Dedicated to my Parents

SOME REACTIONS OF AROMATIC PHOSPHONOUS AND PHOSPHINOUS ACIDS

A thesis submitted to the

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by

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ABSTRACT

Faculty of Science

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SECTION I

The addition of phenyl phosphonous acid PhPH(O)(OH) or $PhP(OH)_2$ is shown to occur at the β— position of sufficiently activated α,β-unsaturated esters (e.g. acetylene dicarboxylic ester) and α,β-unsaturated ketones but at the carbonyl group of aldehydes.

The simplest way of explaining these uncatalysed reactions is to postulate that the acid reacts in the trivalent phosphorus form though it is not detected in the infra-red spectrum. The structures of the compounds obtained have been proved by spectral examinations and by C, H and P analysis.

SECTION II

Cyclic phosphinous acids (phenoxaphosphine oxides) are obtained from the reactions of PCl_3-$AlCl_3$ with diaryl ethers substituted in the p and p' positions. In investigating the scope of this reaction, it has been shown that:

(a) both p and p' positions must be occupied;

(b) not all substituents permit the reaction.

Suitably substituted phenoxaphosphine oxides should be capable of optical resolution and the preparation of two such derivatives has been attempted.

CONTENTS

CHAPTER I

I N T R O D U C T I O N

I N T R O D U C T I O N

HISTORY

The variety of features which phosphorus containing organic compounds display has attracted the attention of research chemists for over a century. Many complex esters and amides of phosphoric and condensed phosphoric acids play an important part in metabolic processes[1]. However, it was not until the beginning of the nineteenth century that a systematic study of organophosphorus compounds was planned. Lassaigne in 1820 and two decades later Thenard and others prepared organic compounds of phosphorus (derivatives of phosphine) containing the carbon-phosphorus bond. Since their pioneer work the chemistry of organophosphorus compounds has developed slowly and at a rapid pace in the last thirty years.

A general survey of the course of this development shows that the bulk of the effort has been directed towards synthetic aspects. The theoretical aspect was not explored and no general and rationalized foundation existed. The outstanding work of Professor C.A. Michaelis and his co-workers and of the Russian chemist Professor A.E. Arbuzov and his school succeeded in establishing the basic principles of the reactions of organophosphorus compounds[2]. British workers like F.G. Mann

and W.G. Davies are outstanding contributors in the study of phosphines and related compounds. Professor A.R. Todd holds the credit of introducing new methods of phosphorylation and achieving the pioneer synthesis of adenosine triphosphate - a constituent of nucleic acids[2].

A look at the literature available in this field reveals that the investigations are mostly directed towards biological and biochemical aspects. The importance of organophosphorus compounds in metabolic processes of life and their applications in industrial and scientific fields is becoming more and more apparent.

Structure and Reactivity of Phosphorus and its Compounds.

The chemical reactivity of phosphorus and its compounds follows closely the electronic structure of the element. It resembles nitrogen in many of its properties, forming compounds similar to amines and their quaternary salts. But since phosphorus is a second row element, it is capable of expanding its octet to a decet, and therefore availability of d-orbitals makes a significant contribution to the chemistry of phosphorus. From the atomic energy level it is evident that the $3s \longrightarrow 3d$ promotional energy in phosphorus (17eV) is much less than in nitrogen (23eV).[3] Therefore in phosphorus the contribution of higher energy states results in reduced electronegativity and higher polarisability of the phosphorus atom. These differences therefore account for different behaviour of phosphorus and nitrogen compounds.

The electronic configuration in the valence shell of phosphorus is ——— $3s^2 3p^3$, consequently a covalency of three is expected and hence all trivalent phosphorus compounds e.g. R_nPH_{3-n} and R_nPX_{3-n}, are stable compounds possessing an unshared pair of electrons.

The characteristic feature of the second row elements is their possession of a weak $p_\pi - p_\pi$ bonding system while a strong p_σ bond exists. Hence as compared to nitrogen, phosphorus does not normally form $p_\pi - p_\pi$ bonded structures. As all the trivalent phosphorus compounds possess an unshared electron pair,

they tend to be nucleophilic. The low ionisation potential of the 3s electrons and the ease of formation of sp^3 bonds in the products enhances the nucleophilicity. On the other hand, the bigger radius and high polarisability of the phosphorus atom tend to make it electrophilic, as it exerts low electronic repulsion towards nucleophilic reagents. Phosphorus therefore shows extremely rapid displacement reactions and most trivalent phosphorus compounds are very rapidly oxidised.

Nucleophilic reactions of trivalent phosphorus lead to three types of compounds[3]:

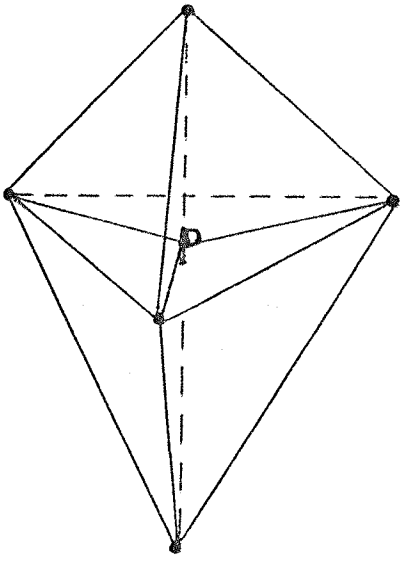
(a) Quaternary phosphonium or quasi phosphonium compounds, e.g. $PA_4^+X^-$ using sp^3 bonding only

(b) Phosphoryl, thiophosphoryl compounds, phosphinimines and phosphine methylenes $R_3P^+ \!\!-\!\!- A^-$, possibly with an sp^3 bonding together with a $p_\pi - p_\pi$ bonding

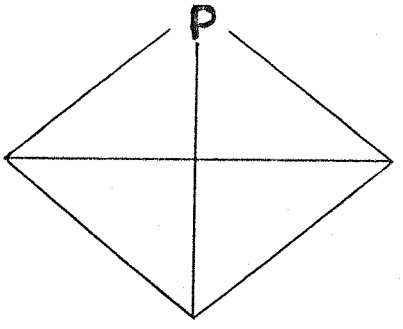
(c) 5- or 6- co-ordinated compounds involving d bonding.

In order to form a pentavalent phosphorus compound it is necessary to uncouple the s electrons, the Pauli principle requiring that one of the s electrons be promoted to a higher energy level, i.e. the d level of the same shell. The energy required for this promotion is of the order of 200 kcal/mole for phosphorus[4], which is recovered during the process of chemical combination and the resulting hybrid orbital appears to possess a lower energy. Such compounds are usually formed

from dsp^3 hybridized orbitals and have a trigonal bipyramidal structure e.g. phosphorus pentaphenyl Ph_5P (I), whereas the trivalent compounds are pyramidal (II) and in contrast to amines may be prepared in optically active forms, indicating that the pyramid is stable and does not invert at room temperature.



I



II

The nucleophilic reactions of trivalent phosphorus are among the most important and widely studied in the field of organophosphorus chemistry.

The greater nucleophilicity of phosphorus arises from the greater polarisability of the lone pair of electrons. Trivalent compounds are strong nucleophiles both towards electron deficient

centres e.g. R.COX, $R_2P(O)X$ etc. and electronically saturated centres e.g. RCH_2X, R–S–X etc. When a good leaving group is present, the trivalent phosphorus acts as an electrophile. This amphoteric behaviour which is very pronounced in phosphorus results from its high polarisability due to which it shows less repulsion energy towards the approaching nucleophile[5].

Among the trivalent phosphorus compounds, the trialkyl phosphites are powerful nucleophiles, and their reactions have been widely studied. It has been shown that the nucleophilic reactivity of these compounds is steric as well as controlled by the combined inductive effects of the substituents[6]. According to Kabachnik the reactivity decreases in order of MeO > EtO > n-PrO > n-BuO,[7] the reverse order is expected if the inductive effect is the only factor involved. Tritert-butyl is the strongest nucleophile as shown by Mark and van Wazer[6].

In case of primary and secondary phosphines, we see that these are strong nucleophiles if a proton is removed, i.e. a basic phosphide anion is formed which is capable of attacking an ether linkage displacing an alkoxide anion[8], and unactivated aromatic halogen compounds to displace bromide or iodide ions[9],

$$Ph_2P^-Na^+ \quad + \quad \text{  } \longrightarrow Ph_2P(CH_2)_4O^-Na^+$$

$$Ph_2P^-Li^+ \quad + \quad Ar \overset{\frown}{-} X \longrightarrow Ph_2P{-}Ar \; + \; LiX$$

X = Br or I ; Ar = p-tolyl, m-tolyl, p-biphenyl, p-diphenyl phosphinophenyl.

Phosphine is a very weak acid with a pK_a of 29. Its derivatives having aromatic substituents are much more acidic than the alkyl substituted phosphines. A second class of compounds with P–H bond(s) is the lower oxyacids and their derivatives. All these compounds have the phosphoryl form, $R_2P(O)H$, which is more electronegative than the trivalent phosphines and hence compounds containing the phosphoryl form $R_2P(O)H$ are more acidic. These compounds are prepared from reactions in which one would expect the structure $R_2P–OH$.

$$R_2PCl \xrightarrow{NaOH} R_2P–OH \longrightarrow R_2P(O)H$$

$$RPCl_2 \longrightarrow RP(OH)_2 \longrightarrow \begin{matrix} R & & O \\ & \diagdown\ \diagup\!\!= & \\ & P & \\ HO & \diagup\ \diagdown & H \end{matrix}$$

The question of this tautomeric (keto–enol) equilibrium in the chemistry of dialkyl phosphonates (III) and aryl phosphinic acids (IV) has been exhaustively studied and clarified in recent times by kinetic studies of deuterium exchange and oxidation reactions[10].

$$(RO)_2\overset{\overset{O}{\|}}{P}–H \rightleftharpoons (RO)_2\overset{\overset{OH}{|}}{P}: \qquad \text{(III)}$$

$$Ph–\overset{\overset{O}{\|}}{\underset{\underset{OH}{|}}{P}}–H \rightleftharpoons Ph–\overset{\overset{OH}{|}}{\underset{\underset{OH}{|}}{P}}: \qquad \text{(IV)}$$

Although these compounds are largely pentavalent (keto) by spectral measurements, their exchange and oxidation reactions evidently proceed by prior enolization to a trivalent phosphite form. Nylen (1938) found that the oxidation of phosphonates to

phosphates by halogen was independent of the concentration of the oxidising agent[11]. This led him to suggest that in the above tautomerism the phosphite form is the active form which undergoes the oxidation. Luz and Silver (1961) studied the kinetics of the acid catalyzed exchange of the phosphorus bonded hydrogen in several dialkyl phosphonates. They found that the exchange reaction follows the same rate law as that for oxidation[10] i.e.

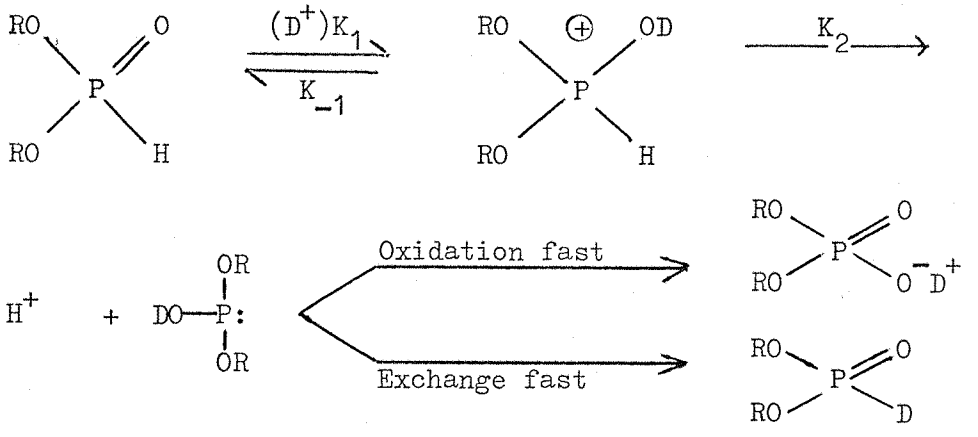
$$k = \frac{R}{[\text{phosphate}]} = k_w + k_H [H^+]$$

where R = Reaction rate

k_w = Catalysis constant for the spontaneous, acid independent exchange

k_H = Catalysis constant for the hydrogen (deuterium) ion exchange

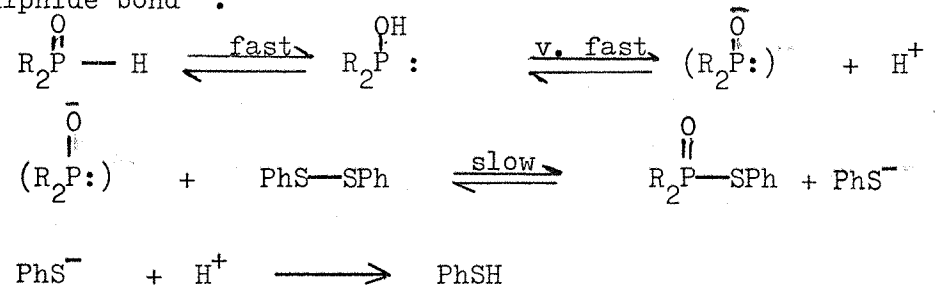
They suggested a general scheme for the acid catalyzed oxidation and exchange reactions,



SCHEME 1

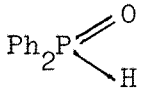
The first step shows that protonation of the phosphoryl group, which is followed by the fission of the P—H bond results in the formation of the active phosphite form of the phosphonate. This phosphite form is extremely reactive, being readily oxidised. In the absence of an oxidising agent, the phosphite form captures a proton from a suitable donor and reverts to the phosphonate form. Not only have oxidation reactions supported the existence of tautomeric forms of (III) and (IV) but also NMR studies done on the exchange of phosphorus bonded hydrogen in dialkyl phosphonates[12]. In the acid catalyzed oxidation of diethyl phosphonate, a kinetic isotope effect (k_H/k_D) of 4 (as compared to a theoretical maximum of 5.3)[12] was observed on substituting deuterium for phosphorus bonded hydrogen. This effect clearly shows that the rate determining step in the phosphite formation is the fission of the P—H bond.

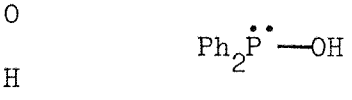
Grayson et al. observed in the reactions of secondary phosphine oxides with disulphides a rapid enolization of the P=O bond giving the active form prior to the cleavage of the disulphide bond[13].

