{-1}\) have been assigned to the C-F bonds. The strong band at 1140 cm\(^{-1}\) masks the P-O-Et band at 1165 cm\(^{-1}\).

2,3,5,6-Tetrachlorobenzoyl diethyl phosphate and 2,3,4,5,6-pentachlorobenzoyl diethyl phosphate have spectra that lack the characteristic C=C skeletal in-plane vibrations 1600-1450 cm\(^{-1}\).
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