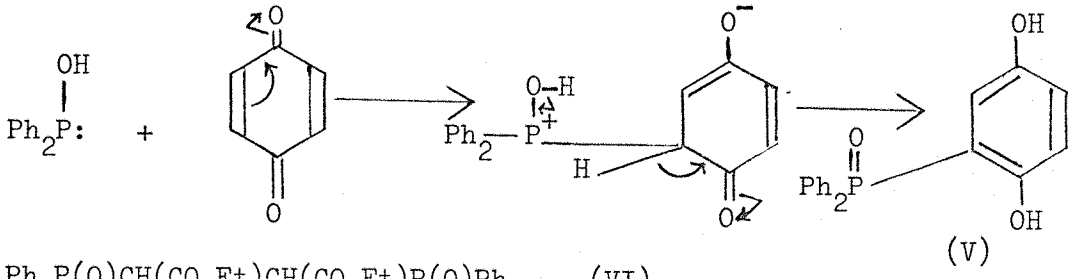


SCHEME 2

A similar observation was made by Campbell and Stevens on the addition reactions of secondary phosphine oxides[14]. Diphenyl phosphine oxide adds to quinone to give high yields of the mono adduct (V), and a di adduct (VI) with ethyl acetylene dicarboxylate. To explain these uncatalyzed addition reactions, they postulated that the oxide reacts in the trivalent phosphite form,



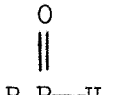




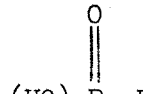
(V)

$Ph_2P(O)CH(CO_2Et)CH(CO_2Et)P(O)Ph_2$ (VI)

All these observations made by several workers clearly prove the hypothesis that a tautomeric equilibrium exists in the structures of (III) and (IV). Analogy between (III) and (IV) and secondary phosphine oxides (VII) has been cited in view of their common structural relation to phosphorous acid, H_3PO_3 (VIII),[13]



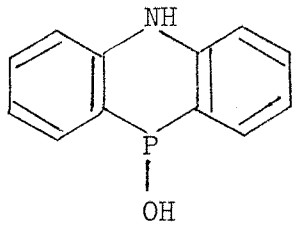
(VII)



(VIII)

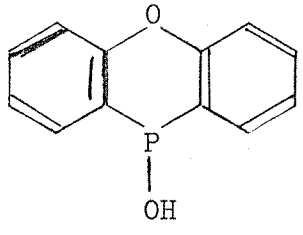
The failure to produce such evidence through spectroscopic investigations is due to the fact that the enol form is not present in a high enough concentration.

Few heterocyclic phosphine oxides are known, although in 1890 Michaelis[15] prepared the phosphazine, (IX), by reaction



(IX)

of PCl_3 on diphenylamine, a reaction which has been studied more recently by Häring[16]. With diphenyl ether, however, the Friedel-Crafts reaction does not introduce phosphorus into the ortho position to give the cyclic compound (X), unless



(X)

both p-positions are occupied[17]. This reaction has not been studied to any extent.

CHAPTER II

RESULTS AND DISCUSSION

EXPERIMENTAL

RESULTS AND DISCUSSION

Phenyl phosphonous acid is prepared by the hydrolysis of phenyl dichlorophosphine, $PhPCl_2$ and would therefore be expected to have the structure, $PhP(OH)_2$. As already stated the acid is monobasic and the phosphorus is in 4-covalent form, structure IV, p-7 .

In order to discover if the acid could react in the "enol" form, $PhP(OH)_2$, we have examined its addition to aldehydes, α,β-unsaturated ketones and esters, maleic anhydride, and phenyl and diphenyl acetylenes.

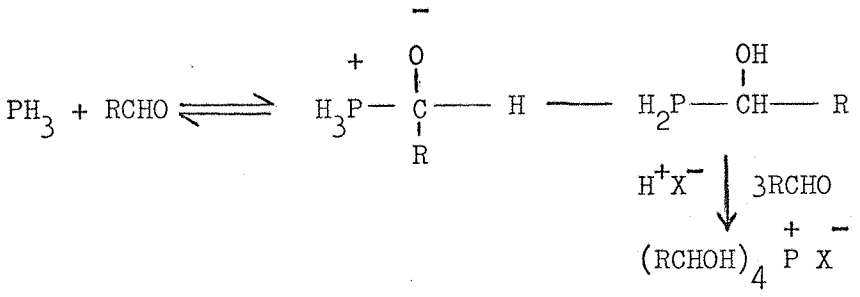
(i) With Aldehydes

The reaction of phenyl phosphonous acid with benzaldehyde and α,β-unsaturated aldehydes results in ready addition at the carbonyl carbon. These reactions appear to be similar to the formation of adducts between aldehydes and amines e.g. aldehyde ammonias, but in this case further reaction occurs to give the imines (Schiff's bases) I, owing to the strong π-bond energies of the nitrogen compound.

$$RCHO + NH_3 \qquad R-\overset{\overset{H}{|}}{\underset{\underset{NH_2}{|}}{C}}-OH \qquad RCH=NH$$

I

With phosphines, however, similar reactions are not observed because of their low basicity and little tendency to form $p_\pi - p_\pi$ bonds. Phosphine reacts with aliphatic aldehydes in strong acid solutions to give quaternary phosphonium salts II,[18]



II

Phosphine reacts in an analogous manner with dry formaldehyde at 100° under pressure, to give trihydroxymethyl phosphine, III;

$$PH_3 + 3CH_2O \longrightarrow P(CH_2OH)_3$$

III

The reaction can be carried out with aryl phosphines,[19] phenyl phosphine for example, gives unsymmetrically substituted compounds and simple aldehydes give $(RCHOH)_4P^+ X^-$. The use of ∝ -branched aldehydes is unsatisfactory for the preparation of this type of quaternary salt.[20]

The reactions of compounds containing the P(O)H group with various aldehydes have been thoroughly investigated. Abramov[21] reported the addition of dialkyl phosphites to the carbonyl groups of simple aldehydes, to give dialkyl 1-hydroxy phosphonates,

$$(RO)_2P(O)H + R'CHO \longrightarrow (RO)_2P(O)CHOHR'$$

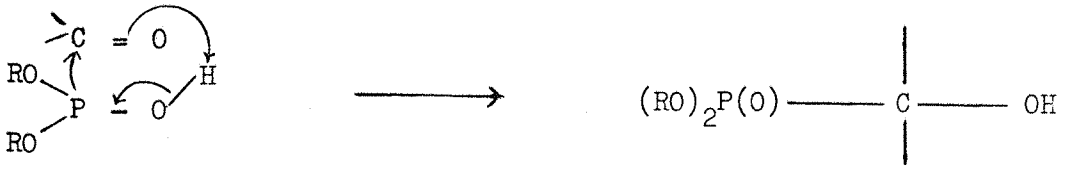
These reactions require a catalytic amount of strong base to form the active species,[22] the anions, which are nucleophiles

usually at phosphorus rather than at oxygen. In a few cases, however, addition occurs in the absence of a base. A strong electrophilic aldehyde such as chloral reacts with the neutral species at room temperature

$$(RO)_2P\text{-}OH + CCl_3CHO \longrightarrow (RO)_2\overset{O}{\overset{\|}{P}}\text{-}CHOHCCl_3$$

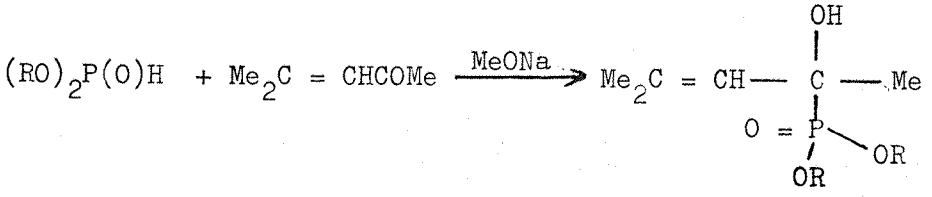
It is suggested that in the above reaction, the dialkyl phosphite reacts in the trivalent form $(RO)_2P\text{-}OH$, and that the rate of reaction with the small proportion of the phosphite form is large enough with a very reactive species.

Addition of dialkyl phosphites to aldehydes generally occurs at the carbonyl carbon, which is represented diagrametically[5] as follows,



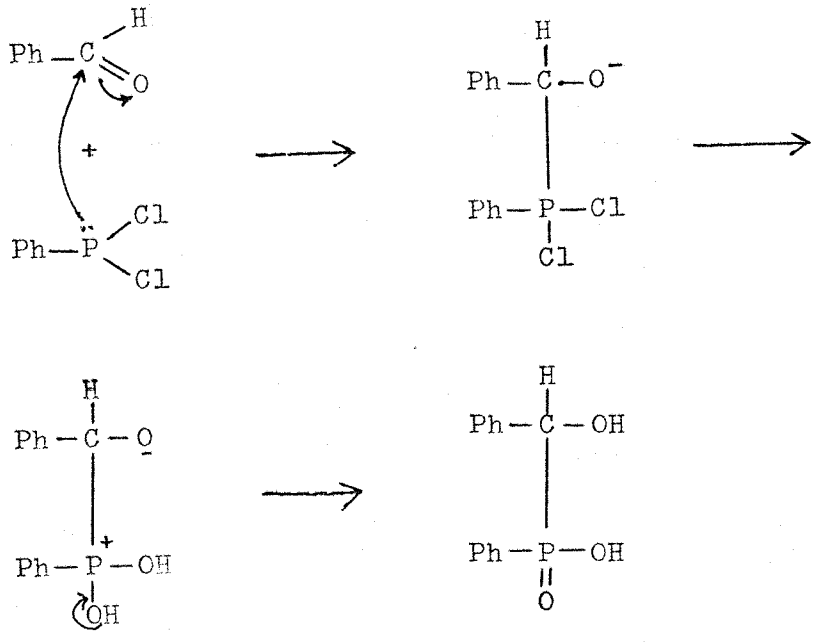
In the above mechanism a proton transfer takes place in order to stabilise the adduct from dialkyl phosphite.

Addition reactions of dialkyl phosphites to α,β-unsaturated carbonyl compounds is usually at the β-carbon atom, but if the vinyl group bears two substituents, for example in the case of mesityl oxide, or if the carbonyl group is aldehydic, phosphorus adds to the carbonyl carbon.



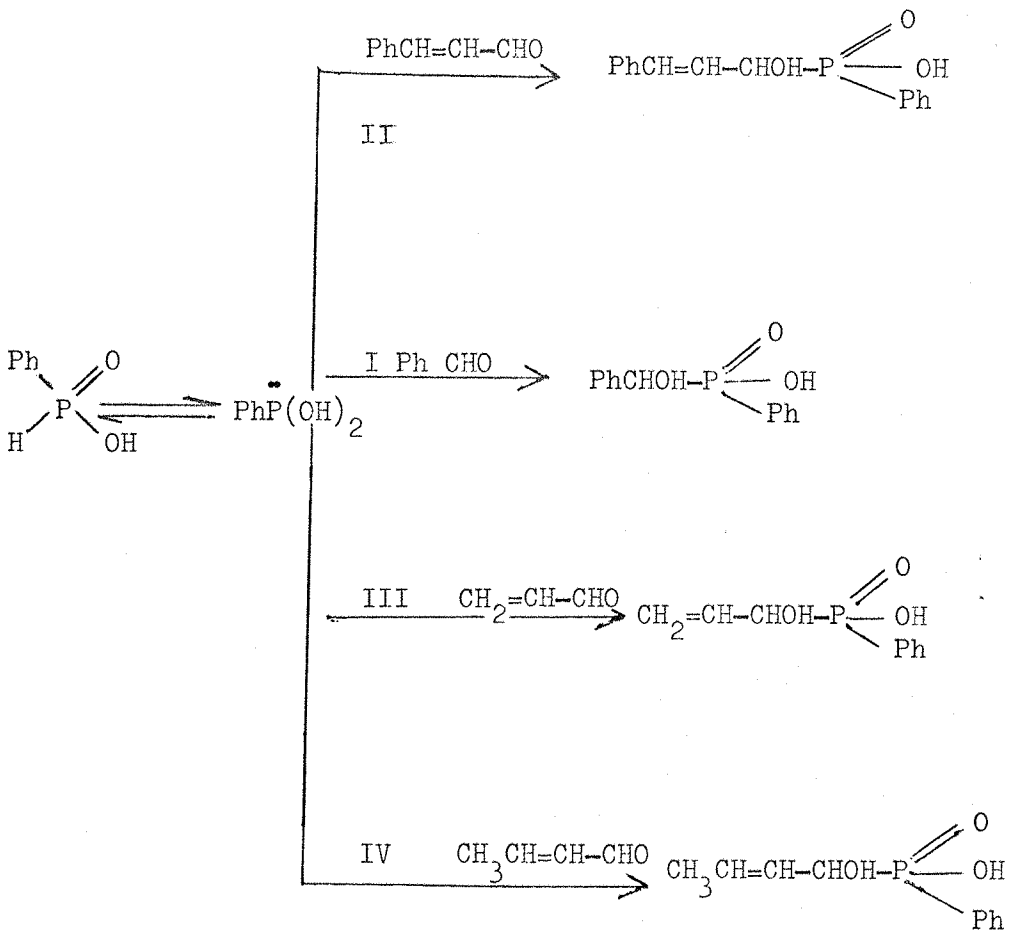
We have found that the reaction of phenyl phosphonous acid with simple or α,β-unsaturated aldehyde is invariably an addition at the carbonyl carbon, and that no catalyst is necessary for these addition reactions. The adducts obtained from these reactions have been listed on page 17 . The above mentioned reactions clearly suggest that the phosphorus reacts in the trivalent form. The presence of a reactive substrate enhances the reactivity of a small proportion of the phosphite form.

A similar reaction of trivalent phosphorus was studied by Michaelis in 1896,[23] while investigating the addition reactions of phenyl dichlorophosphine. He observed that this compound adds readily to benzaldehyde, and he was able to isolate the phosphinic acid derivative on treatment of the addition product with water.



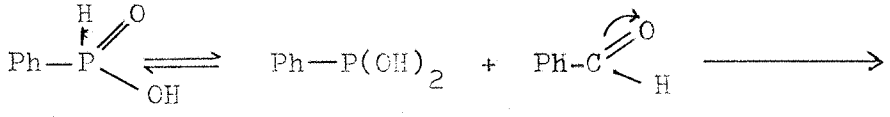
Phenyl (1-hydroxy-benzyl)phosphinic acid

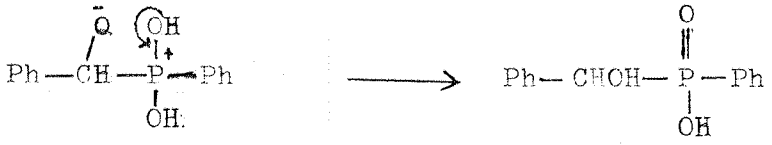
TABLE I



Addition of phenyl phosphonous acid to simple and α,β-unsaturated aldehydes.

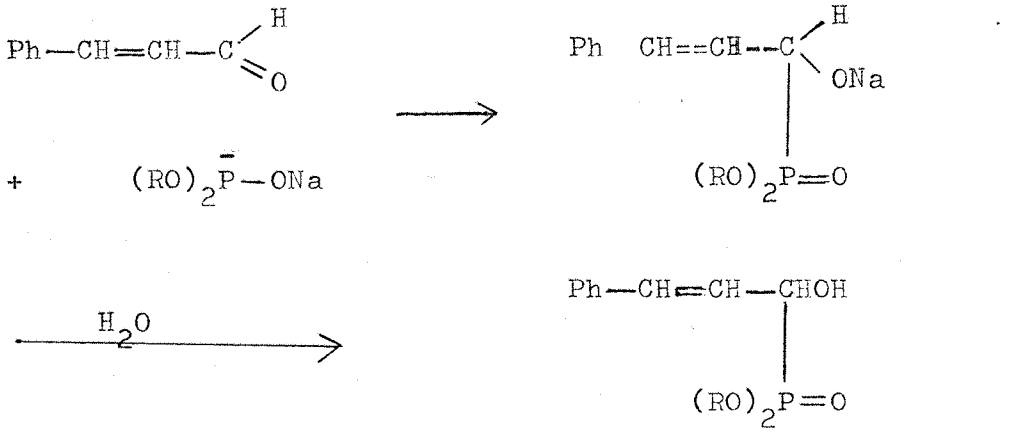
Michaelis reported the melting point of this compound as 112-114°. We found that phenyl phosphonous acid too reacts rapidly with benzaldehyde at the boiling point and adds on to the carbonyl carbon giving a product similar to that which Michaelis obtained. The mechanism of this could be interpreted in terms of nucleophilic addition at the carbonyl carbon followed by the transfer of a proton to stabilise the adduct,





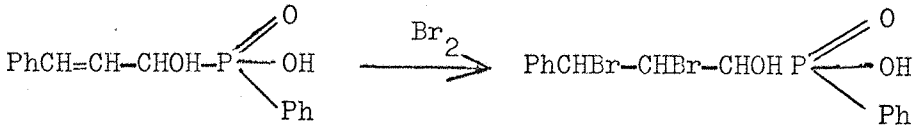
The phosphinic acid obtained in this reaction, however, has a melting point of 200-202°. Elemental analysis and the infra-red absorption spectrum confirm the structure of this compound. The intermediate involved is a zwitter ion which rapidly rearranges by the transfer of a proton.

Neutral dialkyl phosphites add very slowly to unsaturated systems but in the presence of base (usually the alcoholates of alkali metals) show a rapid addition to the carbonyl carbon of the α,β-unsaturated aldehydes.[24]



Phenyl phosphonous acid adds to α,β-unsaturated aldehydes in the absence of base, through a bipolar intermediate. The yields however differed in each case and with acrolein the yield of the product was poorest (26.5%), probably because the rate of polymerisation of acrolein is faster than that of the addition of phosphorus at the temperature of the steam-bath. The fact that the addition occurred at the carbonyl carbon was proved by the appearance of a sharp hydroxyl band at 3300 - 3400 cm^{-1} in the infra-red absorption spectrum of each adduct. Moreover, in the case of cinnamaldehyde adduct, the unsaturation was proved

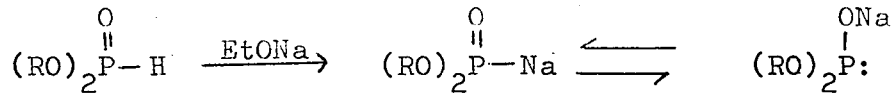
by the formation of a dibromo adduct without the evolution of hydrogen bromide.

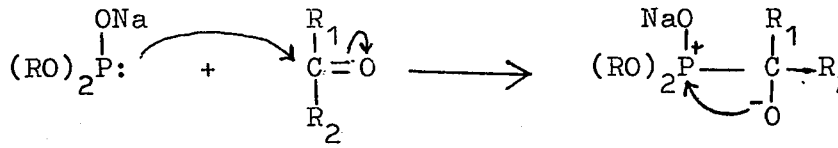


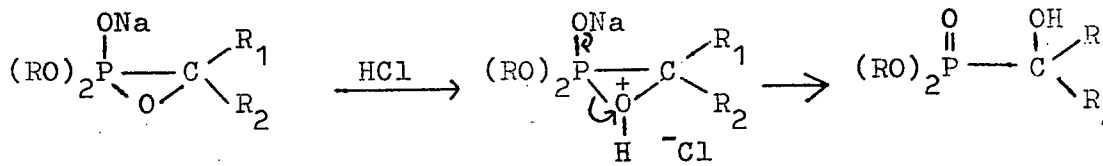
The addition to acrolein and croton-aldehyde occurred through the same mechanism.

(ii) With α - β -unsaturated ketones.

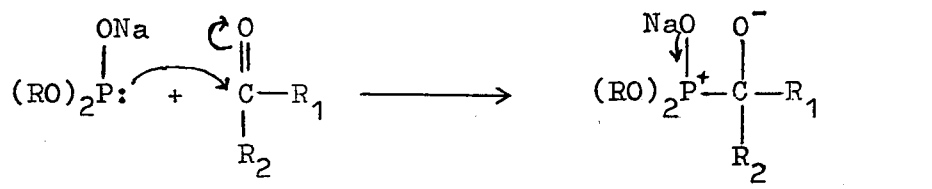
Abramov[27] observed that the addition reactions of dialkyl phosphites to ketones in presence of a catalytic amount of base went through a mechanism where the unshared electron pair of the trivalent phosphorus attacks the electrophilic carbon of the carbonyl group, to yield a positive central phosphorus atom to which the negative ion adds in completion of the reaction. Hydrolysis with acid then cleaves the intermediate giving the hydroxyphosphonate. The mechanism which Abramov suggested can be written in the following way:

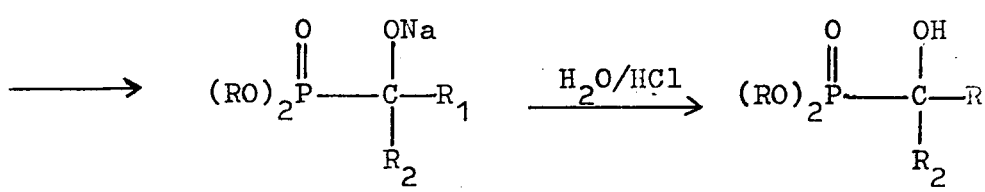




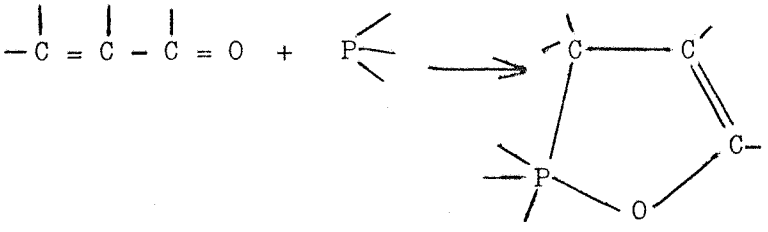


In another mechanism Abramov suggests the following path for the nucleophilic attack and subsequent formation of the adduct,



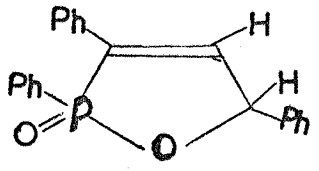


In 1920 Conant and Pollack[25] studied the addition reactions of trivalent phosphorus with α,β-unsaturated ketones. They suggested combination involves the formation of a ring containing a pentavalent phosphorus as one of its members.



These authors used PCl_3 and $PhPCl_2$ in reactions with benzalacetophenone and their inference was mainly based on the formation of a stable dibromo derivative, which proved the existence of a double bond in the intermediate, and subsequent isolation of a mono bromophosphinic acid by hydrolysis. Phenyl phosphonous acid readily combines with benzal acetophenone giving phenyl(1-phenyl-2-benzoyl ethyl) phosphinic acid (V) in a very good yield and also the cyclic phostone (IV), which Conant and Pollack had failed to isolate. Carbon, hydrogen and phosphorus analyses proved the molecular formula of both the ketophosphinic acid, (V), and the phostone, (IV). The infra-red absorption spectrum of the acid clearly indicates the structure by the presence of a strong carbonyl absorption at 1690 cm^{-1} and the broad bands characteristics of a phosphinic acid at 2200 - 2400, 2600-2800 cm^{-1}. In the phostone, however, the normally strong absorption of an enol ether in the 1600 cm^{-1} region was much weaker than expected.

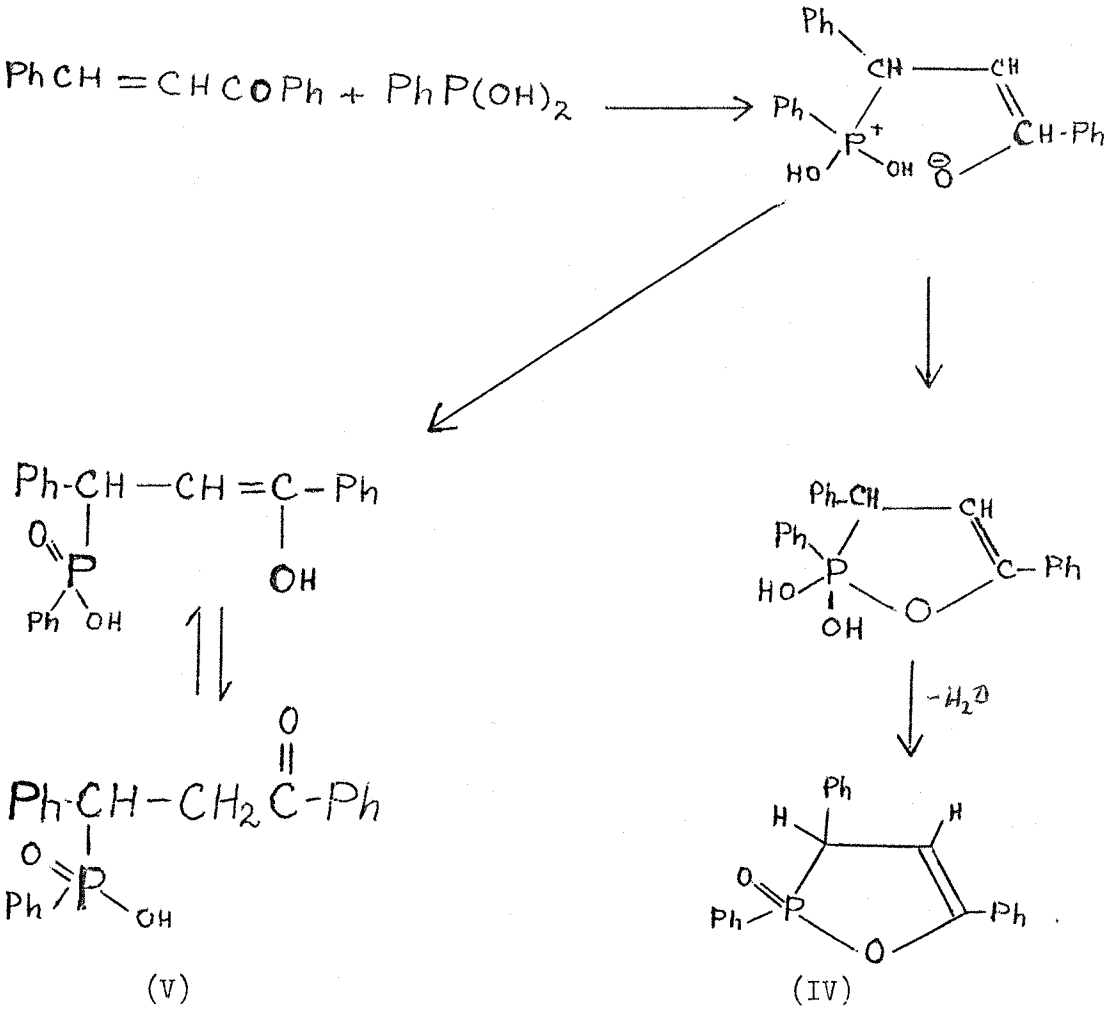
Consequently we originally thought that this structure (IV) could not be present and considered the formation of the isomeric phostone, (VI),



(VI)

The hydrolysis of the phostone to acid rules out this possibility.

The formation of ketophosphinic acid and the neutral phostone appear to follow two different mechanisms from one dipolar intermediate. In one case, there is transference of a proton from the hydroxyl group on the positively charged phosphorus to the oxygen of the carbonyl group to give the enol form of the ketophosphinic acid. But together with this there is an equal possibility of the negative oxygen bonding with phosphorus to give a cyclic pentavalent phosphorane. Loss of a molecule of water from the pentavalent intermediate yields the phostone,

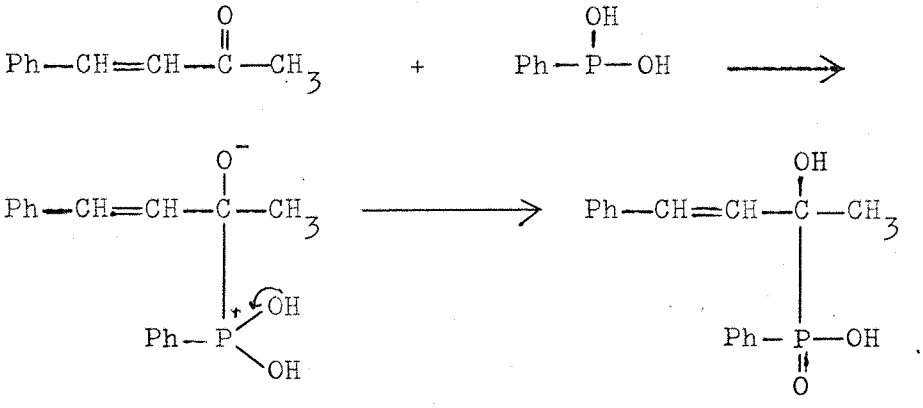


(V) (IV)

The yields of the acid and the cyclic phostone suggest that the two mechanisms are competing with each other, but since the acid (V) is obtained in slightly better yield it suggests that proton shift predominates. That this cyclic phostone behaves like a lactone was proved by its ready hydrolysis with mild alkali when the ketophosphinic (V) was obtained on acidification. An attempt to obtain the methyl ester from the phostone by the reaction of dimethyl sulphate in the presence of alkali failed and the ketophosphinic acid was obtained in quantitative yield. If, however, the phostone was boiled with water, no hydrolysis occurred and it was recovered intact.

The susceptibility of the phostone shows the ready hydrolysis of the P - O - C linkage particularly in a five-membered ring,[5] giving rise to the enol form of the acid which ultimately reverts to the stable keto form.

A similar reaction studied on benzylidene acetone gave a very interesting result. The reaction which failed in neat condition was, however, successful when dry benzene was used as a solvent. The failure of this reaction was because of ready polymerisation of benzylidene acetone, which was, however, not so rapid in a non-polar solvent. The acid obtained in this case was an α-β-unsaturated hydroxy-phosphinic acid (VII). The formation of this acid proves that in this instance there is a nucleophilic attack on the carbonyl carbon and not on the β-carbon atom as we saw in the previous case.

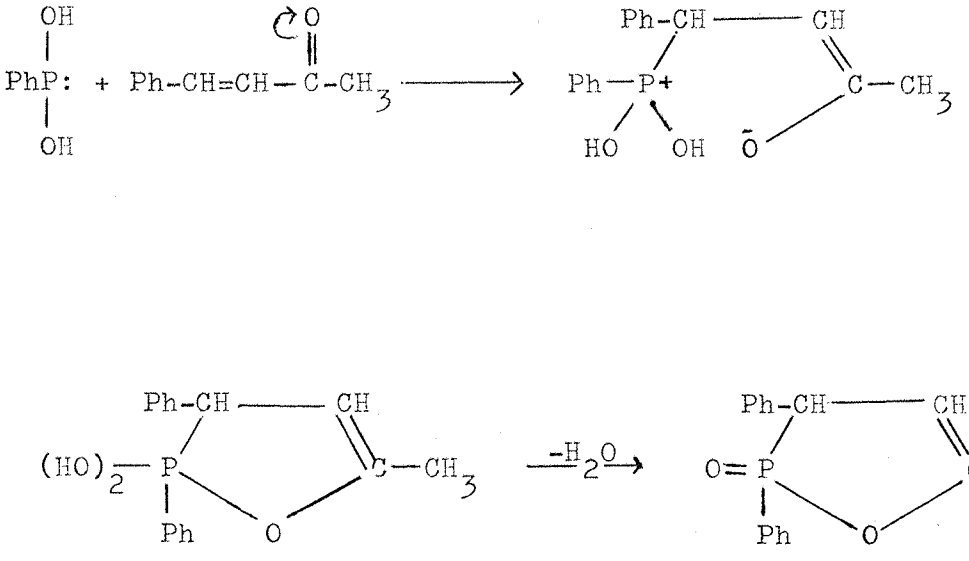


(30%)

(VII)

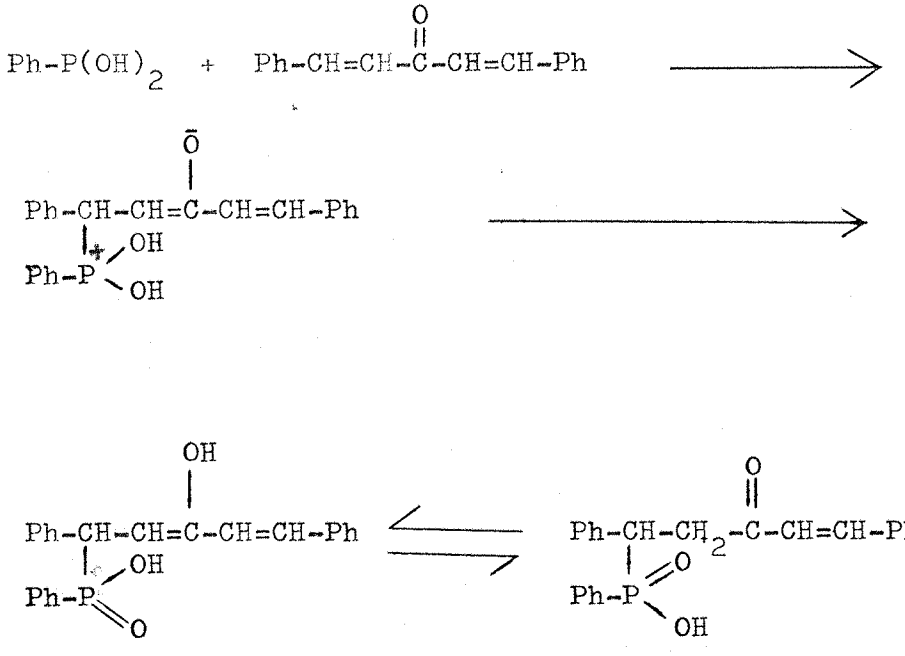
The infra-red absorption spectrum and the elemental analysis confirm the structure (VII) of the hydroxy phosphinic acid. Obviously in the formation of the acid there is no steric hindrance at the carbonyl to the approach of the nucleophile as compared to the formation of adduct at the β -carbon atom in the case of benzylidene acetophenone, where there is a reduction of the electrophilic power of the carbonyl carbon because of the presence of an aromatic ring which allows the electron deficiency to be delocalised into the aromatic ring. This reduction in the electron deficiency at the carbonyl carbon reduces its attraction for a nucleophilic species. Therefore, we have an attack on the β -carbon atom in benzylidene acetophenone. Because of the presence of a methyl group, the electrophilic power of the carbonyl carbon is not so much reduced and hence the approaching nucleophile does not experience any hindrance, and the formation of the adduct at the carbonyl carbon takes place easily.

However, the mechanism stated above, cannot explain the formation of the cyclic phostone (VIII) which was obtained in 35% yield together with the hydroxy phosphinic acid. It seems obvious that besides attacking the carbonyl carbon, the nucleophile is also attacking the β -carbon atom of the α-β -unsaturated system, giving an intermediate similar to the one suggested earlier.



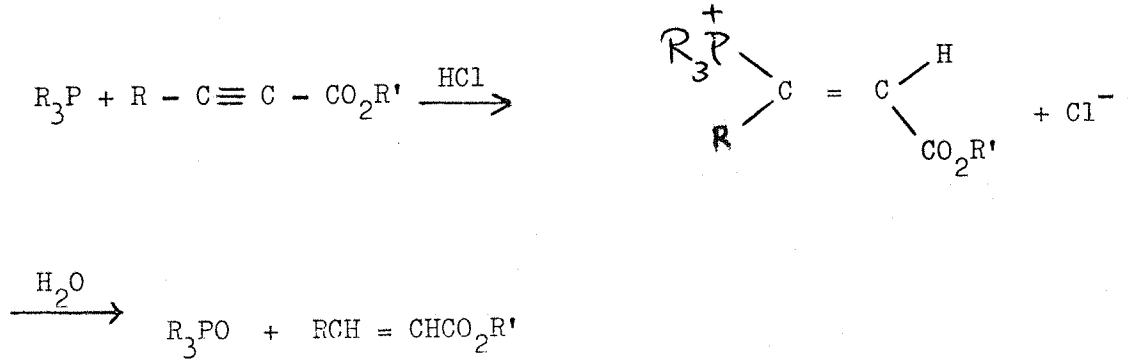
(VIII)

If this mechanism could be taken for the explanation of the formation of the cyclic phostone, it does not, however, explain the non-formation of the ketophosphinic acid which should be formed by the reversion of the enol form into the more stable ketophosphinic acid as in the previous case. The reaction of phenyl phosphonous acid with distyryl ketone provided yet another example of nucleophilic addition to the β -carbon. The formation of this mono-adduct can be summarised in the following scheme.



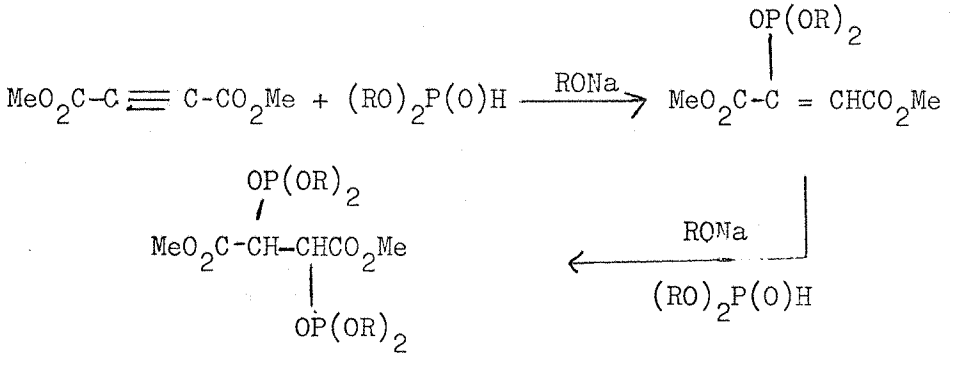
(iii) With acetylenes.

The addition of tertiary phosphines to acetylenic systems in the presence of mineral acids has been studied. Triphenyl phosphine adds smoothly to these systems to give phosphonium salts,[26]

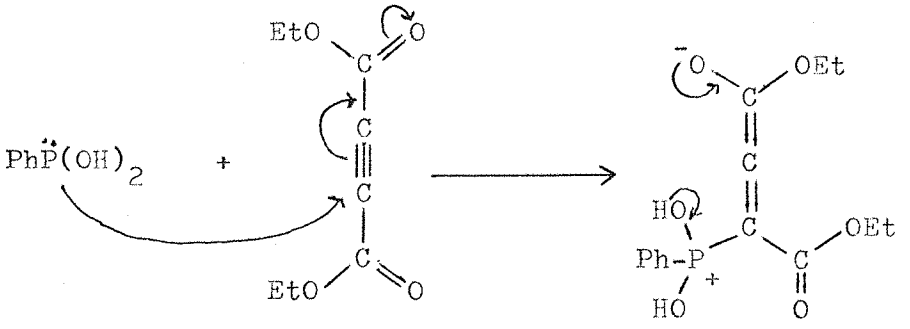


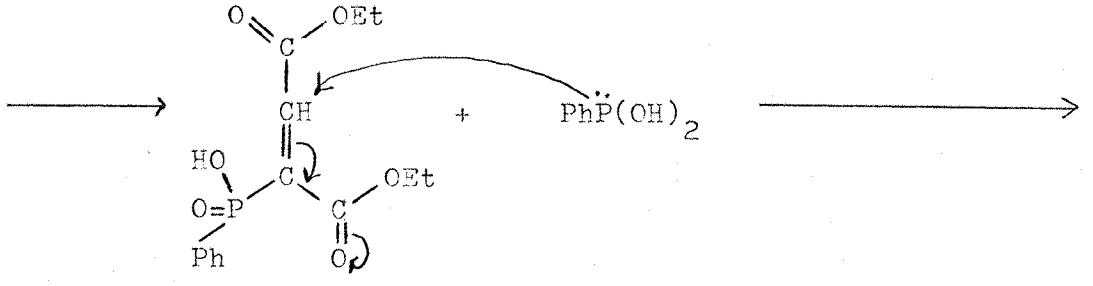
In this reaction the negative charge displaced by the attack of the phosphine is neutralised by protonation. This phosphonium salt, however, on hydrolysis decomposes into phosphine oxide and α,β-unsaturated ester.

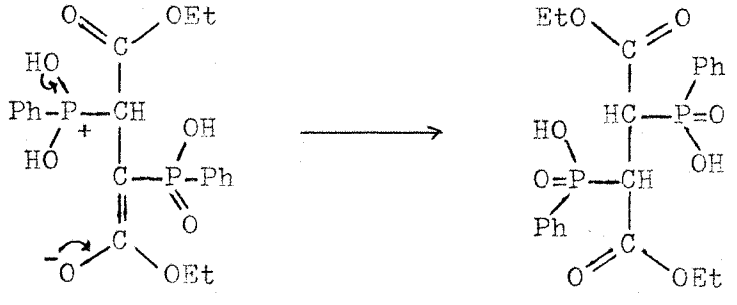
The addition of dialkyl phosphites to acetylenic esters occurs in the presence of base and products of bis-addition are formed.[27]



Phenylphosphonous acid reacts readily with such a system in the absence of a catalyst. We studied the addition of this compound to acetylene dicarboxylic ester and isolated the bis-addition product in 68% yield although the reagents used in each batch of preparation were in equimolecular proportion.





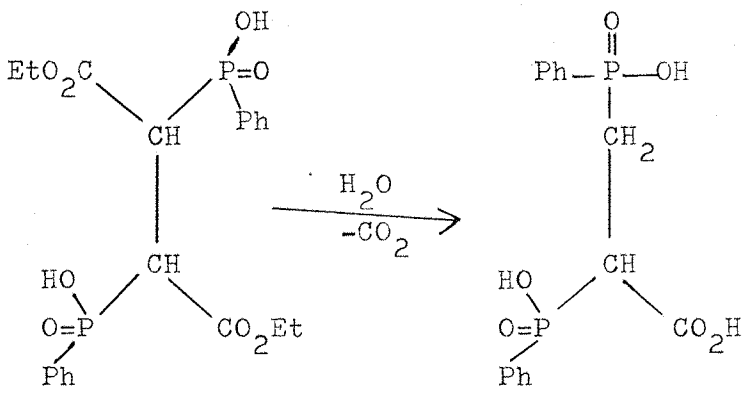


In this addition reaction, as is evident from the suggested mechanism, the electron withdrawing $-CO_2Et$ group plays an important part in the delocalisation of the negative charge developed on the second carbon atom. Although the mechanism suggests the formation of a bipolar intermediate, the charges are, however, dispersed on phosphorus and oxygen of the carbonyl group, so that we have an allene type of intermediate. Transfer of a proton from the intermediate converts the allene system into the mono-adduct of the α,β-unsaturated dicarboxylic ester in the first step. This mono-adduct has three electron-withdrawing groups in the vicinity of the double bond and hence provides a very favourable site for another nucleophilic attack by a second molecule of phenyl phosphonous acid giving the final bis-addition product.

The suggestion that an allene system is involved as an intermediate is strongly supported by the failure of the formation of any adduct with phenyl and diphenyl acetylenes. In both cases the reactants were regained in quantitative yield. Obviously the formation of an allenic intermediate is not possible in phenyl and diphenyl acetylenes.

Hydrolysis of the ester was never perfectly achieved. An attempt to hydrolyse the ester into the corresponding dicarboxylic acid in alcoholic sodium or potassium hydroxides immediately resulted in the separation of sodium salt of the phosphinic acid which on treatment with water gave the unchanged

carboxylic ester. However, after hydrolysis with aqueous sodium hydroxide (2.5N), an acid could be isolated which on analysis gave a rather high percentage of hydrogen, although the percentages of carbon and phosphorus found was consistent with the formula of a mono-carboxylic acid formed by decarboxylation. The infra-red absorption spectrum could provide little information about the acid, though the shift in the sharp peak of the carbonyl group of ester from 1740 cm^{-1} to a broad peak at 1680-1700 cm^{-1} in the acid suggested a change. The peak in the region of 3100 - 3000 cm^{-1} is broad and shallow showing hydrogen bonded hydroxyl groups, when taken in hexachlorobutadiene mull.



The acid has a melting point of 198 - 200° and on taking the melting point of the admixture with IX there was a depression of 5 - 7° in the melting point of the acid. On these observations, one could conclude that the product is a monocarboxylic acid formed by a decarboxylation of the type characteristic of β -keto acids.

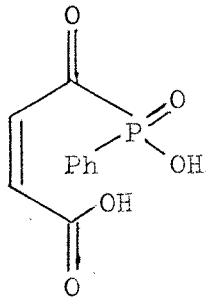
(iv) With maleic anhydride.

The reaction of phenyl phosphonous acid with maleic anhydride provides yet another variation. We expected addition at the β -carbon atom but the product was not an anhydride but an acid which was found to be highly insoluble in organic solvents and could only be rather incompletely purified by solution in bicarbonate and reprecipitation. Whereas the analysis for carbon was very low, the percentage of hydrogen and phosphorus were in agreement with the assigned structure, which was arrived at mainly through ultra-violet and infra-red spectra.

The infra-red spectrum shows a sharp peak at 1185 cm^{-1} due to P = O, a medium peak at 1640 cm^{-1} showing a conjugated -C=C- stretching and a strong carbonyl peak at 1680 together with a prominent hydroxyl peak at 3400 cm^{-1} characteristic of a conjugated carboxylic acid.

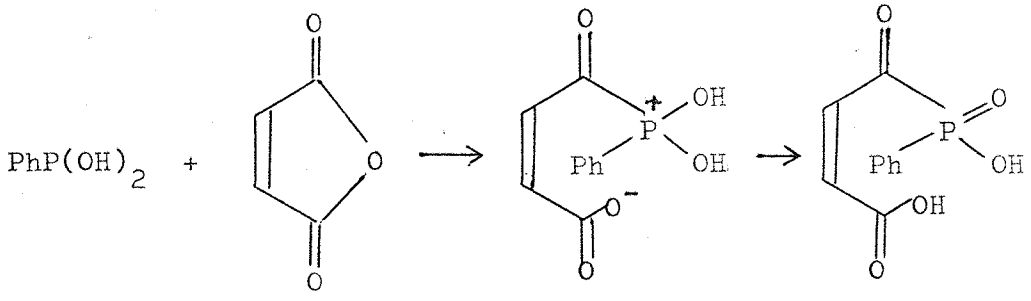
The ultra-violet spectrum taken in aqueous $NaHCO_3$ solution has a broad absorption band at λ_{max} 250, ϵ, 2,060, in contrast to the absorption of phenylphosphonous acid which shows characteristic benzenoid fine structure. This indicates an

extended chromophore. From these data, we assigned the following structure to the adduct(X).



X

The formation of this adduct could be explained through the following mechanism, in which the nucleophilic attack is on the carbonyl carbon with subsequent opening of the anhydride ring giving a bipolar intermediate, which in turn is stabilised by the transfer of a proton.



(v) With diphenyldisulphide.

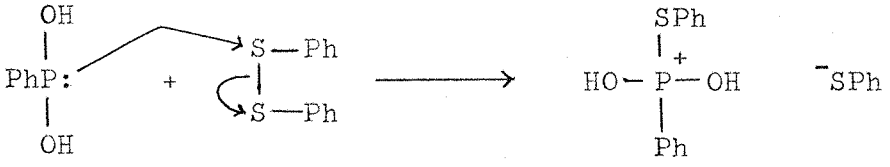
It has been shown that sodium diethyl phosphonate reacts rapidly in an organic disulphide in a non-polar solvent to produce a phosphorothioate ester and a sodium mercaptide (eq-1). If the reaction products are allowed to remain in contact, a secondary reaction takes place (eq-2) to produce sodium O,S-diethylphosphorothioate and diethyl sulphide.[28]

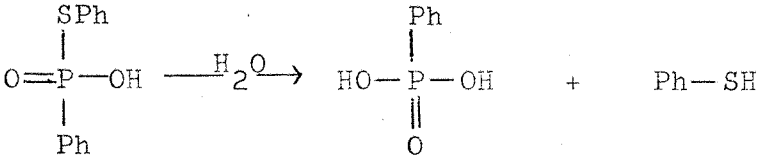
$$RSSR + NaP(=O)(OEt)_2 \xrightarrow{fast} RSP(=O)(OEt)_2 + NaSR' \qquad (1)$$

$$RSP(=O)(OEt)_2 + NaSR' \xrightarrow{slow} RSP(=O)(OEt)ONa + EtSR' \qquad (2)$$

where $R = R' = C_2H_5$

In the reaction of phenyl phosphonous acid with diphenyl disulphide, it was observed that the reaction proceeds quite rapidly at the temperature of steam bath, but on working up, the products isolated were phenyl phosphonic acid and thiophenol, an overall oxidation of the phosphorus and reduction of the disulphide.





From this suggested mechanism it is evident that in the presence of a base, the weaker P - S bond is rapidly cleaved producing phenyl phosphonic acid. The attack of OH^- ion on phosphorus is quite conceivable since because of its ability to expand its outer valence shell, phosphorus is the most electrophilic centre.

EXPERIMENTAL

Preparation of Phenyl(1-hydroxybenzyl)phosphinic acid.

Phenylphosphonous acid (1.4 g.) and benzaldehyde (2.5 ml) were heated to boiling point for three minutes. On cooling the adduct (1.82 g.) crystallised out, and was filtered off and washed with ether. The adduct had m.p. 170 - 180° and after crystallisation from ethylacetate containing a little ethanol had m.p. 200 - 202°.

Found: C, 63.0; H, 5.4; P, 12.6%. $C_{13}H_{13}O_3P$ requires: C, 62.9; H, 5.3; P, 12.5%

I.R. P-O, 965; C-O, 1120; P-O, 1160; Pph, 1400; 1600-1750; 2100-2200, 2600-2800, $-P\begin{matrix}=O\\ \diagdown OH\end{matrix}$; and 3450 cm^{-1} OH.

Phenyl-1-hydroxyallylphosphinic acid.

A mixture of phenylphosphonous acid (1.424 g. 0.01M) and well dried acrolein (0.53 g. 0.01M) was heated under reflux for four hours. The solvent was distilled off and the black gum obtained was dissolved in $CHCl_3$ (10 ml) and extracted with saturated $NaHCO_3$ (5 ml x 2). Acidification of the alkaline layers with HCl (1 : 1) and extraction into $CHCl_3$ (10 ml x 3) yielded a gum (1.26 g.). Redissolving the gum in $CHCl_3$ (5 ml) and precipitation with petroleum ether (60 - 80°) gave a dirty coloured solid, m.p. 126-127° (0.61 g., 32%). Recrystallisation twice from EtOAc gave the pure compound, m.p. 144-5°.

Found: C, 54.0; H, 5.7; P, 15.6%. $C_9H_{11}O_3P$ requires C, 54.4; H, 5.6; P, 15.6%.

I.R. 920, CH_2=CH–, 965, P–O, 1140, C–O, 1175, P=O 1440, P–Ph, 1640 C=C and broad bands at 1540–1750, 2300–2400, 2600–2800 characteristic of —P(=O)(OH) and 3400 cm^{-1} (sharp) OH.

Phenyl-1-hydroxycinnamylphosphinic acid.

A mixture of phenyl phosphonous acid (2.85 g.) and cinnam-aldehyde (2.72 g.) was heated under reflux for six hours. The separated solid was dissolved in saturated $NaHCO_3$ and precipitated with 1 : 1 HCl. A yellowish compound (4.305 g., 76%) m.p. 182–3° was obtained. Recrystallisation twice from a mixture of EtOAc : EtOH (2 : 1) gave white flakes, m.p. 190–1°.

Titration with 0.04N sodium hydroxide using phenolphthalein as indicator gave a value of 277.6 for the equivalent weight (calc. 274.00).

Found: C, 65.5; H, 5.56; P, 11.4. $C_{15}H_{15}O_3P$ requires C, 65.7; H, 5.5; P, 11.3.

I.R. 940 (sharp) P–O; 1140 (sharp) P=O; 1440 (sharp) P–Ph and 3350 cm^{-1} (sharp) –OH.

Phenyl(2,3-dibromo-1-hydroxypropyl-3-phenyl) phosphinic acid.

The hydroxycinnamylphosphinic acid, m.p. 190 - 1° (0.58 g.) was suspended in 25 ml $CHCl_3$ and heated under reflux; bromine was added drop by drop until the colour of the bromine was permanent. The solid went into solution as the reaction continued and at the end a clear solution resulted. The mixture was heated under reflux for ½ hour. The solvent was distilled to 10 ml. On cooling, a solid separated (0.541 g., 59.7%) m.p. 193-5°, which was washed with $CHCl_3$ (5 ml x 4). Recrystallisation from EtOH gave a white powder, m.p. 197-8°.

Found: C, 41.7; H, 3.5; Br, 36.8; P, 7.2%

$C_{15}H_{15}O_3Br_2P$ requires C, 41.7; H, 3.5; Br, 36.9; P, 7.1%

I.R. 940 (sharp) P-O; 1160 P=O; 1440 (sharp) Ph-P, 3300 cm^{-1} (sharp) OH, in addition to the usual $-P(=O)(OH)$ band.

Phenyl(1-hydroxycrotonyl)phosphinic acid.

Phenylphosphonous acid (1.4 g.) and crotonaldehyde (0.71 g.) were heated under reflux for twelve hours. A blackish gum was obtained which was washed with ether (5 ml x 4). The gum was then extracted with saturated $NaHCO_3$ and acidified with HCl (1 : 1), filtered and extracted into $CHCl_3$. On distillation of the solvent a gum (1.21 g.) was obtained which was repeatedly washed with a mixture of $CHCl_3$/petroleum ether (60-80°) (1 : 5). Redissolving the gum in $CHCl_3$ (few drops)/petroleum ether (60-80°)

5 ml gave a semi-solid (40 mg.). Crystallisation from EtOAc gave the compound, m.p. 121-2°.

Found: C, 55.6; H, 6.0; P, 14.7.

$C_{10}H_{13}O_3P$ requires C, 56.6; H, 6.1; P, 14.6%.

I.R. 1180 (sharp) P=O; 1445 (sharp) P-Ph 2300, 2600 (broad) —P(=O)OH 3380 cm^{-1} (sharp)-OH

Phenyl(1-phenyl-2-benzoylethyl)phosphinic acid.

Benzylidene acetophenone, m.p. 58° (4.2 g.) and phenyl phosphonous acid (2.85 g.) were heated under reflux for 72 hours on a steam bath. A solid m.p. 168-170° (2.95 g.) separated which was washed with dry ether (5 ml x 5). The gum (3.51 g.) obtained on the distillation of the solvent was treated with dry ether (2 ml) and left overnight, when another fraction of the solid m.p. 168-170° (0.86 g.) was obtained. The total yield of the adduct was thus (3.81 g.) 87%, calculated on benzylidene acetophenone converted.

2.95 g. of the adduct m.p.168-170° was dissolved in chloroform (20 ml) and extracted with saturated $NaHCO_3$ (10 ml) and then with water (5 ml x 2). On acidification of the alkaline layer, a precipitate m.p. 227-8° was obtained. Recrystallisation from ethanol gave a white powder, m.p. 242-3°.

Titration with 0.047N NaOH using phenolphthalein as indicator gave a value of 346 for the equivalent weight (Calc. 350).

Found: C, 71.9; H, 5.1; P, 8.9%. $C_{21}H_{19}O_3P$ requires C, 72.0; H, 5.4; P, 8.9%

I.R. 960 (sharp) P-O; 1225 (sharp) P=O; 1690 (sharp) C=O; 1590-1760, 2200-2240, 2600-2800 $-P\overset{O}{\underset{OH}{<}}$ and 3500 cm^{-1} (broad) -OH.

Preparation of the DNP derivative.

The acid (500 mg.) was heated under reflux with 2 ml Brady's reagent (2:4 dinitrophenylhydrazine in MeOH-H_2SO_4). On cooling, the dinitrophenylhydrazone (359 mg.) m.p. 203-5° separated. Recrystallisation from MeOH gave the orange coloured compound, m.p. 212-3°.

Found: C, 61.1; H, 4.3; N, 10.5; P, 5.8%

$C_{27}H_{23}O_6N_4P$ requires C, 61.1; H, 4.3; N, 10.3; P, 5.8%

I.R. 965 (P-O) 1220 (P=O) 1340 (NO_2) 1510 and 1520 (NO_2) 1625 (C =N-) and at 3300 cm^{-1} (NH) in addition to the usual $-P\overset{O}{\underset{OH}{<}}$ absorption bands.

Cyclic Phostone

The $CHCl_3$ layer from the bicarbonate extraction was dried over anhydrous $MgSO_4$ and distilled to give a residue (1.52 g.) m.p. 168-171°. Recrystallisation from MeOH gave the neutral compound as crystals, m.p. 181-3°.

Found: C, 76.1; H, 5.2; P, 9.5% $C_{21}H_{17}O_2P$ requires C, 75.9; H, 5.2; P, 9.3%.

I.R. 950 (sharp) P-O; 1220 (sharp) P=O; 1440 cm^{-1} (sharp) P-Ph. No C=O band, and no $-P\overset{O}{\underset{OH}{<}}$ absorption.

Methylation of the cyclic phostone.

A solution of 332 mg. of the cyclic phostone in EtOH (5 ml) was kept immersed in an ice-bath and treated with 2.5N NaOH solution (4 ml). $(CH_3)_2SO_4$ (0.33 ml) was dropped in carefully, while stirring the solution occasionally. The mixture was then heated under reflux for 0.5 hours when a solid separated which was filtered and washed with water (10 ml). The dried solid (313 mg, 95%) melted at 235-7°. Recrystallisation from EtOH gave a compound m.p. 243-5°. Comparison with the I.R. of the ketophosphinic acid and the m.p. of the admixture confirmed it to be the acid and not the ester which was expected.

Phenyl-2(2-hydroxy-4-phenylbut-3-enyl)phosphinic acid.

A mixture of phenylphosphonous acid (1.42 g.) and benzylidene acetone (1.46 g.) was suspended in 10 ml dry benzene and heated under reflux for 65 hours. The reaction mixture was cooled and extracted with saturated $NaHCO_3$ (10 ml) and then with water (5 ml). The alkaline layer was acidified with HCl (1 : 1) and extracted with $CHCl_3$ (10 ml x 3). The solvent extract was washed with water (10 ml) and dried over anhydrous $MgSO_4$. On removal of the solvent a gum (1.43 g.) was obtained, which was treated with acetonitrile to give a semi-solid precipitate. This was washed repeatedly with a mixture of $CHCl_3$: petroleum ether (60 - 80°) (1 : 10) and the washings decanted off. After 14 - 15 washings, a solid (118 mg.)

m.p. 133-5° separated. Recrystallisation from a mixture of $CHCl_3$: cyclohexane (1 : 10) gave a white crystalline compound, m.p. 135-7°. From the washings, 0.830 g. of unreacted phenylphosphonous acid was recovered.

Found: C, 66.2; H, 5.5; P, 10.5%. $C_{16}H_{17}O_3P$ requires C, 66.6; H, 5.9; P, 10.1%.

I.R. 950 (sharp) P-O; 1160 (sharp) P=O; 1440 (sharp) P-Ph 3400 cm^{-1} (broad) OH.

Cyclic phostone.

The benzene layer obtained from the above experiment was dried over anhydrous $MgSO_4$. The solvent was distilled (in vac) to yield a gum (1.13 g.) which was dissolved in dry ether. Petroleum ether (60 - 80°) was added drop by drop until precipitation was complete. On filtration, a compound m.p. 138-140 was obtained. Recrystallisation from cyclohexane gave 303 mg. of the neutral compound, m.p. 142-3°.

The filtrate was evaporated to give unreacted benzylidene acetone (580 mg.).

The yield of adducts amounted to 35.4% calculated on phenylphosphonous acid used.

Found: C , 71.0; H, 5.6; P, 11.7%. $C_{16}H_{15}O_2P$ requires C, 71.1; H, 5.5; P, 11.5%

I.R. 950 (sharp) P-O; 1200 (sharp P=O; 1220 (sharp) C-O; 1610 cm^{-1} (weak) -C=C-. No hydroxyl or carbonyl peak or peaks due to $-P\overset{O}{\underset{OH}{\diagdown\!\!\diagup}}$.

Addition of phenylphosonous acid to distyryl ketone.

A mixture of phenylphosphonous acid (1.4 g.) and distyryl ketone (2.3 g.) in benzene (15 ml) was heated under reflux for 32 hours, cooled and extracted with an $NaHCO_3$ solution. On acidification a precipitate m.p. 226-8° (0.37 g.) was obtained. Crystallisation twice from ethanol gave the compound m.p. 230-2°.

Found: C, 71.2; H, 5.7; P, 8.1%. $C_{23}H_{21}O_3P$ requires C, 73.2; H, 5.6; P, 8.2%.

I.R. 945 (sharp) P-O; 1185 (sharp) P=O; 1450 (sharp) P-Ph; 1635 (medium) PhCH=CH- ; 1675 (C=O) 2300, 2600 cm^{-1} (broad) $-P\begin{matrix}=O\\ \diagdown OH\end{matrix}$.

1,2-bisEthoxycarbonylethane-1,2-bisphenylphosphinic acid.

Phenylphosphonous acid (2.84 g.) and ethyl acetylene dicarboxylate were heated under reflux for 45 hours, when a solid separated. The reaction mixture was cooled and washed with petroleum ether (60 - 80°). The residue was then treated with ethyl acetate, whereby the gum dissolved and the solid, m.p. 185-7° (2.13 g.) was isolated after filtering and washing with ethyl acetate. The washings were extracted with saturated $NaHCO_3$. The alkaline layer acidified with HCl (1 : 1) and extracted with chloroform (5 ml x 4). Evaporation of the solvent gave a further yield of the adduct, m.p. 185-7°. In

all, 3.1 g. of the adduct, m.p. 185-7°, 68% was isolated. Crystallisation from ethyl acetate containing a little ethanol gave shiny needles, m.p. 187-8°.

Titration with NaOMe in MeOH (0.047N) using bromothymol blue as indicator gave a value of 226.9 for the equivalent weight (Cal. 227.0 for the bis-phosphinic acid).

Found: C, 52.7; H, 5.2; P, 13.5%. $C_{20}H_{24}O_8P_2$ requires C, 52.9; H, 5.3; P, 13.7%.

I.R. 1180 (sharp (P=O); 1250 (medium) C-O; 1440 (sharp) P-phenyl; 1740 (sharp) C=O and 2700 cm^{-1} (broad) $-P\begin{matrix}=O\\ \diagdown OH\end{matrix}$.

Hydrolysis of the Acetylene dicarboxylic ester adduct.

The adduct (0.53 g.) was heated under reflux for twelve hours with 2.5N-NaOH when a clear solution was obtained, cooled and acidified with HCl (1 : 1). A precipitate (0.46 g.) was obtained which was washed with water and dried. Crystallisation from ethyl acetate gave a white powder, m.p. 198-201°.

Found: C, 51.4; H, 5.3; P, 17.4%. $C_{15}H_{16}O_6P_2$ requires C, 51.0; H, 4.2; P, 17.5%.

I.R. 1185 (sharp) P=O; 1220 (sharp) C-O; 1440 (sharp) P-phenyl; 1700 (broad) C=O; 2500 (broad) $-P\begin{matrix}=O\\ \diagdown OH\end{matrix}$ and at 3000 cm^{-1} (shallow and broad) hydrogen bonded OH group.

Attempted Preparation of diphenylacetylene adduct.

Phenylphosphonous acid (2.84 g.) and diphenylacetylene (3.56 g.) were heated under reflux on a steam-bath for 48 hours. The reaction mixture was cooled and dissolved in chloroform (15 ml) and extracted with saturated $NaHCO_3$, and then washed with water. The alkaline layer was acidified and extracted into chloroform (10 ml x 3). Distillation of the solvent gave the unreacted phenylphosphonous acid (2.5 g.) m.p. 78–9°. Evaporation of the solvent from the neutral layer gave unreacted diphenylacetylene (3.0 g.) m.p. 50 – 9°.

The reaction was repeated in dry benzene (15 ml) with half the above quantities. Phenylphosphonous acid (1.4 g.) and diphenylacetylene (1.8 g.) were regained after heating under reflux for 48 hours and working up in the usual way. No adduct formation occurred and starting materials were regained when phenylacetylene was used in similar experiments.

Maleic anhydride adduct.

Phenylphosphonous acid (2.85 g.) and maleic anhydride (1.99 g.) were heated together under reflux for three hours, when a semi-solid separated. The whole mass was treated with ethyl acetate (5 ml x 3) when the adduct, m.p. 207 – 209° (1.62 g.) was obtained. The adduct was highly insoluble in all the common solvents. The best method of achieving considerable purity was through repeated treatment with $NaHCO_3$ solution and subsequent

reprecipitation with HCl (1 : 1), whereby the m.p. was raised to 235 - 7° and did not change on further treatment.

Found: C, 48.2; H, 3.9; P, 12.2%. $C_{10}H_{11}O_6P$ requires C, 46.5; H, 4.3; P, 12.0%.

I.R. 960 (m. sharp) P-O; 1185 (sharp) P=O; 1445 (sharp) P-Ph; 1640 (sharp) and 1680 (broad) two different C=O; 2600 (broad) $-P\begin{matrix}=O\\ \diagdown OH\end{matrix}$ and 3400 cm^{-1} (broad) -OH.

Reduction of diphenyl disulphide by phenylphosphonous acid.

Phenylphosphonous acid (2.85 g.) and diphenyl disulphide (3.92 g.) were heated under reflux for 65 hours, cooled and washed with dry Et_2O (10 ml x 3). A gum was obtained which was extracted with saturated $NaHCO_3$ solution and acidified with HCl (1 : 1). On standing, a solid (1.98 g.) m.p. 79 - 80° separated. Crystallisation from water gave a solid (1.20 g.) m.p. 162-3°.

comparison with the I.R. of a pure sample of phenylphosphonic acid and the m.p. of the admixture confirmed it to be phenylphosphonic acid.

Evaporation of ether from the washings yielded an oily liquid (3.12 g.) with a penetrating odour. The liquid was purified by distillation at 70 - 5°/20 - 25 mm. Comparison of the I.R. spectrum with that of a pure sample of thiophenol confirmed that the liquid was thiophenol.

I.R. of phenylphosphonic acid 940 (sharp) P-O; 1210 (broad) P=O (H- bonded); 1440 (sharp) P-Ph; 2600 cm^{-1} (broad and shallow) P - OH.

CHAPTER III

RESULTS AND DISCUSSIONS

EXPERIMENTAL

In 1961, Doak[17] and his co-workers succeeded in preparing a derivative of phenoxaphosphinic acid by heating p -tolyl ether with phosphorus trichloride and aluminium chloride.[17] The authors noted that the unsubstituted diphenyl ether was attacked by these reagents in the 4-position to give p -phenoxyphenylphosphonic acid but they apparently did not investigate diphenyl ethers substituted in only one p -position, nor did they attempt the reaction with substituents in the p-position other than methyl groups.

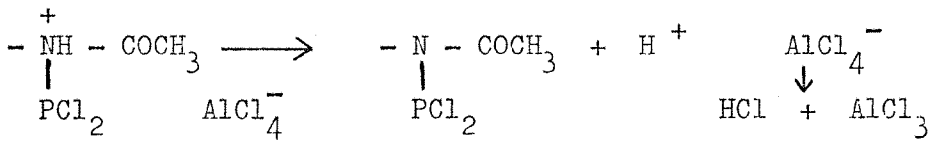
Campbell[29] succeeded in preparing unsymmetrically substituted phenoxaphosphines in the hope of comparing their optical activity with that of the phenoxarsines prepared by Lesslie and Turner in 1936. The preparation of 2-chloro-8-methylphenoxaphosphine-10-oxide (I) was achieved in good yield by Doak's method.[17]

The purpose of this work was to examine the scope of this Friedel-Crafts reaction and to synthesise phenoxaphosphine with differen t substituents in the p- and p'- positions of the aromatic rings and to attempt the optical resolution of these compounds.

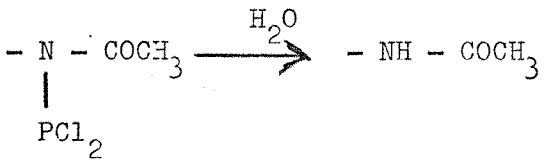
The first compound that we selected for this reaction was p-tolylphenyl ether. A polymer was obtained and no cyclic-phosphine was isolated. Presumably substitution occurred at the unsubstituted p-position and possibly also at the ortho position

followed by further reaction of the PCl_2 group with another molecule of ether.

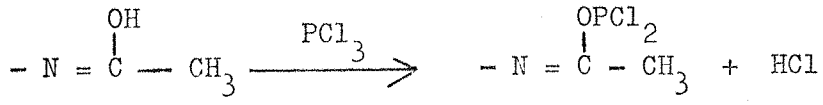
We than attempted the preparation of 2-methyl-8-acetamido phenoxphosphine-10-oxide by the reaction on p-acetamido p'-methyl diphenyl ether. The procedure adopted was similar to that described in the literature[17]. Hydrochloric acid gas was evolved and the reaction appeared to have occurred, but on working up the starting material was regained. The failure of the acetamido ether to undergo the Friedel-Craft's reaction cannot be easily explained. However, two mechanisms are possible which explain the regeneration of the acetamido ether. In the first step electrophilic attack of $\overset{+}{P}Cl_2$ on the secondary nitrogen could yield the ionic complex (II), which would evolve hydrochloric acid gas, and,



II



would also inhibit further attack of the electrophile ($\overset{+}{P}Cl_2$). Hydrolysis of (II) in the aqueous work up would regenerate the acetamido group and phosphorous acid. It is also possible that the acetamido group acts in the enol form as in Bischler-Napieralsky reaction with PCl_5.

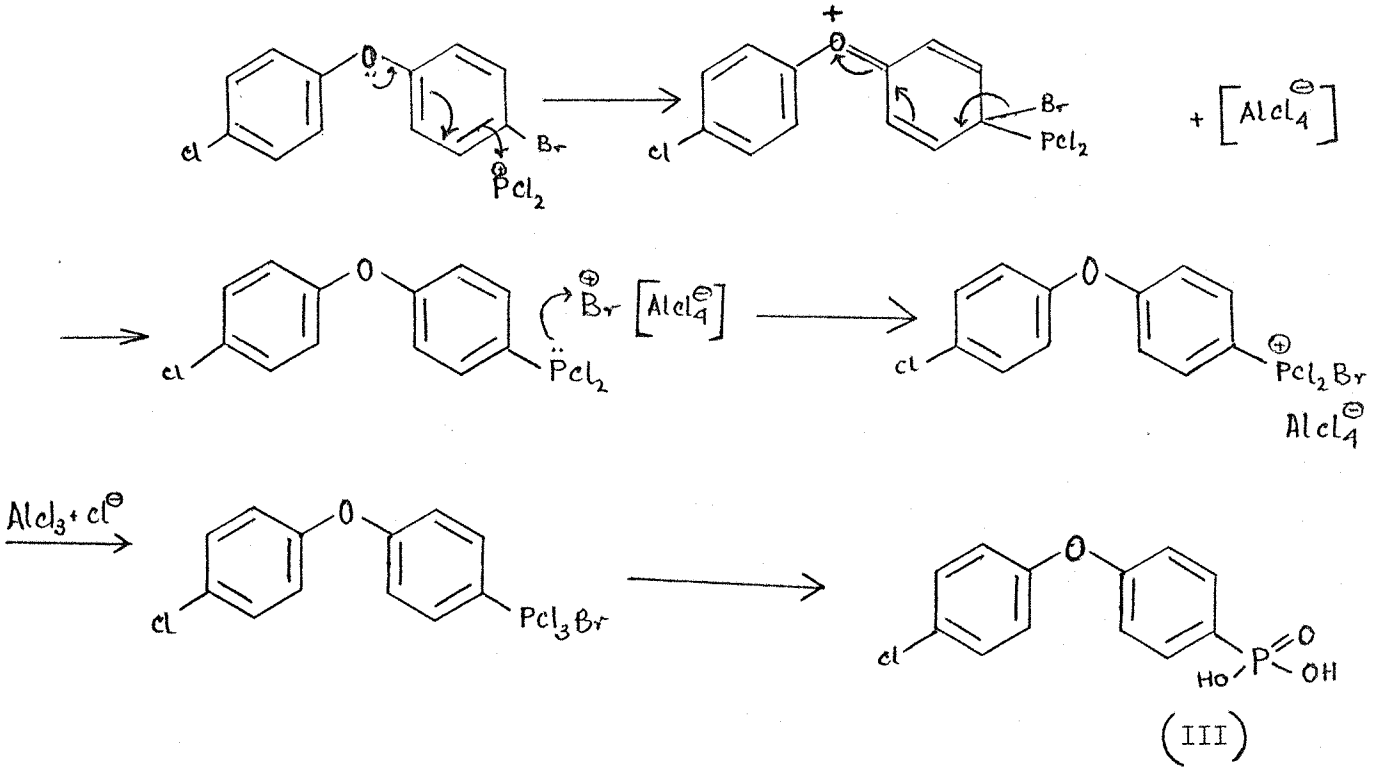


Again hydrolysis would regenerate the starting material.

When preparation of 2-bromo-8-chlorophenoxaphosphine-10-oxide from 4-bromo-4'-chlorodiphenyl ether was attempted the product was 4-p -chlorophenoxy phenyl phosphonic acid (III). This reaction represents a simple electrophilic displacement of bromine by phosphorus trichloride in the presence of aluminium chloride.

A similar observation was made during an attempted preparation of a bromine containing phenothiaphosphinic acid when a p-arylthiophenyl phosphonic acid was obtained.[31]

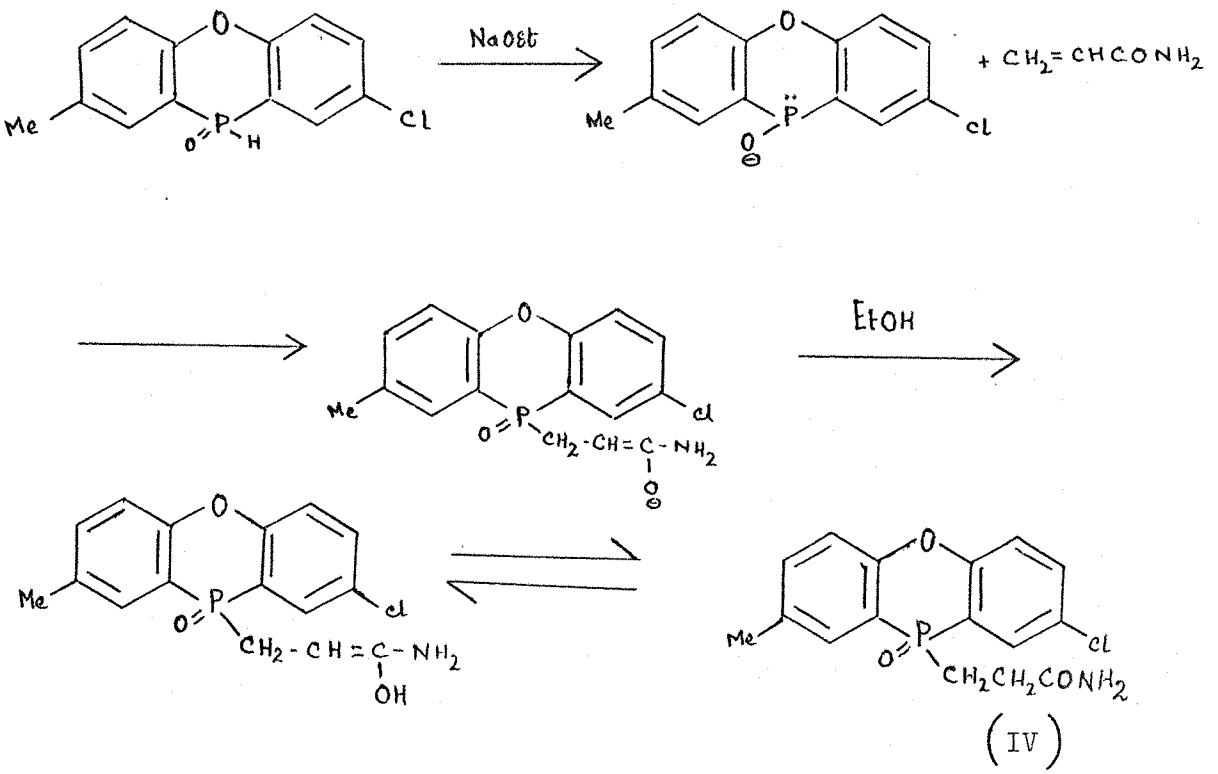
The reaction could very well be summarised in the following scheme.



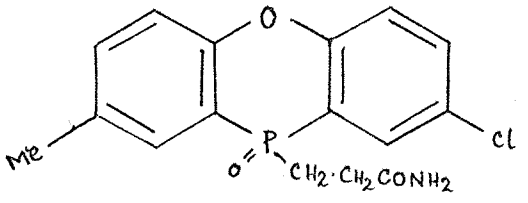
(III)

As none of these reactions proved to be successful we decided to modify the 2-chloro-8-methylphenoxaphosphine-10-oxide by introducing other groups on phosphorus. The addition reactions of disubstituted phosphine oxides to activated systems have been extensively studied.[24,34] It has been shown that they add readily to α,β-unsaturated systems in the presence of base to give addition products in good yields.

We studied the addition of 2-chloro-8-methylphenoxaphosphine-10-oxide to acrylamide and observed that the phosphinyl group adds to β-carbon atom to form the adduct (IV) in 70.6% yield. The mechanism of this reaction appears to be the same as suggested earlier[24,34] where the reaction proceeds via the addition of the anion $(RO)_2\dot{P}^{\bullet} - \bar{O}$ to the unsaturated link, with subsequent acceptance of a proton supplied by the solvent.



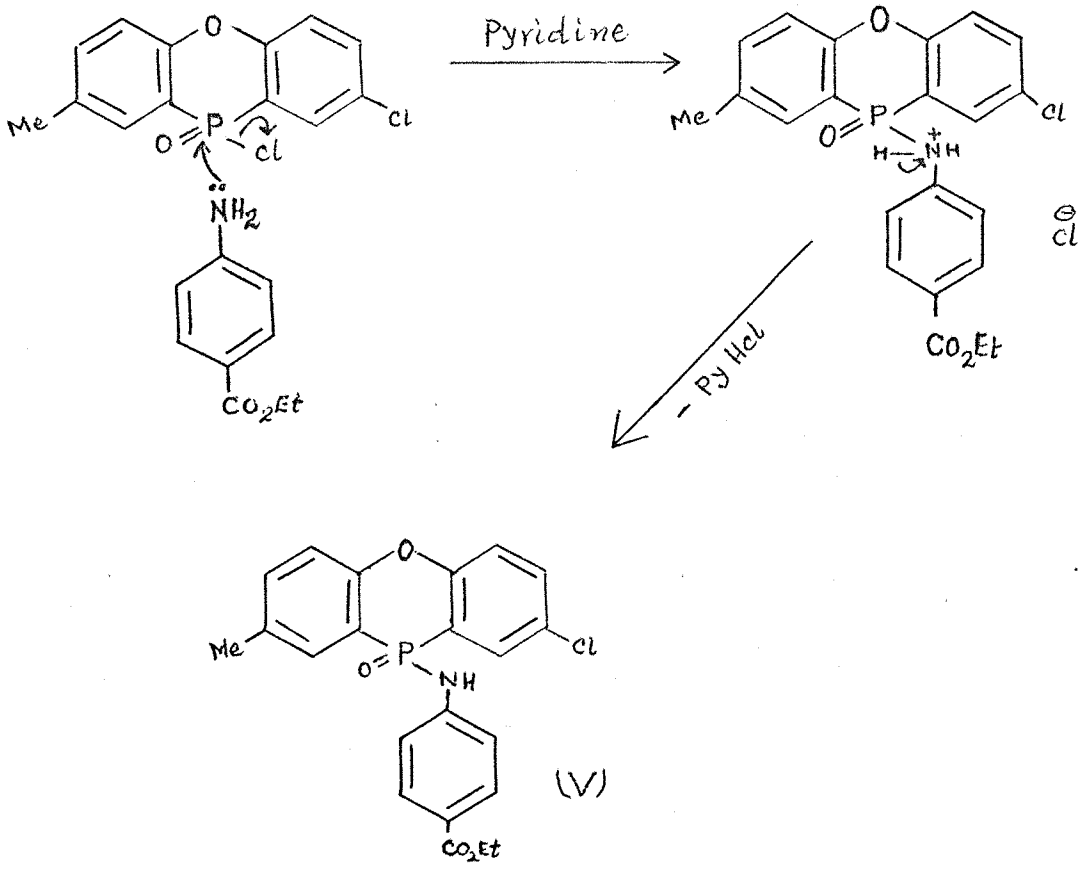
(IV)



IV

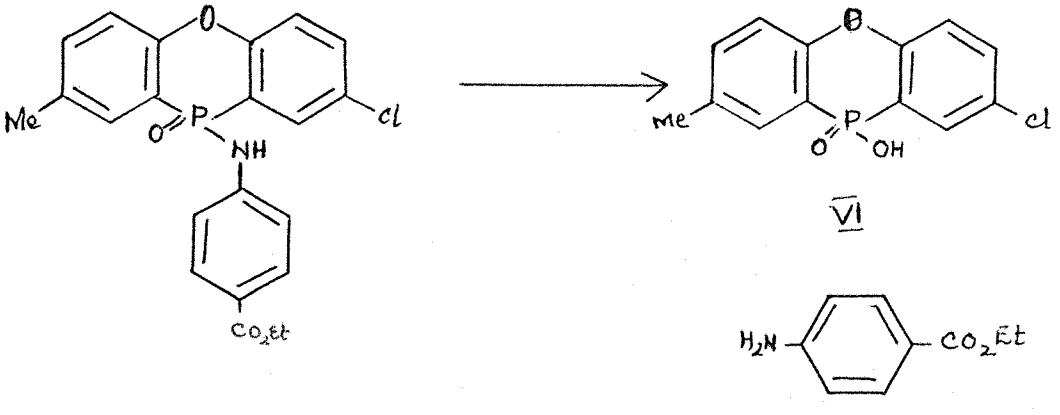
The addition product (IV) was hydrolysed to the known carboxylic acid.

We studied the reaction of the phenoxaphosphinic acid chloride with p-aminobenzoate in the presence of pyridine and obtained the anilide (V) in good yield. The formation of this anilide clearly shows a nucleophilic attack on the 4-covalent phosphorus. It is known that in the presence of a good leaving group phosphorus acts as an electrophile.[3] This reaction amply proves the fact.



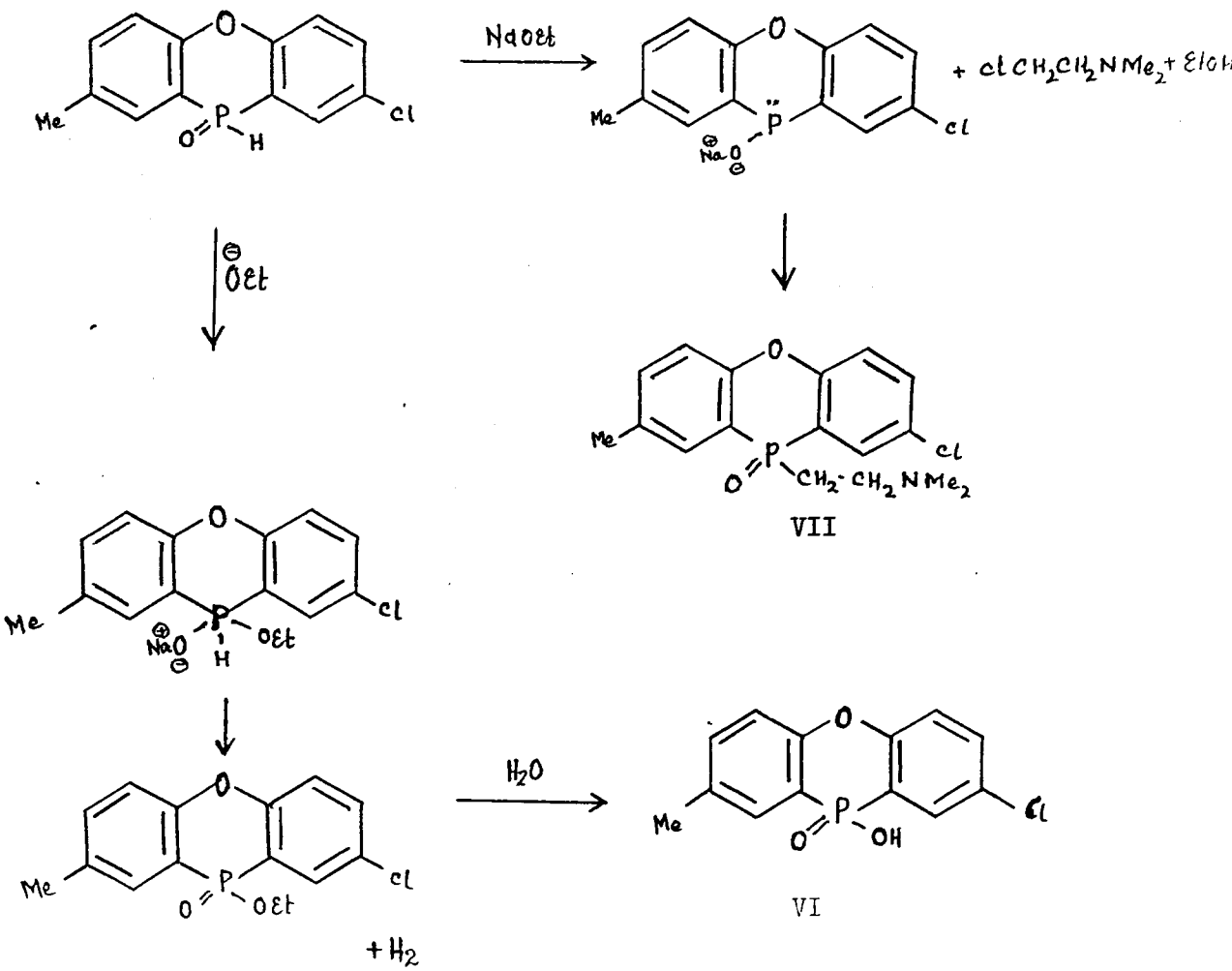
(V)

An attempt to obtain the carboxylic acid by hydrolysis of the ester group with alkali failed, and instead the phenoxaphosphinic acid (VI) was obtained. The isolation of this acid indicates the instability of P – N bond in the presence of a strong nucleophile e.g. the base, where the amino benzoate group acts as a better leaving group.



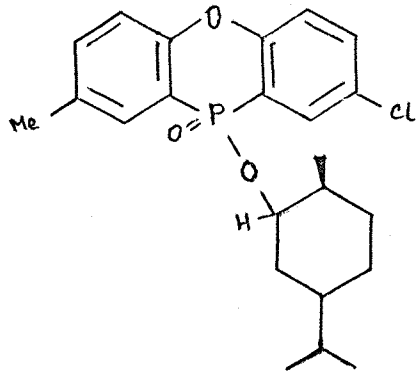
VI

We attempted to resolve the phenoxaphosphine oxide by condensing its anion with 2-chloroethyldimethylamine hydrochloride. Once the amine was obtained the quaternisation was a simple process, and hence the isolation of an optically active salt appeared to be quite feasible. However, we encountered tremendous difficulty in preparing the base in good yield. Unfortunately, during the experiment the oxidation of phenoxaphosphine oxide into phenoxaphosphinic acid took place more rapidly than the condensation. It appears, therefore, that the reaction of the anion with 2-chloroethyldimethylamine is a much slower process than the oxidation.



The dimethyl amino ethyl derivative (VII) obtained in low yield, was readily converted to quaternary methiodide and from this a specimen of dibenzoyltartrate was obtained but in such a small quantity that fractional crystallisation was not possible. The salt had $[\alpha]_D$ + 14.7° and its analysis evidently proved difficult, though carbon and hydrogen values were acceptable, the percentage of phosphorus was impossibly high.

The acid obtained as the by-product was converted into the acid chloride and condensed with menthol in the presence of pyridine to get the menthyl ester (VIII) of the phenoxaphosphinic acid. This was successfully prepared but evidence of separation into diastereoisomers could not be obtained.



VIII

Fractional crystallisation from petroleum ether (60 - 80°) containing a little ethyl acetate gave specimens with values of

$[\alpha]_D$ + 41.8 - + 41.9 (in ethanol) but insufficient material was available for many crystallisations.

Campbell[29] attributed the failure of resolution of phenoxaphosphines to the optical lability of the diastereoisomeric salts whereby asymmetric induction permits the separation of either the (+) or (-) salt. In the case of the menthyl ester, this cannot occur and the separation of diastereoisomers should be effectively achieved. This problem therefore is far from being solved and presents an interesting field for further work.

EXPERIMENTAL

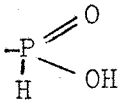
Attempted preparation of 2-methylphenoxaphosphine-10-oxide.

4-Methyldiphenyl ether (9 g.), aluminium chloride (8 g.) and phosphorus trichloride (15 ml) were heated together under reflux on a magnetic stirrer for twenty hours, until the evolution of HCl ceased. The cooled reaction mixture was poured onto ice and the sticky mass obtained was washed with (HCl (dil.) and water. The product remained sticky and no satisfactory solvent for crystallisation was found. The I.R. spectrum indicated the presence of a phosphonic or phosphonous acid rather than the expected phosphine oxide. A small quantity was treated with 4N-NaOH and filtered from insoluble material. The filtrate on acidification gave a precipitate

m.p. $> 320^{\circ}$ for which no suitable solvent could be found.

The remainder of the product was dissolved in benzene and an attempt was made to separate the mixture by chromatography on silica. Some material came off the column very slowly in $CHCl_3$ as gelatinous drops. As this seemed to indicate a polymer no further experiments were tried.

Attempted preparation of 2-bromo-8-chlorophenoxaphosphine-10-oxide.

4-Bromo-4'-chlorodiphenyl ether (5.7 g.), aluminium trichloride (3 g.) and phosphorus trichloride (8 ml) were heated together under reflux and stirred magnetically for twelve hours. The mixture was cooled and poured into ice. The sticky mass obtained was washed with HCl (dil.) and water and was extracted with ether and 4N-NaOH, when a small insoluble residue was left. Acidification of the alkaline solution gave a precipitate (1.52 g.) m.p. 320°. This acid was recrystallised from acetic acid - water (2 : 1) and then had m.p. $250 - 5^{\circ}$. It contained chlorine but no bromine and on investigating the solution from initial precipitation it was shown to contain bromide ion by oxidation and extraction with chloroform. Elimination of bromide ion indicated replacement by the $-PCl_2$ group, hydrolysed on work up to  or $-P(=O)(OH)_2$, and analysis indicated the latter.

Found: C, 49.9; H, 3.5; P, 10.9% $C_{12}H_{10}C\,l_0{}_4P$

requires C, 50.6; H, 3.4; P, 11.0%.

From the ether extract unchanged 4-bromo-4'-chlorodiphenyl ether (1.54) m.p. 39 - 42° was regained.

Attempted preparation of 2-acetamido-8-methylphenoxaphosphine-10-oxide.

p-Aminophenyl-p-tolyl ether (5.01 g.) and acetic anhydride (6.4 ml) were mixed in an ice-bath and 3 - 4 drops of dried pyridine were added with occasional shaking. The mixture was then heated under reflux for one hour, cooled and poured on 200 g. of crushed ice. The solid (5.52 g., 91%) was filtered and washed with water at the pump. Recrystallisation twice from cyclohexane containing a little ethyl acetate gave the amide as shiny flakes, m.p. 130-1°, (reported m.p. 131°).

To a mixture of the amide (4.8 g.) and anhydrous aluminium chloride (3 g.), phosphorus trichloride (15 ml) was added drop by drop with constant stirring. At first the mixture was heated under reflux at 50 - 5° for one hour and then at 90 - 5° for eighteen hours when the evolution of HCl completely ceased. After cooling it was poured on 250 g. of crushed ice, when a gum (12.2 g.) was obtained. The gum was dissolved in $CHCl_3$ (20 ml) and extracted in saturated $NaHCO_3$. The neutral solvent layer was washed with water (10 ml x 4) and dried over anhydrous $MgSO_4$. Distillation of the solvent gave unreacted amide, m.p. 127-8° (4.6 g.). Acidification of the alkaline layer gave a small amount of dark brown gum which decomposed at 210 - 5°. All efforts to crystallise the gum failed. The gum was dissolved in

chloroform (5 ml) and petroleum ether (60 - 80°) was added drop by drop, when a precipitate was obtained. Recrystallisation of the precipitate from petroleum ether (60 - 80°)/EtOAc gave a trace of the unreacted amide, m.p. 128-9°.

Preparation of 2-chloro-8-methylphenoxaphosphine-10-oxide.

p-Chlorophenyl p-tolyl ether was prepared from p-aminophenyl p-tolyl ether by the Sandmeyer process and isolated by prolonged steam distillation. The distillate solidified and gave the ether (58%) as leaflets, m.p. 54-5°. 2-Chloro-8-methyl-phenoxaphosphine-10-oxide was prepared by Campbell's method. The oxide (10.5 g.) was obtained as needles, m.p. 156-7° (from ethanol).

2-Chloro-8-methylphenoxaphosphine-10-propionamide.

2-Chloro-8-methylphenoxaphosphine-10-oxide (2.64 g., 0.01M) and acrylamide (0.71 g., 0.01M) were suspended in ethanol (25 ml) and sodium metal (0.23 g.) was added. The reaction was extremely exothermic and the flask was cooled occasionally. The mixture was stirred for two hours and filtered from slight precipitate. The clear solution was left in a refrigerator for 24 hours when a solid, m.p. 241-3° (2.4 g., 70.6%) separated. Recrystallisation twice from aqueous ethanol gave shiny crystals, m.p. 242 - 3°.

Found: C, 57.3; H, 4.70; N, 4.0; P, 9.3%

$C_{16}H_{13}O_3NClP$ requires C, 57.2; H, 4.5; N, 4.2; P, 9.2%

I.R. 1220 (sharp) P = O; 1239 (sharp) C - O; 1680 (sharp) $CONH_2$; 1690 (sharp) C = O; 3200 and 3325 cm^{-1} (sharp), typical amide $-NH_2$ pair of bands.

Hydrolysis of the amide.

Amide (1.1 g.) was suspended in 2.5 N-NaOH (7 ml) and heated under reflux for 18 hours until no more evolution of ammonia was observed and a clear solution obtained. Cooled and acidified with HCl (1 : 1) when a precipitate was obtained. Recrystallisation of the damp precipitate from aquecus ethanol gave the acid (1.03 g., 79.2%) m.p. 210-2°. From a comparison of the I.R. and the cited m.p., the acid was identified as 2-chloro-8-methylphenoxaphosphine-10-propionic acid.

2-Chloro-8-methyl-10-phenoxaphosphinic-4'-carbethoxy anilide.

2-Chloro-8-methyl-10-phenoxaphosphinic acid chloride (0.6 g.) and ethyl p-aminoe[illegible] benzoate (0.66 g.) were heated together under reflux for 1½ hours, when the whole mass became red, but the colour soon disappeared to give a semi-solid. The product was cooled and suspended in HCl, washed with water and dried. Treatment with ethyl acetate (5 ml) gave a solid (0.57 g.) m.p. 121-2°. Recrystallisation from ethyl acetate containing a little ethanol gave the anilide m.p. 192-3°.

Found: C, 61.4; H, 4.4; P, 7.6% $C_{22}H_{19}O_4NCl$

requires C, 61.7; H, 4.4; P, 7.3%.

I.R. 1180 (sharp) P = O; 1220 (medium) C – O;

1285 (sharp) –C–N ; 1610 (sharp) P–NH;

1705 (sharp) C = O and 3300 cm^{-1} (sharp) NH.

Hydrolysis of the Anilide.

The anilide (200 mg.) was heated under reflux with 2.5N-NaOH (5 ml) for two hours, and on acidifying the cooled mixture with HCl (1 : 1) a precipitate (110 mg.) was obtained. It was identified as the phenoxaphosphinic acid (by mixed m.p. and comparison of the I.R.) and not the carboxylic acid the preparation of which was attempted.

2-Chloro-8-methyl(2'-dimethylaminoethyl)phenoxaphosphine-10-oxide.

The phenoxaphosphine oxide (2.64 g.) was suspended in 50 ml ethanol, 2-chloroethyl dimethyl amine hydrochloride (1.47 g.) was added to the suspension and warmed until a clear solution was obtained. Sodium metal (0.48 g.) was then dropped in the warm sclution and the mixture was heated under reflux for 14 hours. Excess of ethanol was distilled off and the oily liquid obtained was poured into 100 ml ice-cold water. A gum was obtained which was extracted into ether. Distillation of ether left a syrup which soon solidified to give the compound (1.14 g.) m.p. 95–6°. Crystallisation from cyclohexane gave a solid m.p. 98–100°.

The solid separated with a molecule of water and recrystallisation twice from cyclohexane failed to remove it.

Found: C, 58.0; H, 5.9; N, 4.0; P, 8.5%

$C_{17}H_{19}O_2ClNP,H_2O$ requires C, 57.7; H, 6.0; N, 4.0; P, 8.7%

I.R. 1210 (sharp) P = O; 1220 (sharp) -C-N and 3500 cm^{-1} (sharp) hydroxyl group due to a molecule of water.

Acidification of the aqueous extract gave 2-chloro-8-methyl phenoxaphosphinic acid (1.51 g.) m.p. 307-9° (Reported m.p. 318-320°).

Preparation of the methiodide.

The dimethylaminophosphine oxide was dissolved in excess of Na-dry ether and methyl iodide (5 ml) was added carefully. The mixture was heated under reflux on a steam bath for 10 - 15 minutes when the methiodide (1.5 g. - 63.5%) m.p. 241-2° separated. Recrystallisation from MeOH gave a white powder, m.p. 243-5°. The methiodide too held a molecule of water on recrystallisation.

Found: C, 43.7; H, 4.7; P, 6.4% $C_{18}H_{22}O_2ClNI.H_2O$ requires C, 43.7; H, 4.9; P, 6.3%

I.R. 1200 (sharp P = O; 1220 (sharp) -C-N and 3400 cm^{-1} (broad) hydroxyl group due to a molecule of water.

Preparation of Silver D(-)dibenzoyl hydrogen tartrate.[32,33]

N-Ammonium hydroxide (14.4 ml) was added to a slurry of 5 g. of D(-)dibenzoyl tartaric acid in 150 ml of distilled water. The mixture was heated until all the solid material had dissolved and was then cooled to 45°. A solution of 2.3 g. of silver nitrate in 35 ml of distilled water was added dropwise. A flocculent precipitate of silver D(-)dibenzoyl hydrogen tartrate was obtained. The precipitate (2.86 g., m.p. 190-2°) was washed with water and dried.

Attempted Isolation of the Salt.

Silver D(-)dibenzoyl hydrogen tartrate was heated under reflux in methanol (25 ml) and treated with a boiling solution of methiodide (1.31 g. in 20 ml methanol). The blackish yellow precipitate was filtered and methanol (35 ml) was distilled off. The solution was cooled under running water and then kept in a refrigerator for four days. No crystallisation occurred. On complete removal of methanol a gummy residue (1.3 g. m.p. 98-9°) was obtained. Crystallisation from acetone produced 463 mg. of the compound, m.p. 178-180°.

Found: C, 61.5; H, 4.2; P, 13.3 $C_{36}H_{35}ClNO_{10}P$

requires C, 61.1; H, 5.0; P, 4.4.

The salt had $[\alpha]_D$ + 14.7 (C, 0.5 EtOH).

Preparation of Menthyl 2--chloro--8--methyl--10--phenoxaphosphinate.

The phenoxaphosphinic acid (2.64 g.) was suspended in redistilled chloroform (15 ml) and redistilled thionyl chloride (1.5 ml) was slowly added. The mixture was first heated gently under reflux for one hour until all the solid had dissolved. A rapid evolution of HCl gas was observed. It was then boiled under reflux for another four hours when the evolution of HCl gas had completely ceased. Chloroform was removed by distillation and thionyl chloride was removed by repeated distillation with Na-dry benzene. A yellow solid (2.9 g.) m.p. 151-2° was obtained. Crystallisation from Na-dry benzene gave a white solid, m.p. 195-6°, which presumably was the acid chloride.

The acid chloride (2.85 g. m.p. 195-6°) was dissolved in 25 ml Na-dry benzene, menthol (1.45 g. in 5 ml Na-dry benzene) was then added followed by pyridine (0.80 g.). The mixture was stirred magnetically overnight. Pyridine hydrochloride separated, was filtered off and benzene was removed (vac), when a semi-solid was obtained. Treatment with dry ether gave a solid (1.5 g.) m.p. 305-7°. The solid was unreacted phosphinic acid. The ethereal filtrate was washed with water (10 ml x 3) and dried over anhydrous $MgSO_4$. Distillation of ether gave a gum (2.76 g.) having a pronounced odour of menthol. The gum was subjected to sublimation when unreacted menthol (0.96 g.) was isolated. The purified gum was then treated with petroleum ether (60 - 80°) and was left overnight. A solid (0.87 g.) m.p. 102-3°

separated. Recrystallisation from petroleum-ether (60 - 80°) containing a little ethyl acetate gave shiny crystals, m.p. 124-5°. The mother liquor was concentrated to give second fraction (0.62 g.) of the compound m.p. 124-5°. Both fractions had $[\alpha]_D$ between + 41.8 and 41.9 (C, 0.5, EtOH). Repeated crystallisation did not significantly alter the m.p. or rotation of the ester.

Found: C, 67.5; H, 6.8; P, 7.5% . $C_{23}H_{28}O_3ClP$

requires C, 67.4; H, 6.7; P, 7.4%

I.R. 990 (sharp) P-O-C; 1220 (sharp) P=O, and 1240 cm^{-1} (sharp) C-O.

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